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The Effect of Meloxicam, a Selective COX-2 Inhibitor, on the Microvasculature of Small Metastatic Liver Tumors in Rats

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Background: COX-2 is involved in tumor angiogenesis and modulation of the production of angiogenetic factors by colorectal carcinoma cells. It has been shown that COX-2 inhibitors have inhibitory activities against various types of tumor, including colorectal carcinoma. In this study, we investigated the tumor vessels of small metastatic liver tumors in rats and the effect of meloxicam, a selective COX-2 inhibitor, on their growth and microvasculature.
Methods: The metastatic liver tumors were produced by intraportal inoculation of RCN-H4 cells in male F344/DuCrj rats ($n = 40$). The microvasculature was examined by scanning electron microscopy and stereomicroscopy. Microvascular casts were produced by perfusion via the abdominal aorta 14 days after tumor inoculation. Four groups (control, groups 1–3) of rats were treated with meloxicam 0, 0.6, 1.0 and 3.0 mg/kg/day, respectively, by oral gavage 5 days/week for two weeks from the day of inoculation of RCN-H4 cells.
Results: The mean number of tumors was significantly decreased in groups 1–3 (5.6 ± 0.8 standard deviation, SD; 3.6 ± 1.1; and 5.5 ± 1.1, respectively) compared with control (11.2 ± 2.7; $P = 0.0002$, each). Meloxicam also significantly reduced the mean diameter of the tumor: 730 ± 254, 685 ± 212 and 644 ± 139 in groups 1–3, respectively, in comparison with 870 ± 276 in control ($P = 0.0025$, 0.0011 and <0.0001, respectively).
Conclusions: Meloxicam's anti-angiogenic activity interferes with the growth of metastatic liver tumors. Meloxicam might have therapeutic potential for liver metastasis of colorectal carcinoma.

Key words: COX-2 – colorectal carcinoma – liver metastasis – microvasculature

INTRODUCTION

Colorectal carcinoma is widespread and frequently fatal in the West (1) and its incidence in Japan is also increasing (2). The liver is one of the major targets for colorectal carcinoma metastases and liver metastases indicate a poor prognosis. Therefore, effective therapeutic agents against liver metastasis would be of high clinical importance.

Epidemiological studies have suggested that non-steroidal anti-inflammatory drugs (NSAIDs) might reduce the risk of colorectal carcinoma (3–7) and decrease the number and size of polyps in patients with familial adenomatous polyposis (8–10). These studies imply that NSAIDs could modulate carcinogenesis and the development of colorectal carcinoma. NSAIDs are known to inhibit cyclooxygenase (COX), the key enzyme in the conversion of arachidonic acid to prostaglandins. Two isoforms of COX, COX-1 and COX-2, are recognized (11). COX-1 is constitutively expressed in many normal tissues to regulate and maintain normal cellular functions. In contrast, COX-2 is induced by several inflammatory stimuli, such as cytokines, growth factors and tumor promoters (11), and expressed in colorectal carcinoma (12,13). COX-2 is thought to influence carcinogenesis and the development of colorectal carcinoma. Recent studies on clinical materials have shown that COX-2 levels are increased in approximately 85% of colorectal carcinoma (12,14–16), indicating that it might play an important role in colon carcinogenesis (17). Tsujii et al. reported that COX-2 is involved in tumor angiogenesis and modulates the production of angiogenic factors by colon carcinoma

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cells (18). Several reports have suggested that COX-2 inhibitors attenuate the growth and metastatic potential of colorectal carcinoma (19,20).

The mechanism of liver metastasis of colorectal carcinoma consists of multiple steps (21). Angiogenesis is known to be essential for the growth of both primary and metastatic tumors: growth beyond 1–2 mm^3 requires an adequate blood supply (22). Angiogenic activity is one of several requirements for metastasis; as neovascularization appears to be necessary for cells to escape from the primary tumor and may also be necessary for growth of a metastatic implant (23), angiogenesis is a crucial factor at the initial and final stages of the metastatic sequence (24–26).

Angiogenesis has been studied using various methods. The microvascularization of liver and lung metastatic tumors of colorectal carcinoma has been studied in rats by a resin corrosion technique and a stereomicroscope (27,28). This technique allows visualization of the three-dimensional microvasculature of metastatic liver tumors, which cannot be observed by cross-sectional techniques.

The aim of our study was to examine the effect of meloxicam, a selective COX-2 inhibitor, on the growth and microvascularization of liver metastatic tumors in rats, using scanning electron microscopy (SEM).

MATERIALS AND METHODS

COX-2 Inhibitor

Meloxicam was suspended in 0.5% methyl cellulose. The dosing volume was kept constant (0.5 ml/rat), and the concentration was adjusted twice weekly based on body weight. Meloxicam has a COX-1 IC_{50} of 3.27 μM and a COX-2 IC_{50} of 0.25 μM; i.e. it is 13.1 times more inhibitory for COX-2 (29).

Animals

A total of 40 male F344/DuCrj rats, 5 weeks old and weighing 100–120 g, were purchased from Japan SLC (Shizuoka, Japan). The rats were housed in polycarbonate cages on wood-chip bedding in an animal room under controlled conditions: a 12 h light/12 h dark cycle, 45 ± 5% humidity and 23 ± 1 C room temperature, with free access to tap water and standard rodent chow (CE-2, Nihon Clea, Tokyo, Japan).

Tumor Cells

We used the highly metastatic rat colon carcinoma cell line RCN-H4 (30). RCN-H4 is a subclone established by Inoue (31) according to Fidler's method; it has a high potency for forming experimental liver metastatic tumors. The RIKEN Cell Bank kindly donated the RCN-H4 line, and the cells were stored at −80 C. Frozen tumor cells were washed in phosphate-buffered saline (PBS) then seeded in 10 cm culture dishes (Falcon, Lincoln Park, NJ, USA) and cultured in 10 ml RPMI 1640 medium (Sigma Chemicals, St Louis, MO, USA) containing 10% fetal bovine serum (FBS; Sigma) and 0.05% penicillin streptomycin solution (Sigma) at 37 C, 0.5% CO_2, for 7 days until they became semiconfluent on the culture dish.

Experimental Procedures

Rats at 6 weeks of age, after 1 week of acclimatization, were divided randomly into four groups of 10. The rats in groups 1–3 were treated with meloxicam by oral gavage at 0.6, 1.0 and 3.0 mg/kg/day, respectively, five times weekly from the day of inoculation of RCN-H4 cells to the end of the experiment for two weeks. The control group received the same volume of vehicle in the same manner. Body weight, water and food consumption were measured weekly during the experiment.

Formation of Metastatic Liver Tumors

Under ether anesthesia, rats underwent laparotomy through a midline abdominal incision and were inoculated intraportally with a tumor suspension containing 5×10^6 RCN-H4 cells in 0.5 ml PBS using a 30-gage needle and a 1 ml syringe. A small fragment of gelatin sponge was applied to the site of inoculation to prevent bleeding and peritoneal dissemination.

Preparation of Vascular Casts

Microvascular casts were prepared according to the method of Murakami (32). All rats were sacrificed under ether anesthesia 2 weeks after the start of the experiment, and, for arterially perfused casts, the abdominal aorta was cannulated in a retrograde manner using an 18-gage catheter; the tip of which was placed just rostral to the renal arteries. A mixture of resin, Mercox (Oken Shoji, Tokyo, Japan) and methyl methacrylate (20 ml) was injected through the catheter until the inferior vena cava was filled with injected resin. Immediately after resin injection, each liver was removed and placed in a water bath at room temperature, and then subjected to corrosion overnight in a 20% solution of KOH. The specimen was then washed in tap water and the number of tumors appearing on the surface of the liver of each rat counted and added up in each group.

