tumor periphery to the intermediate region when vascular density was lower in the intermediate region compared with the periphery. To explain this paradox, we posited that insufficient blood supply in the intermediate region might stimulate production of the angiogenic factors in question, given that *VEGF* is a putative hypoxia-inducible gene.[37] The relatively hypoxic environment in the intermediate portion as compared with the periphery was verified by RT-PCR analysis of another hypoxia-inducible gene, *GLUT1*[38] (glucose transporter gene-1) (Ogawa M et al., unpublished data, 2003). In support of this hypothesis, there is evidence that hypoxia can induce *ANG2* expression in vascular ECs and glioma cells.[21,39–41]

Another possible link between Ang-2 and tumor-associated angiogenesis could be inferred from the histopathologic features of the tumor vessels observed. Tumor vessels appeared to be immature, with tortuous morphology and a relatively small luminal size, significantly different from the ordinary straight vessels in normal liver tissue. Other studies also suggested that Ang-2 may be associated with vessel immaturity. The characteristically small luminal size of tumor vessels was reported in *ANG2* transgenic mice and in Ang-2-dependent corneal neovascularization in mice.[10,13] It is noteworthy that PESCs were not sufficiently recruited to surround ECs in these Ang-2-associated *in vivo* models. In addition, it was demonstrated that overexpression of the *ANG2* gene produced a lower degree of vessel maturation in *in vivo* experiments involving gastric cancer cells.[16] We consistently found that insufficient recruitment of PESCs around ECs became more evident going from normal liver tissue to the tumor periphery, and also going from the periphery to the intermediate portion of the tumor, and that expression of Ang-2, but not Ang-1, increased accordingly with increasing proximity to the center of the tumor (Figs. 6, 10D). Because Ang-1 maintains and stabilizes mature vessels, these findings suggest that high expression of *ANG2* RNA relative to *ANG1* RNA may prevent vessel maturation.

In conclusion, we have demonstrated that Ang-2/*ANG2* is preferentially expressed at the protein and RNA levels in metastatic CRC in the liver. The current data suggest that Ang-2 may cooperate with VEGF in tumor-associated angiogenesis and thus assist in tumorigenesis of CRC metastases in the liver. Therefore, with respect to anti-VEGF therapy, inhibition of Ang-2 activity may be an alternative or additional strategy in the prevention of CRC-related liver metastasis.

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N0大腸癌における免疫染色による微小転移検出の利点と欠点

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臨床

N0大腸癌における免疫染色による微小転移検出の利点と欠点

Benefit and drawback of immunohistochemical detection of micrometastasis in N0 colorectal cancer

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はじめに

微小転移とは，通常の病理検査では検出されない程度のわずかな癌細胞の転移である[1]．免疫染色による微小癌細胞の検出は古くからなされてきており，大腸癌リンパ節中の微小癌細胞の存在と患者予後との関係については盛んに検討されてきたが，その結論はcontroversialである(表1)[2)-11)]．このことは，検索切片数の問題や，どういう場合に微小転移陽性とするかなど診断基準が統一されていないこと，さらには，切片の切削レベルによる再現性の問題などが関係している可能性が考えられる．本研究では，まず検索枚数の違いによる微小転移の検出率について検討し，その結果に基づいて，大腸癌のリンパ節中の微小癌細胞の存在

表1　N0大腸癌の微小転移と予後について

著者	対象	抗体	微小転移	予後
Nicholson 2)	Dukes A, B 33症例，542リンパ節	CAM5.2	 6リンパ節(1.1%)	—
Sasaki 3)	Dukes A, B 19症例，358リンパ節	CAM5.2	19症例(100%) 90リンパ節(25.1%)	—
Yasuda 4)	Dukes B 42症例，1013リンパ節	CAM5.2	32症例(76.2%) 136リンパ節(13.4%)	—
Cutait 5)	Dukes A, B 46症例，603リンパ節	CK(AE1+AE3) CEA	12症例(26%) 22リンパ節(3.7%)	有意差なし
Jeffers 6)	Dukes B 77症例，559リンパ節	CK(AE1+AE3)	19症例(25%)	有意差なし
Adell 7)	Dukes B 100症例，467リンパ節	Anti-CK	39症例(39%) 81リンパ節(17.3%)	有意差なし
Oberg 8)	Dukes A, B 147症例，609リンパ節	CAM5.2	47症例(32%) 77リンパ節(11.6%)	有意差なし
Greenson 9)	Dukes B 50症例，568リンパ節	CK(AE1+AE3)	14症例(28%) 33リンパ節(5.8%)	予後不良
Isaka 10)	Dukes B（直腸癌のみ) 42症例，644リンパ節	CAM5.2	9症例(21.4%) 19リンパ節(2.9%)	予後不良