Scanning Electron Microscopy

The vascular samples were trimmed into suitable blocks with a hand saw and razor blades under a stereoscope, coated with a thin layer of gold by an evaporation method, and observed under a scanning electron microscope (SEM; S-4500; Hitachi, Tokyo, Japan). The accelerating voltage was 15 kV and the working distance was 15 mm. In addition to identifying each component of the intrahepatic microvasculature, the maximum diameters of tumors were

measured using a scale displayed in the monitor of the scanning electron microscope.

All the metastatic foci which were on the surface of liver were observed using a scanning electron microscope, and the image data of those SEM were input into the personal computer and analyzed. The analysis of the area was performed on a Macintosh computer using the public domain NIH Image program (developed at the US National Institutes of Health and available from the Internet by anonymous FTP from zippy.nimh.nih.gov or on floppy disk from the National Technical Information Service, Springfield, Virginia, part number PB95-500195GEI). The tumor vascular density (TVD) was defined as the ratio of tumor vessel area to whole tumor area.

Scanning Stereomicroscopy

We used the stereomicroscopy (SZX-12; Olympus Optical, Tokyo, Japan) for a diagnosis of liver metastasis. We counted the number of all the metastatic tumors on the surface of the liver by stereomicroscope. We diagnosed a part with the formation of an irregular tumor vessel as metastasis in the part which the sinusoid structure came out of.

Statistical Analysis

All data are expressed as mean ± standard deviation. The Kruskal–Wallis test analyzed the effect of COX-2 inhibitor on the diameter and TVD of metastatic tumors. The Mann–Whitney test was used to compare two groups. $P < 0.05$ was considered to be significant.

RESULTS

Arterially Perfused Casts

In arterial perfusion casts from normal rats, not only the hepatic arteries and sinusoids but also the portal veins were filled with resin. The vascular beds were formed by the network of sinusoids, which were partitioned by the portal canals conducting the portal veins into individual lobules, where they converged to the central vein and, in turn, the hepatic vein (Fig. 1).

Microvasculature of Metastatic Tumors (Control)

Arterially perfused metastatic tumors appeared by SEM as a blank space surrounded by newly developed vessels (Fig. 2). The tumors were almost round and the lesions were surrounded by a normal sinusoidal pattern. The metastatic tumors appeared as a blank space with a network of newly developed vessels. The diameter of the vessels was larger than sinusoidal vessels, but irregular and with narrow parts.

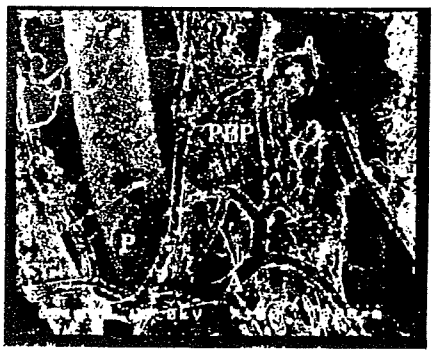

Figure 1. Microphotograph of the vascular cast from a normal rat. P, portal vein; A, hepatic artery; PBP, peribiliary plexus; S, hepatic sinusoid.

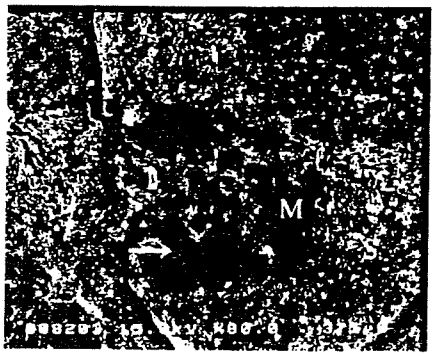

Figure 2. Scanning electron micrograph: a vascular cast of liver metastases in a rat inoculated with RCN-H4 (control). Metastatic tumors appeared as a blank space surrounded by newly developed vessels (white arrow). M, metastatic tumor; S, hepatic sinusoid.

Inhibitory Effect of Meloxicam on Liver Metastasis

Final body weights of rats were 148 ± 11.4, 138 ± 20.8, 135.2 ± 10.6 and 129.2 ± 13.3 g in the control group and groups 1–3, respectively. Slightly reduced final body weights were observed in the groups with Meloxicam but the decrease was not statistically significant ($P = 0.1634$).

The mean number of tumors in each rat was significantly decreased in groups 1–3 (5.6 ± 0.8 standard deviation, SD; 3.6 ± 1.1; and 5.5 ± 1.1, respectively) compared with control (11.2 ± 2.7; $P = 0.0002$, each). The mean diameter of liver metastatic tumors in the control group was 870 ± 276 (ranging from 360 to 1744) μm (Tables 1 and 2).

The number of metastatic tumors in group 1 was approximately half of that of the control group ($P = 0.0002$). The number of tumors was also significantly decreased in groups 2 and 3 compared with the control group. There were no significant differences in number of tumors between the three meloxicam-treated groups.

Meloxicam significantly reduced the diameter of metastatic tumors compared with the control ($P < 0.0001$; Fig. 3). The mean diameter of metastatic tumors in the meloxicam-treated groups was 688 ± 209 (ranging from 316 to 1640) μm. The mean tumor size was 734 ± 254 (ranging

Table 1. The effect of meloxicam on liver metastasis in rats

Group	Tumor diameter (μm)	*P*-value	Tumor vascular density (%)	*P*-value
Control	870 ± 276		32.9 ± 10.5	
Group 1 (0.6 mg/kg meloxicam)	734 ± 254	0.0025	30.2 ± 8.80	0.1107
Group 2 (1.0 mg/kg meloxicam)	685 ± 212	0.0011	20.1 ± 5.30	<0.0001
Group 3 (3.0 mg/kg meloxicam)	644 ± 139	<0.0001	16.6 ± 7.10	<0.0001

P-value was estimated between control and each group.

Table 2. The number of liver metastases in each rat

Group	Number of liver metastases	*P*-value
Control	11.2 ± 2.7	
Group 1	5.6 ± 0.8	0.0002
Group 2	3.6 ± 1.1	0.0002
Group 3	5.5 ± 1.1	0.0002

P-value was estimated between control and each group.

from 316 to 1640) μm in group 1, 685 ± 212 (ranging from 328 to 1149) μm in group 2 and 644 ± 139 (ranging from 422 to 934) μm in group 3. However, the differences in diameters between groups 1 and 2 ($P = 0.6686$) and groups 2 and 3 ($P = 0.2425$) were not significant.

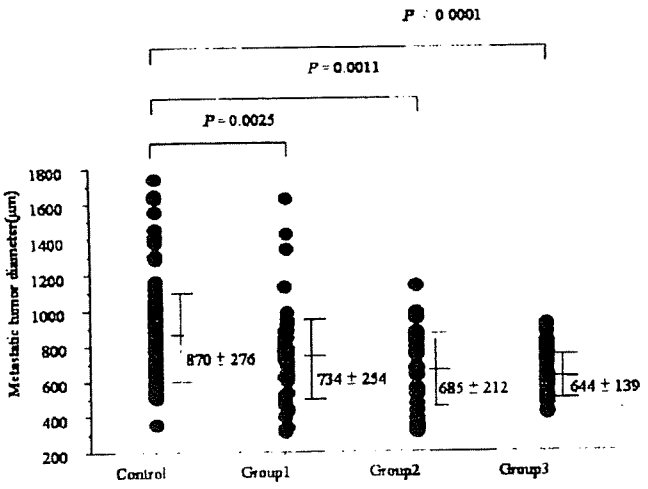

Figure 3. Metastatic tumor diameters. The size of the metastatic tumors decreased in meloxicam-treated groups

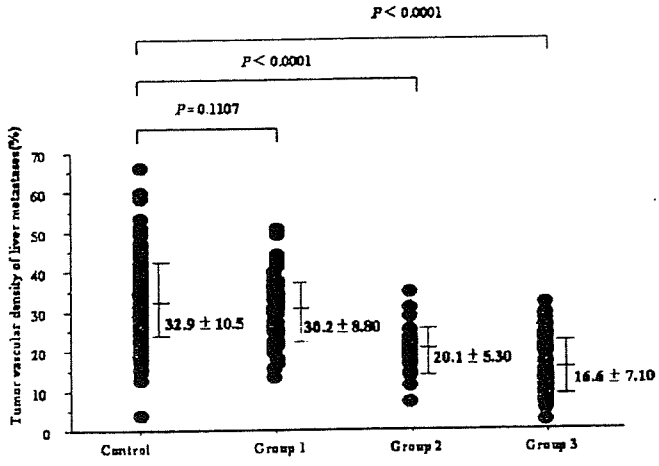

Figure 4. Metastatic tumor TVDs. There was difference in TVD between control group and group 2 or 3. However, there was no difference in TVD between control and group 1. TVD, tumor vascular density.

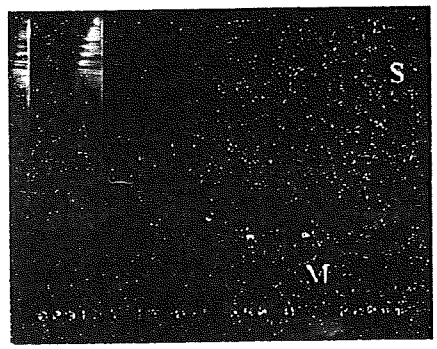

Figure 5. Vascular cast of liver metastases in a rat inoculated with RCN-H4 in group 3 (meloxicam-treated). M, metastatic tumor.

Meloxicam also reduced the TVD of metastatic tumors. The mean TVD of metastatic tumors in the control group was 32.9 ± 10.5% (ranging from 3.9 to 66.3%). The mean TVD of metastatic tumors in groups 1–3 was 30.2 ± 8.80, 20.1 ± 5.30 and 16.6 ± 7.10% (ranging from 12.7 to 51.1%, from 6.4 to 34.3% and from 1.7 to 31.4%, respectively). TVD was significantly decreased in groups 2 and 3 compared with the control ($P < 0.0001$, $P < 0.0001$), while the difference between the control and group 1 ($P = 0.1107$) was not significant (Fig. 4).

The morphologic characteristics of each tumor and tumor vessel in the groups treated with meloxicam were similar (group 3 shown in Fig. 5). Tumor vessels in meloxicam-treated groups were sparse and did not fill the blank space.

DISCUSSION

We have shown that meloxicam inhibits the growth of metastatic liver tumors. The size of the metastatic tumors decreased in the meloxicam-treated groups, as shown by SEM with a resin corrosion technique and there was

difference in TVD between control group and group 2 or 3. The number of metastatic tumors was also smaller in the meloxicam-treated groups.

A great deal of evidence supports the view that COX-2 contributes to tumorigenesis and that its inhibition might be useful in the prevention of intestinal polyposis and colorectal carcinoma (10,33,34). Sheehan et al. detected no COX-2 staining in normal colons, weak staining in normal mucosa adjacent to COX-2 positive tumors and varying degrees of COX-2 staining in tumor cells (35). We have previously reported a positive relationship between COX-2 expression and tumor growth in colorectal adenoma and adenocarcinoma (15,36,37). Specific COX-2 inhibition, either by targeted knockout of the COX-2 gene or by pharmacological intervention, has been shown to effectively decrease the growth of murine intestinal adenomas (33,38,39).

The COX-2 inhibitor celecoxib reduces the incidence and multiplicity of colon tumors in rats by approximately 93 and 97%, respectively (40), while rofecoxib attenuates the growth and metastatic potential of colorectal carcinoma in mice (39,41). As with other COX-2 inhibitors, meloxicam has been shown to inhibit the growth of HCA-7 colorectal tumors in nude mice (42), and the growth of transplantable colon adenocarcinoma in a murine model (43).

Cancer metastasis consists of multiple interdependent processes. To metastasize, tumor cells must invade, embolize, survive in the circulation, settle in distant capillary beds, and extravasate into and multiply in the organ parenchyma (21). Ishida et al. have reported that tumor emboli were seen in the interlobular portal venules, inlet venules and sinusoids within 2 h of AH60C injection (44): we gave the rats meloxicam 4–6 h after the injection of cancer cells. Our results, namely the significantly decreased number of metastatic tumors in meloxicam-treated groups, demonstrate some influence of meloxicam to restrain the process after their entrapment in the capillary beds of metastatic site.

We have also shown that meloxicam decreased the diameter of metastatic tumors. Several previous studies have shown that COX-2 inhibitors interfere with the growth of metastatic tumors (28,45). The mechanisms of action of COX-2 inhibitors have been postulated to include their antiangiogenic effects (18), suppression of matrix metalloproteinase (MMP) production, induction of apoptosis (46,47), inhibition of cellular proliferation and adhesion, and others (19,48). In this study, there was difference in TVD between control group and group 2 or 3. This might indicate that meloxicam restricts the growth of tumors mainly by interfering with the growth of tumor vessels to reduce blood flow.

In order to investigate the angiogenesis of liver metastasis, many studies have used vascular endothelial growth factor, MMP and microvessel density (19,49–51). We previously reported that the neovasculature of metastatic liver and lung tumors in rats can be examined using a resin cast (27,28). Kobayashi et al. evaluated the effect of a COX-2 inhibitor on neovascularization of metastatic lung tumors by using resin casts to measure the diameter of tumor vessels and the three-dimensional architecture of vascularization (28). They suggested that the COX-2 inhibitor reduced the growth rate of the tumors through poor tumor vessel formation. Here, we have introduced a new concept. TVD (the ratio of tumor vessel area to tumor area), which gives an objective evaluation of vascularity in tumors.

In conclusion, we have demonstrated that meloxicam decreases the number, size and TVD of metastatic liver tumors in rats. Its therapeutic potential for liver metastases of colorectal carcinoma should further be investigated.

Acknowledgments

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Conflict of interest statement

None declared.

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特集 Stage IV 大腸癌と診断したらどうするか

Stage IV 大腸癌の治療方針はどう変わったか

Trend of treatment strategy for stage IV colorectal cancer

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大腸癌遠隔転移の診断技術や肝切除・肺切除技術の改善により，最近の20年間でStage IV大腸癌の治療方針が変わってきた．遠隔転移巣が切除可能であれば，原発巣とともに遠隔転移巣も切除することが奨められる．遠隔転移巣が切除不能であっても，原発転移巣は切除したほうが，改善されてきている全身化学療法の治療効果により，予後の改善が期待できる．

はじめに

2006年3月に刊行された大腸癌取扱い規約第7版[1]ではStage IVの定義が変更され，従来の肝転移，肺転移，腹膜播種，それ以外の遠隔転移(骨，脳，副腎，脾など)に加え，領域リンパ節以外のリンパ節転移をも加えている．したがって，大腸脈周囲リンパ節への転移があればStage IVとなる．大腸癌研究会の全国登録のデータからStage IVは大腸癌全体の18.2%であり，肝転移が10.7%，肺転移が1.6%，腹膜播種が5.0%，その他が0.9%であった[2]．

大腸癌が診断された時点ですでに遠隔転移があれば，局所治療である手術治療では治癒が期待できないと以前は判断されており，肉眼的にすべて取りきれたとしても治癒切除として扱われなかった．そのため，大腸癌取扱い規約では初版以来第4版までは相対的非治癒切除として分類されていた．しかし，同時性肝転移や腹膜播種がすべて切除された場合には治癒が得られる症例も出てきたことから，1994年4月に出版された第5版以降は根治度Bとして分類されるようになった．

2005年に大腸癌研究会から出版された「大腸癌治療ガイドライン　医師用2005年版」[2]に記載されているStage IV大腸癌の治療方針では，まず，遠隔転移巣切除が可能か否かで，分類されている(図1)．遠隔転移巣が切除可能であれば原発巣を根治的切除し，遠隔転移巣切除を行う．不可能であれば，原発巣に起因する症状により，原発巣を切除するか否かを決めている．