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表2 対象症例

性差	男性	36例
	女性	19例
腫瘍部位	結腸	30例
	直腸	25例
腫瘍径	0.8～12.0cm	(5.0±2.4cm)
年齢	41～80歳	(59.8±8.6歳)
腫瘍分化度	高分化	31例
	中分化	24例
stage(TNM分類)	stage I	9例
	stage II	46例

様式や癌細胞数，所属リンパ節中の広がり，などこれまで明らかにされていない点について調べ，免疫染色による微小転移診断の臨床的意義とその限界について考察した．

I. 対象と方法

1989～1996年までに当科で治癒切除を受けたN0大腸癌55例を対象とした(表2)．1症例あたりの平均検索リンパ節個数は，12.0個であり，平均術後経過観察期間は80.5±39.0ヵ月である．術前化学療法や放射線治療は行っていない．術後化学療法は，stage Iの11.1%，stage IIの37.0%に対して，5-FU系薬剤(ときにマイトマイシンCを併用）が投与されていた．ホルマリン固定パラフィン包埋されたのべ662個のリンパ節より，6枚の連続切片を作製し，1枚はHE染色を，5枚はサイトケラチンの免疫染色を行った．また主病巣についても，2枚の切片を作製し，HE染色とサイトケラチン染色を行った．脱パラ後，切片の抗原賦活を行い(クエン酸緩衝液(pH 6.0，10 mM)に95℃40分間温浴)，抗サイトケラチンモノクローナル抗体(AE1/AE3：1μg/ml)とペルオキシダーゼ標識dextran polylinker付加二次抗体(Envision plus(DAKO))を用いて水平式自動免染機による染色を行った．陽性コントロールとして大腸癌組織サンプル，陰性コントロールとして一次抗体の代わりに非免疫マウスIgGを使用した．

II. 結　　果

1．サイトケラチン抗体による大腸癌組織とリンパ節染色

原発巣の検討では，大腸癌組織55例全例でサイトケラチンの発現がみられた(図1A)．正常の細胞成分の中では，リンパ節の骨格を作る紡錘形の細網細胞(reticular cell)がしばしば弱い染色性を

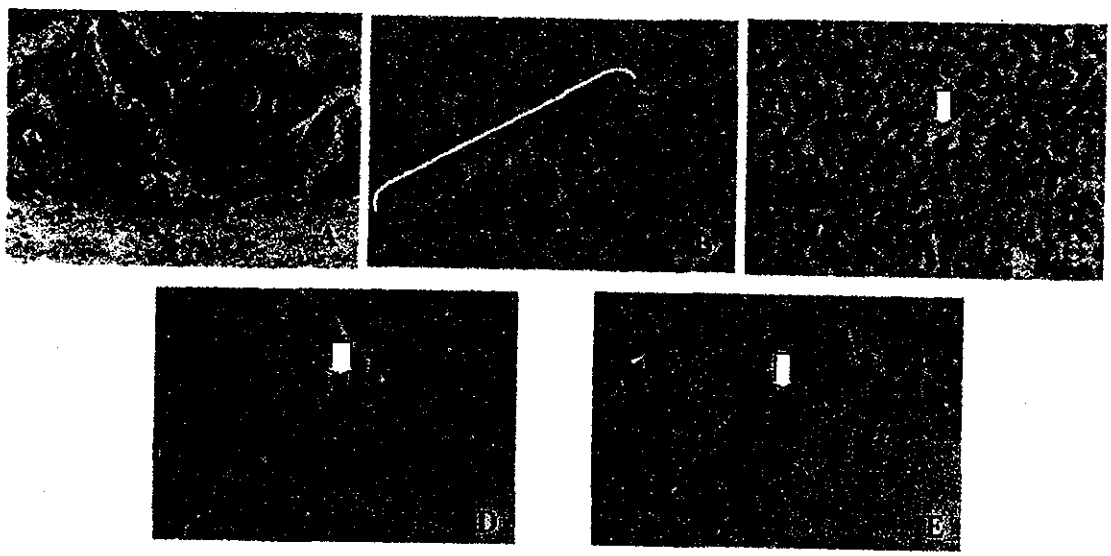

図1 主腫瘍とリンパ節のサイトケラチン染色
A 大腸癌組織のサイトケラチン発現　B 細網細胞　C 組織球　D 癌細胞
E 隣接切片では，癌細胞の一端が切れているので，どの種の細胞か不明

表3　検索切片数による微小転移の検出率

検索切片数	リンパ節	症例数
1切片	4.1%(27/662)	32.7%(18/55)
2切片	5.7%(38/662)	41.8%(23/55)
5切片	11.9%(79/662)	49.1%(27/55)

表4　微小転移の解剖学的広がり

	微小転移陽性数			
	1群	2群	3群	計
リンパ節	59/373	16/203	4/86	79/662(11.9%)
症例	15	8	5	27/ 55(49.1%)