本特集では遠隔転移臓器別に治療方針が独立して論じられていることから，本稿では各遠隔転移に関し概説するとともに，遠隔転移巣が切除不可能な場合の原発巣切除に関し考察する．

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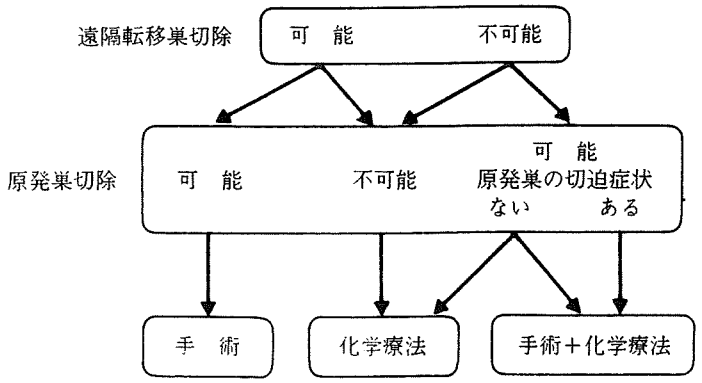

図1 Stage IV の治療方針

I. 遠隔転移の治療方針

1．肝 転 移

1）カスケード理論

血行性転移ではその広がりに関してカスケード理論がある．Weiss ら[3]は結腸癌1,541例の剖検を行い，大腸癌血行性転移の機序を検討した．その結果，「大腸癌の大部分の症例では，まず，肝に血行性転移が成立し，ある程度の大きさになるとそこから肺に転移する．さらに，肺から全身に癌細胞が散布される」にしたがっていると結論した．肝転移がなければ他の血行性転移がない率は85%，また，肝転移症例で肺転移がなく他の血行性転移を有する率は27%であった．したがって，カスケード理論に当てはまらない血行性転移は14%であった．ちなみに，肝転移がなく肺転移を伴う率は4%であり，肝転移がない症例での他の血行性転移臓器は骨髄，副腎，腎であり，肝転移があって肺転移がない症例での他の血行性転移臓器は副腎，脾，骨髄であった．したがって，血行性転移では肝に限局している時期がある．その段階で肝転移巣をすべて切除できれば根治が可能となる．

2）肝切除の適応

大腸癌肝転移に対する肝切除の適応は，肝画像診断や肝切除手技，周術期管理の進歩とともに変化してきた．1980年以前は単発例のみが手術の対象であったが，1980年代には転移個数が3個以下が切除の適応となっていた[4]．1990年代に入り，積極的に肝切除を行っている施設からの多数例の分析で，4個以上であっても長期生存を得る症例が少なからずあることが報告されるようになった．また，1986年に3個までが切除適応であると報告したIwatuki ら[5]は8年後に新たに分析し，4個以上でも長期生存例があり，切除の対象となる症例があると結論している．

3）同時性肝転移の予後は悪い

Stage IV である同時性肝転移は，異時性肝転移と比べ予後は不良である[6]．大腸癌研究会での同時肝転移446症例のアンケート調査では，肝切除が36.3%に，肝動注が23.8%に，全身化学療法が24.7%に行われ，無治療は12.6%であった[7]．当科では1990年から2004年までに同時性肝転移129例を経験し，同時性が異時性に比べ有意に予後不良であった（5年生存率は同時性40.7%，異時性18.0%）．その原因の一つには肝切除率が低いことがあげられ，同時性肝転移の肝切除率は24.8%で(異時性では60%)であった．しかし切除例の5年生存率には差がなく，同時性50.5%，異時性51.5%であった．

4）同時切除か異時切除か

同時性肝転移で肝切除が適応になった場合，原発巣との同時切除か異時切除かが問題になる．1980年代後半から1990年代半ばまでは，同時切除では侵襲が大きくなることによる合併症の増加が懸念されていた．しかし，同時切除でも合併症は増加しないとの報告が相次いだ[8)-10)]．これとは

別に，腫瘍学的問題として，転移巣が2 cm 以下の小さな場合，2～3ヵ月観察期間をおいてから再度肝切除の適応を検討したほうが良いとの意見がある[11]．肝画像診断の質的問題から，小さな転移巣がある場合，画像に描出されないより小さな転移巣が潜んでいる可能性がある．それらを顕在化させるために，一定期間観察して，適応を再検討するとの考えである．どちらの考えにも利点と欠点があり，症例ごとに判断すべきと考える．

5）ネオアジュバント

大腸癌に対する化学療法の進歩が著しく，奏効率や生存期間が有意に改善してきている．その効果的な化学療法を切除不能大腸癌肝転移に用いて転移巣を縮小させて切除可能にし，予後を改善することが試みられている[12)-14)]．確かに最近の大腸癌化学療法の進歩には目を見張るものがあり，大腸癌肝転移に対するネオアジュバントとして用いられる可能性がある．ただ，ここで問題なのは肝切除不能の判断である．欧米での肝切除手技はmajor hepatectomy であるため，転移巣が両葉存在する場合は切除の対象にならないことが多い．また，大腸癌治癒切除後のフォローアップでは画像診断が定期的に行われていないため，肝転移が進行した状態で発見されることが多い．肝転移の切除率は，フランスでは同時性肝転移で6.3%，異時性肝転移で16.9%と報告されている[15]．同時性と異時性を合わせての切除率は，米国では12%，ドイツでは24%であった[16)17)]．

一方，本邦では肝部分切除が中心であるため，両葉に転移があっても切除が可能である．大腸癌研究会のデータでは同時性肝転移の肝切除率は36.3%であり[7]，異時性の切除率は46.1%であった[18]．これからただちに本邦ではネオアジュバントの意味がないとは考えない．肝切除できたとしても同時性肝転移，Grade B ないしは H2 では再発率が高いことから，術前に微小転移を抑えたり，また，ダウンステージにより安全で癌を露出させない手術をめざしてのネオアジュバントには意味があると思う．

2．肺 転 移

肺転移に関しては，大腸癌取扱い規約第7版[1]や大腸癌治療ガイドライン[2]に分類や治療方針が記載されているが，肝転移ほど明確にはなっていない．切除ができれば30%～60%の5年生存が報告されている．しかし，いずれも単一施設からの少ない症例数の報告であり，また，手術適応にもコンセンサスが得られていない．多施設共同研究により，staging を定め，手術適応や治療効果を明らかにする必要がある．

3．腹膜播種

欧米の一部では，大腸癌腹膜播種に対して積極的な治療を行う考えがある．これは腹膜切除(peritonectomy)と温熱化学療法を組み合わせた方法であり[19]，2007年3月に開催された米国の第60回 Cancer Symposium of the Society of Surgical Oncology でも2時間の発表と討論が組まれていた．しかし，この治療法の対象は主に虫垂偽粘液腫による腹膜播種である．この疾患は本邦には少なく，通常の大腸癌の腹膜播種がこの治療法の対象になることはまれと考える．本邦では，腹膜播種に関する多数例の報告はないが，大腸癌取扱い規約(第7版)[1]では腹膜播種があっても肉眼的に取りきれればR0で，根治度Bである．大腸癌治療ガイドライン[2]では，「P_1 の場合は完全切除が望ましい」「P_2 で容易に切除可能なものは完全切除を考慮する」と記載されている．望月[20]は，腹膜播種が取りきれれば予後は切除しない場合より良好であり，P_1 の5年生存率は30%と報告している．

4．遠隔リンパ節転移

大腸癌取扱い規約(第7版)[1]では，それまで N_4 として扱われていた大動脈周囲リンパ節が，遠隔リンパ節(M)として分類された．これまでは郭清範囲の対象であった大動脈周囲リンパ節に関する研究は少ない．第44回大腸癌研究会で行われたアンケート調査[21]では，84施設のうち75%の施設で適応を決めて予防的大腸脈周囲郭清を行ってい

た．53施設からの症例では大動脈周囲リンパ節陽性率はS状結腸癌で2.1%，直腸癌で1.9%であった．大動脈周囲リンパ節陽性例では肝転移(31%)や腹膜播種(21%)の頻度が高く，57%が根治度Cであった．アンケート調査のため，大動脈周囲リンパ節郭清の効果は明らかではないが，転移頻度と根治性から見て，少なくとも予防的大動脈周囲リンパ節郭清の意義はほとんどないと思われる．

II. 遠隔転移巣が切除不可能の場合，原発巣を切除するか

遠隔転移巣が切除不能である場合，原発巣による症状(腸閉塞，出血・貧血)があれば原発巣の切除が奨められる．しかし，癌が広範転移しているに直腸癌では，原発巣切除の侵襲が大きいと判断した場合は人工肛門造設を選択することが多い．

切除不能な遠隔転移を伴うStage IV大腸癌の治療では，原発巣を切除したほうが予後の改善が期待できるが，切除の頻度は右側結腸癌では高く，直腸癌では低いと報告されている．Cookら[22]は，Stage IV大腸癌26,754例のうち原発巣切除は66%に行われ，切除率は右側結腸癌と左側結腸癌でそれぞれ75.3%，73.0%であったが，直腸癌では45.6%であり，原発巣切除例と非切除例での50%生存期間はそれぞれ結腸では11ヵ月と2ヵ月，直腸癌では16ヵ月と6ヵ月と報告している．Templeら[23]はSEERのデータを用いて65歳以上のStage IV大腸癌9,011例を検討した．原発巣切除率は72%で，遠隔転移巣も切除された症例は3.9%であり，直腸癌では切除＋吻合されたのは31%で，切除+人工肛門造設が69%であった．診断から原発巣切除まで4ヵ月以内の症例では，非切除例ないしは4ヵ月以上たって切除された症例に比べ明らかに生存期間が長かった．これらの報告では，手術が行える症例選択にバイアスがかかっているので，原発巣切除例と非切除例の生存期間を比較することには意味がないが，切除が行われれば12ヵ月以上の生存が期待できることを示している．また，これらの報告の症例集積期間ではまだFOLFOXやFOLFIRI，分子標的薬が使われていない時代であったことから，現在ではより長期間の生存が期待できる．Ruoら[24]はStage IV大腸癌422症例のうち，無症状で原発巣切除を受けた127例と非切除例103例を比較検討した．切除例の術後30日以内の死亡率は1.6%，合併症率は20.5%であった．切除例には，右側結腸癌が多く，遠隔転移臓器数が少なく(1ないし2臓器)，肝転移例では癌の肝占拠率が小さく，また，50%生存期間は16ヵ月(非切除例では9ヵ月)であった．この結果から，遠隔転移切除不能Stage IV大腸癌症例が無症状であっても，全身への転移が広範ではなく，肝転移が高度でなければ，原発巣切除を推奨している．

一方，切除不能遠隔転移を伴ったStage IV大腸癌で，原発巣は切除可能であるが症状がないためまず全身化学療法を行って経過を見た報告がある[25]．24例のうち，経過中に大腸閉塞が合併した症例が4例あり，2例には切除を行い，2例にはステントを留置した．また，3例では腹痛のため切除が行われた．肝転移が縮小した1例には根治的手術がなされた．24例の50%生存期間は10.3ヵ月であった．

以上の研究結果からは，切除不能遠隔転移を伴うStage IV大腸癌では，無症状であっても，肝転移が広範でなければ原発巣を切除し，残存病巣には最近成績の向上した全身化学療法に期待することが推奨される．

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Multicenter Phase II Study of Irinotecan Plus Bolus Fluorouracil/*l*-Leucovorin for Metastasic Colorectal Cancer

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Multicenter Phase II Study of Irinotecan Plus Bolus Fluorouracil/*l*-Leucovorin for Metastasic Colorectal Cancer

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Abstract. *Treatment of metastatic colorectal cancer remains inadequate. Patients and Methods: In a multicentre Phase II study, irinotecan (100 mg/m^2), 5-fluorouracil (5-FU) (500 mg/m^2), and l-leucovorin (l-LV) (250 mg/m^2) were administered on days 1, 8, and 15 of a five-week cycle. Forty-five patients were enrolled. Results: The objective response rate was 26.7%. The median survival time was 21.8 months and the one-year survival rate was 73.3%. The median number of cycles was 4.0, with a median relative dose intensity of 83.3% for both irinotecan and 5-FU. Grade 3 or 4 haematological toxicities were anaemia in four patients, leukopaenia in six patients, and neutropaenia in 15 patients, while non-haematological toxicities were diarrhoea in three patients, and nausea, vomiting, anorexia and increased transaminases in two patients each. No treatment-related deaths occurred. Conclusion: Irinotecan plus 5-FU/l-LV can be used to treat metastatic colorectal cancer on an outpatient basis.*

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In Japan, approximately 40, 000 people die of colorectal cancer annually and mortality due to this cancer is still rising. In 2004, colorectal cancer became the chief cause of death from malignancy among Japanese women (1).

Combinations of 5-fluorouracil (5-FU) as the base drug with irinotecan or oxaliplatin (FOLFIRI or FOLFOX) have been the standard chemotherapy regimens for colorectal cancer.

Irinotecan is an anticancer agent that inhibits topoisomerase I (2), and it has come into widespread use combined with 5-FU+leucovorin (5FU/LV) for metastatic colorectal cancer since an additive effect of this combination was demonstrated in patients with colorectal cancer (3, 4).

In Japan, continuous infusion of 5-FU/LV was approved in February 2005 and oxaliplatin was approved in April 2005. The previously approved 5-FU/LV regimen was once-weekly administration of a combination of "bolus 5-FU + high dose LV" (RPMI regimen), while irinotecan was approved for use at a dose of 100 mg/m^2 once weekly or 150 mg/m^2 every two weeks. Accordingly, the regimens of combined therapy with irinotecan plus 5-FU/LV established by Douillard *et al.* (3) and Saltz *et al.* (4) were outside the coverage of the Japanese national health insurance scheme. It was therefore necessary to establish a Japanese version of combined therapy with irinotecan plus 5-FU/LV.

A phase I clinical study was started in May 2000 with a fixed dosage of 5-FU/*l*-LV (RPMI regimen) (500/250 mg/m^2)

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Table I. *Criteria for dose reduction or discontinuation.*

Criteria (toxicity in the previous course)	Irinotecan and 5-FU
- Grade 3/4 leucopaenia, neutropaenia, thrombocytopaenia - Grade 3/4 non-haematologic toxicity (excluding nausea, vomiting, anorexia and alopecia) - Increase of PS to 2 - Administration ommitted twice in succession during the previous course	Dose reduction by 1 level
- Grade 3-4 increase of ALT/AST - Increase of PS to 3 or more	Discontinuation
- When toxicity meeting the dose reduction criteria occurred again after an initial dose reduction	- Reduction of both drugs again by 1 level or discontinuation when dose reduction was not possible

PS: Performance status (Eastern Cooperative Oncology Group).

and escalating doses of irinotecan. According to a modified version of the schedule devised by Saltz *et al.* (4), irinotecan plus 5-FU/*l*-LV were administered on days 1, 8, and 15 of a five-week cycle. The dose of irinotecan was increased from level 1 (50 mg/m^2) to level 6 (100 mg/m^2) in 10 mg/m^2 increments. With the exception of one patient in whom grade 4 diarrhoea occurred at dose level 1, no dose-limiting toxicity (DLT) was detected and the maximum tolerated dose (MTD) was not reached, even at level 6. For the phase II study, the recommended dose of irinotecan was set at 100 mg/m^2. The relative dose intensity of irinotecan and 5-FU/*l*-LV was 90% or more regardless of the dose level or cycle number, suggesting that this regimen was safe (5).

Against this background, an open-label, multicenter phase II clinical study (OGSG0201) was conducted to evaluate the efficacy and safety of irinotecan + 5-FU/*l*-LV (weekly IFL regimen) for metastatic colorectal cancer. Since marked individual differences of the adverse reactions to irinotecan are known to occur (6, 7), dose reduction criteria were established with two lower dose levels (75 mg/m^2 and 50 mg/m^2) of this drug in consideration of safety. The minimum dose of irinotecan was set at 50 mg/m^2 because some subjects responded at this dose level in the phase I study.

Patients and Methods

Patient eligibility. Patients with metastatic colorectal cancer were eligible for enrollment in the study. Other eligibility criteria were as follows: histologically or cytologically confirmed advanced colorectal cancer or postoperative recurrent cancer with metastasis to other organs (liver, lung, lymph nodes, *etc.*); at least one measurable lesion (at least twice the slice thickness and with a maximum diameter ≥20 mm on CT or ≥10 mm on spiral CT); no prior chemotherapy (patients receiving postoperative chemotherapy with oral fluorinated pyrimidines or 5-FU/LV were acceptable if recurrence occurred at least 26 weeks after the completion of such therapy); no prior radiotherapy (except to a region other than the target lesion of the present study); age between 20 and 75 years; an Eastern Cooperative Oncology Group performance status of 0-1; a life expectancy ≥13 weeks from the start of treatment; acceptable major organ function (white blood cell count between 4,000/mm^3 and 12,000/mm^3, neutrophil count ≥2,000/mm^3, platelet count ≥100,000/mm^3, haemoglobin ≥8.0 g/dL, serum AST/ALT <2.5 times the institutional upper limit of normal (ULN), serum total bilirubin <1.5 times the ULN, serum creatinine ≤ULN and normal electrocardiogram) and written informed consent provided by the patient.

Chemotherapy schedule. On days 1, 8, and 15, irinotecan (100 mg/m^2) was administered as a 90-minute intravenous infusion, followed by l-LV (250 mg/m^2) as a 2-hour infusion. After one hour of *l*-LV infusion, 5-FU (500 mg/m^2) was given as an intravenous bolus. Treatment was repeated every five weeks until unacceptable toxicity occurred, consent was withdrawn, or disease progression was noted. Patients then received second-line therapy based on the preference of their attending physician.

Treatment criteria. Prior (on the same day or previous day) to receiving treatment on days 8 and 15, each patient was screened to ensure that the white blood cell count was ≥3,000/mm^3; the neutrophil count was ≥1,500/mm^3; the platelet count was ≥100,000/mm^3; the temperature was <38°C with no detectable infection and that no diarrhoea or other toxicities >grade 2 (except nausea, vomiting, alopecia, anorexia, or malaise), as assessed according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2 (8) were apparent. The scheduled dose was not administered when any of the criteria described above were not fulfilled. Even if a dose was omitted, the subsequent cycle was started as scheduled on day 36. Similar checks were made before the second or subsequent cycles to ensure that the above criteria and the serum creatinine level of ≤1.5 mg/dL were fulfilled. If any of these criteria were not met, treatment was suspended until the patient recovered. However, if the administration criteria were not fulfilled until five weeks or more had elapsed since the last day (day 1, 8, or 15) of the preceding cycle, the patient was removed from the study.

Dose modification criteria. Patients were checked for toxicity during each cycle and the doses of irinotecan and 5-FU were reduced according to the dose modification criteria (Table I) and dose reduction schedule (Table II). When a patient experienced similar

Table II. *Dose modification.*

	Irinoteçan	5-FU	*l*-LV
Starting dose	100 mg/m^2	500 mg/m^2	
Level 1	75 mg/m^2	400 mg/m^2	250 mg/m^2
Level 2	50 mg/m^2	300 mg/m^2	

Table III. *Clinical characteristics of the patients.*

No. of patients	45	Tumour	
Gender			
Male	27	Primary	31
Female	18	Recurrent	14
Median age (range)			
	64 yr	Histology	
	(40-75)	Adenocarcinoma	42
PS			
0	24	Mucinous	3
1	21	Sites of metastasis:	
		Lymph nodes	7
Prior treatment			
None	8	Liver	26
Surgery	33	Lungs	14
Surgery + Adjuvant	4	Others	7
		T-Bil value at registration	
		1≤	2
		1>	43

PS: Performance status (Eastern Cooperative Oncology Group). T-Bil: total bilirubin.

toxicity again after dose reduction, the doses of both irinotecan and 5-FU were reduced once more. When a patient experienced toxicity again after a second dose reduction that patient was withdrawn from the study. After dose reduction, the dose was not increased again.

Endpoints and evaluation criteria. The antitumor effect of therapy (response rate) was selected as the primary endpoint and was evaluated by extramural review according to the response evaluation criteria in solid tumors (RECIST) (9). The secondary endpoints consisted of safety (incidence and grade of adverse events), overall survival and relative dose intensity. For grading of adverse events, NCI-CTC version 2.0 (8) was used. The relative dose intensity was calculated for each drug and cycle using the following equation:
Relative dose intensity (%) = (actual dosage/planned dosage) x (35/actual no. of days per cycle) x100. Overall survival was calculated by the Kaplan-Meier method (10).

Sample size. In other Japanese studies, irinotecan monotherapy achieved a response rate of 27% in patients with advanced/recurrent colorectal cancer (including those with prior chemotherapy) (11), while 5-FU/*l*-LV has achieved response rates of 28% and 32% in patients receiving initial chemotherapy (12, 13).

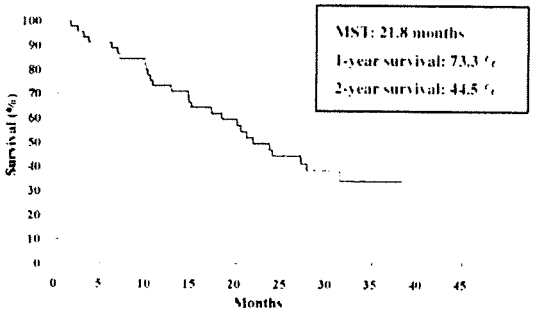

Figure 1. *Overall survival. MST: median survival time.*

Saltz *et al.* (4) reported that the response rate to irinotecan plus 5-FU/*l*-LV (IFL regimen) as first-line chemotherapy was 39%, while the response rates for 5-FU/*l*-LV or irinotecan alone were 21% and 18%, respectively. Accordingly, 40% was taken as the expected response rate and ±15% as the 95% confidence interval, so the required number of patients was estimated to be 41. Therefore, the target number of patients was set at 45 to allow for some exclusions from analysis.

Results

Patient characteristics. Between July 2002 and October 2003, 45 patients with metastatic colorectal cancer were enrolled at 11 institutions and all of them were eligible for analysis. Thirty-one patients had initial tumours and 14 had a recurrence. Twenty-seven patients were men and 18 were women. The median age was 64 years (range: 40-75 years). Twenty-four patients had an initial performance status of 0 and the remaining 21 had a performance status of 1. Among the 45 patients, 8, 33, and 4 had received no prior therapy, surgery alone, or a combination of surgery and adjuvant chemotherapy, respectively. The histological diagnosis was adenocarcinoma in 42 patients and mucinous carcinoma in 3 patients. The sites of metastasis were the liver in 26 patients, the lungs in 14 patients, lymph nodes in 7 patients, and other organs in 7 patients. The patients' clinical characteristics are shown in Table III.

Tumor response and survival. The objective response rate was 26.7% (96% CI: 14.6%-41.9%). There was a complete response (CR) in one patient, partial response (PR) in 11 patients, stable disease (SD) in 28 patients, and progressive disease (PD) in five patients (according to RECIST) (9). The tumour stabilization rate (including SD) was 88.9%. The median survival time (MST) was 21.8 months and the median follow-up time was 20.5 months (range: 1.6-38.3 months). Furthermore, the 1-year survival rate was 73.3% and the 2-year survival rate was 44.5% (Figure 1).

Table IV. *Haematological toxicity.*

	Grade				≥ Grade 3	Total
	1	2	3	4		
Anaemia	21	12	2	2	4 (8.9%)	37 (82.2%)
Leucopaenia	15	13	5	1	6 (13.3%)	34 (75.6%)
Neutropaenia	3	13	12	3	15 (33.3%)	31 (68.9%)
Thrombocytopaenia	4	0	0	0	0 (0%)	4 (8.9%)

Toxicity. A high incidence of haematological toxicity occurred, as shown in Table IV, but the therapy was regarded as tolerable and all of the toxicities were controllable. The main non-haematological toxicities were diarrhoea in 14 patients (31.1%), nausea in 19 patients (42.2%), vomiting in 17 patients (37.8%), anorexia in 17 patients (37.8%), alopecia in 23 patients (51.1%), fatigue in 13 patients (28.9%), increased total bilirubin in six patients (13.3%), and increased AST/ALT in five patients (11.1%). The main non-haematological toxicities of grades 3-4 were diarrhoea in three patients (6.7%), nausea in two patients (4.4%), vomiting in two patients (4.4%), anorexia in two patients (4.4%), and increased AST/ALT in 2 patients (4.4%). None of these toxicities became serious and all were controllable (Table V). Furthermore, no treatment-related deaths occurred within 60 days of starting this therapy.

Relative dose intensity. The median number of cycles completed was 4.0 (range: 1-11), with a mean of 4.3. The median relative dose intensity was 83.3% (range: 33.3%-100%) for both irinotecan and 5-FU, while the mean relative dose intensity was 81.1% for irinotecan and 82.5% for 5-FU. The median relative dose intensity for each cycle ranged from 43.8% to 97.2% and the mean relative dose intensity for each cycle was 43.8% to 85.8% (Table VI).

Discussion

The chemotherapy regimen used in the present study, unlike the IFL regimen of Saltz *et al.* (4), was based on the RPMI regimen (bolus 5-FU + high dose LV) in combination with irinotecan given weekly.

Although the objective response rate was not very high (26.7%), the tumour stabilization rate was 88.9%, while the MST was 21.8 months and the 1-year survival rate was 73.3%. These results were superior to other published data (4, 14, 15) and were similar to the results (MST of 20.3 months and 1-year survival rate of 74.3%) obtained by addition of bevacizumab to IFL, as reported by Hurwitz *et al.* (16). Goto *et al.* also conducted phase I and II studies using the modified IFL regimen of Saltz *et al.* (17), which was CPT-11 (100 mg/m^2), *l*-LV (10 mg/m^2), and 5-FU (500 mg/m^2) on days 1 and 8 with the duration of one cycle being set at 21 days. They reported an overall response rate of 58% (11/19), while the relative dose intensity of CPT-11 and 5-FU was about 90%. Although the response rate was higher than in the present study, the incidence of grade 3-4 adverse reactions was also higher

Table V. *Non-haematological toxicity.*

	Grade				≥ Grade 3	Total
	1	2	3	4		
Diarrhoea	4	7	2	1	3 (6.7%)	14 (31.1%)
Abdominal pain	3	0	0	0	0 (0%)	3 (6.7%)
Nausea	10	7	2	-	2 (4.4%)	19 (42.2%)
Vomiting	10	5	2	0	2 (4.4%)	17 (37.8%)
Anorexia	9	6	2	0	2 (4.4%)	17 (37.8%)
Constipation	3	0	0	0	0 (0%)	3 (7.7%)
Alopecia	15	8	-	-	-	23 (51.1%)
Fatigue	11	2	0	0	0 (0%)	13 (28.9%)
Stomatitis	2	0	0	0	0 (0%)	2 (4.4%)
Back pain	1	0	0	0	0 (0%)	1 (2.2%)
Numbness	1	0	0	0	0 (0%)	1 (2.2%)
Pigmentation	1	1	0	0	0 (0%)	2 (4.4%)
↑ T-Bil	4	2	0	0	0 (0%)	6 (13.3%)
↑ AST/ALT	3	0	1	1	2 (4.4%)	5 (11.1%)
↑ ALP	2	0	0	1	1 (2.2%)	3 (8.9%)

Table VI. *Relative dose intensity.*

	Irinotecan		5-FU	
	Median	Mean	Median	Mean
1st cycle (n=45)	97.2%	85.8%	97.2%	85.1%
2nd cycle (n=42)	83.3%	81.9%	83.3%	83.7%
3rd cycle (n=33)	83.3%	82.3%	84.8%	84.7%
4th cycle (n=23)	78.6%	82.2%	83.3%	84.5%
5th cycle (n=15)	74.5%	79.9%	80.0%	80.6%
6th cycle (n=13)	78.6%	78.2%	83.3%	79.8%
7th cycle (n=9)	71.4%	70.0%	83.3%	74.2%
8th cycle (n=8)	71.4%	70.6%	71.4%	73.6%
9th cycle (n=3)	83.3%	77.8%	83.3%	77.8%
10th cycle (n=2)	69.4%	69.4%	69.4%	69.4%
11th cycle (n=1)	43.8%	43.8%	43.8%	43.8%
Total	83.3%	81.1%	83.3%	82.5%

No. of cycles
Median 4.0 cycles
Mean 4.3 cycles
Range 1-11

Relative dose intensity (%) = (actual dose / planned dose) x (35 / actual days of cycle) x100.

(leucopenia in 47%, neutropenia in 56%, decreased hemoglobin in 81%, fatigue in 60%, anorexia in 32%, nausea in 29%, and diarrhoea in 24%), indicating that their regimen caused more severe toxicity than ours (17).

In the present study, unlike other reports, all of the haematological and non-haematological toxicities (including gastrointestinal toxicities) were controllable. During two phase III clinical trials (N9741 and C89803) conducted in the United States, the IFL group showed more than twice the mortality of the control group within 60 days (18), so an analysis of early deaths was conducted. As a result, reduction of the dose to 100 mg/m^2 for irinotecan and 400 mg/m^2 for 5-FU was recommended for the first cycle only. Eventually, the Oncologic Drugs Advisory Committee demonstrated that careful patient selection is needed for the safe administration of IFL (19, 20).

Since the toxicity of irinotecan is known to show marked individual variations (6, 7), two dose reduction levels were established for the present study. As a result, the median relative dose intensity of both irinotecan and 5-FU was 83.3% and the mean relative dose intensity was more than 80%. This suggests that appropriate postponement of therapy and dose reduction could alleviate serious toxicity and improve the delivery of this therapy at general hospitals in Japan.

The recent package insert for irinotecan states that the dosage should be reduced in *UGT1A1*28* homozygous individuals. In addition, the NCCN Guideline 2006 (version 2) states that irinotecan should not be used in patients with a high total bilirubin level (20, 21). In the present study, total bilirubin was elevated in two patients, but the remaining patients had levels in the normal range. Although the initial dose of irinotecan was lower with the present regimen than with the IFL regimen of Saltz *et al.* (4), the relative dose intensity was similar for the two regimens and no serious adverse events occurred in our study. This was considered to be partly attributable to the low percentage of patients with high total bilirubin levels. In addition, infusion of 5-FU over three min or less and the criteria for postponing treatment with this regimen are considered to be other factors contributing to the lack of serious adverse reactions.

Idelevich *et al.* conducted a multicenter phase II study of 138 patients treated with IFL and reported that toxicity was manageable and the dose intensity was appropriate, suggesting that the regimen may be a good option as first-line treatment for metastatic colorectal cancer (15).

The main problem with our weekly regimen is the duration of administration. Although this therapy can be given on an outpatient basis, four hours are required for treatment (including premedication), because a 90-minute infusion of irinotecan is followed by a 120-minute infusion of *l*-LV. This problem might be solved by simultaneous administration of irinotean and *l*-LV which would reduce the time required to about two hours.

In recent years, FOLFIRI and FOLFOX have been widely used as first- and second-line treatments for metastatic colorectal cancer. On the other hand, concomitant administration of bevacizumab is recommended in the NCCN Guideline 2006 (version 2) (20, 21). However, bevacizumab and cetuximab have not been approved for use in Japan and most chemotherapy for colorectal cancer is delivered at general hospitals, rather than specialist hospitals. Among the 45 patients in the present study, 43 were enrolled by general surgeons rather than by oncologists. In consideration of this situation, it is necessary to develop a simple and effective regimen for colorectal cancer treatment (*e.g.*, concomitant use of an oral drug or the RPMI regimen).

Our weekly regimen is easy to administer on an outpatient basis and does not require a central venous catheter.

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臨床

大腸癌同時性肝転移に対する治療戦略

Strategy of synchronous liver metastasis from colorectal cancer

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大腸癌肝転移は，肝切除が可能なら積極的な切除で延命が期待できる．しかし同時性肝転移では異時性肝転移と異なり，肝切除時に微小肝転移が存在する可能性が高く，肝切除後の残肝再発や肝外再発の予防が，さらなる予後向上のためには重要である．肝切除後の予防的肝動注療法(5-FUの総投与量15ｇ以上)は残肝再発予防効果を認め，肝切除後に肝動注療法と全身化学療法を併用した治療の実施は，同時性肝転移の治療戦略として重要である．

はじめに

大腸癌肝転移に対する治療戦略は，大腸癌治療ガイドライン[1]にもあるように，肝切除可能であれば肝切除を，切除不能であれば化学療法を選択することになる．肝転移は同時性，異時性にかかわらず，転移個数と転移部位や大きさで治療方針が決定される．しかし同時性と異時性では肝転移の発見状況が異なる．つまり，異時性肝転移では経過観察中に発見されることがほとんどであり，肝転移発見までに経過観察期間があり，たとえば単発の肝転移と診断した場合は単発である可能性が高い．しかし，同時性肝転移では経過観察期間がないため，単発の肝転移と診断しても単発でない場合がある可能性があると思われる．肝転移の存在診断も1 cmを超えないと転移としては同定できないことを考慮すると，画像診断では発見できない微小肝転移の存在をとくに同時性肝転移では念頭においた治療手段を選択することがより臨床に即した治療法の選択であると考える．

本稿では，大腸癌同時性肝転移の治療戦略について，肝転移に対する治療効果から検討する．

I. 同時性肝転移と異時性肝転移の肝転移切除後再発形式の相違

大腸癌肝転移に対する治療方針は，肝切除が可能なら肝切除を行うことで延命効果が得られるため，一般的なコンセンサスが得られている[1]．しかし，肝切除後の残肝再発および肝外再発は高頻度に出現し，肝転移切除後の再発を予防することは，さらなる予後向上のためには重要である．大腸癌肝転移であっても，同時性肝転移と異時性肝転移では，肝転移の発見状態が異なり，とくに同時性肝転移では画像上発見できない微小肝転移の存在について念頭に置く必要があると思われる．

図1は大腸癌肝転移肝切除例を，同時性と異時性に分けてその予後を比較したものであるが，肝切除術後の5年生存率は，同時性(N＝116)で

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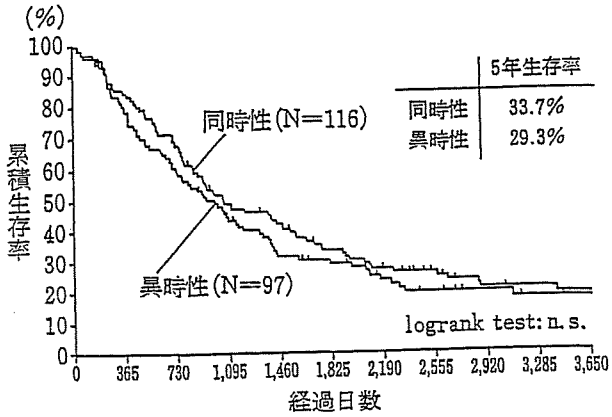


図1 肝切除後の予後の比較

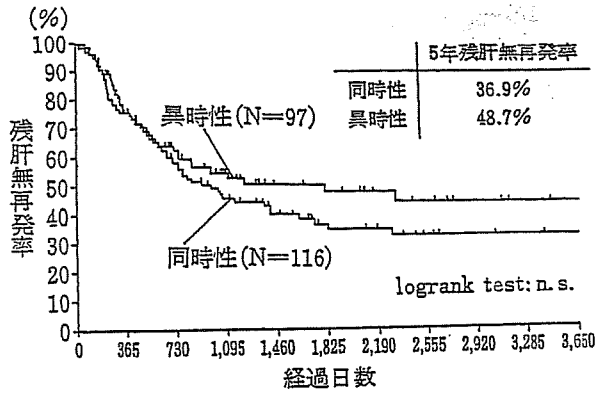


図2 肝切除後残肝無再発率の比較

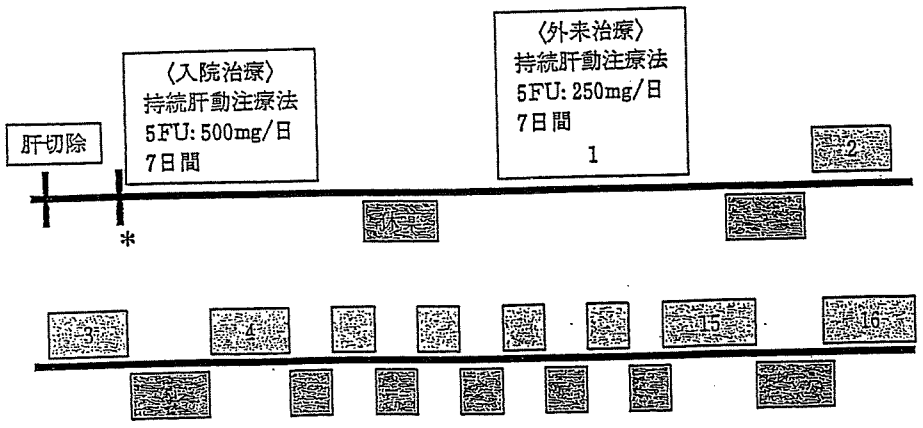
33.7%，異時性(N＝97)で，29.3%で有意差はなかった．一方，肝切除後の残肝無再発曲線を図2に示すが，5年残肝無再発率は，同時性(N＝116)で36.9%，異時性(N＝97)で48.7%で，有意差はなかったが，同時性肝転移で残肝再発がやや高い傾向を認めた．

われわれは，図3に示すように，残肝再発予防を目的として肝切除後の予防的肝動注療法を施行し，その有用性を報告した[2]．5-FU の7日間持続投与による肝動注療法を基本にして実施した．5-FU の投与期間と総投与量が残肝再発予防に寄与すると考え，5-FU の総投与量別に表1のように3群に分類した．すなわちA群：15 g 以上投与群，B群：15 g 未満投与群，C群：肝動注非施行群に分類し，図4は同時性肝転移を5-FU の投与量別に残肝無再発率を比較したものである．

表1 5-FU 総投与量別分類

A群	15 g 以上投与
B群	15 g 未満投与
C群	肝動注非施行

5年残肝無再発率は，同時性肝転移でA群：62.2%，B群：10.0%，C群：15.6%で，肝動注療法が不十分であったB群は，肝動注療法を行わなかったC群と同様の治療成績で，肝動注療法を一定の投与量以上施行した症例(5-FU の総投与



*血中トランスアミナーゼ値が正常値の3倍以下

図3 肝切除後の予防的持続肝動注療法