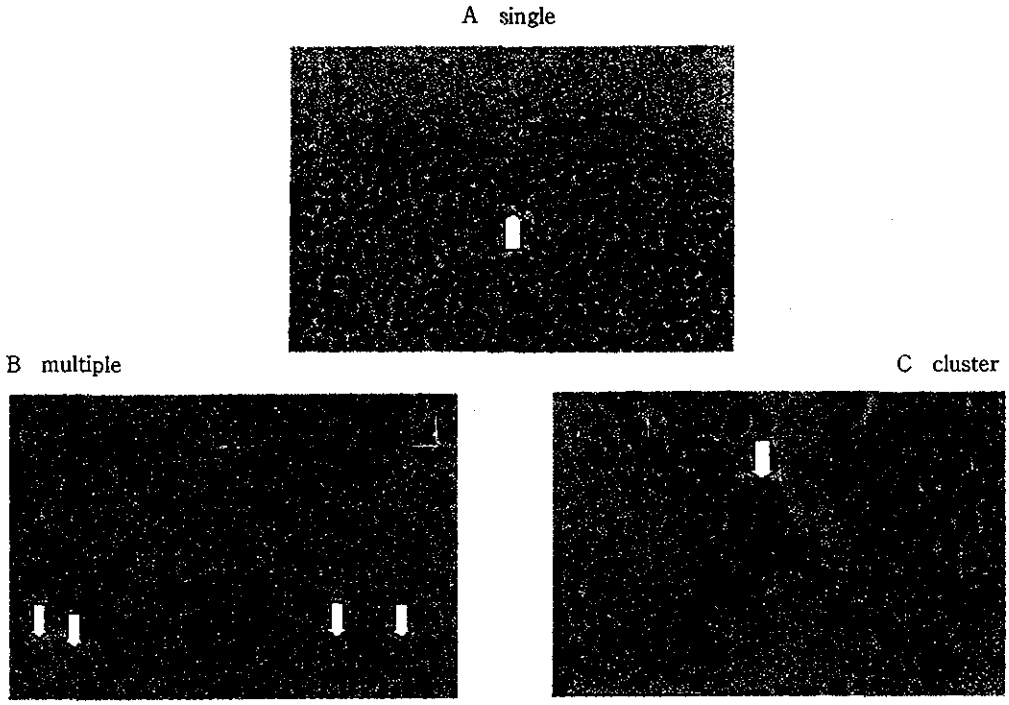

図2　微小転移細胞の存在様式
微小転移細胞の存在様式として，A　微小転移の多くは孤立性であり(single)，B　複数の孤立性細胞が見つかる場合(multiple)，C　さらに島状に集合体を形成するもの(cluster)がある．

示す他に，大食細胞(マクロファージ)もときに染色性を示した(図1B，C)．癌細胞は，形態的に正常細胞との判別が容易である(図1D)．しかし，切片が癌の中心付近ではなく，端をかすめるような場合は，診断が困難であった(図1E)．微小転移の診断にあたっては，5枚の染色切片を二人で検鏡し，サイトケラチンが陽性で，形態的に大きな細胞体と核異型を有し明らかに癌細胞といえるものだけを陽性とした．表3に，検索切片枚数と微小転移検出率の結果について示す．

2．微小転移リンパ節の頻度と分布

微小転移は，N0症例55例中27例(49.1%)に，662個のリンパ節中79個(11.9%)に認められた．微小転移リンパ節の解剖学的広がりを表4に示す．

3．微小転移細胞の存在様式

微小癌細胞は多くは被膜下の類洞かリンパ濾胞周囲の類洞に存在した．その多くは1個の癌細胞としてみつかるが(single)，ときにそのような孤立性細胞が，複数みつかることがあり(multiple)，さらに島状に集合体を形成するものもみられる(cluster)(図2)．微小転移存在様式と微小転移細胞の個数について症例の内訳を表5，6に示す．

表5 微小転移存在様式

存在様式	なし	single cell	culster	single＋culster
症例数	28	22	1	4

表6 微小転移細胞個数

細胞個数	0	1-5	6-10	11-20	20<
症例数	28	16	7	2	2

表7 微小転移と臨床病理学的所見

	リンパ節微小転移		
	陽性 (N＝27)	陰性 (N＝28)	p値
年齢	60.6±8.5	59.0±8.7	$p=0.517$
性			
男性	17	19	$p=0.703$
女性	10	9	
腫瘍占居部位			
結腸	14	16	$p=0.694$
直腸	13	12	
組織型			
高分化	14	17	$p=0.508$
中分化	13	11	
深達度			
～固有筋層	1	8	$p=0.013^*$
漿膜下層～	26	20	
リンパ管侵襲			
陰性	15	17	$p=0.698$
陽性	12	11	
静脈侵襲			
陰性	20	25	$p=0.144$
陽性	7	3	
腫瘍径(cm)	5.7±1.7	4.3±2.8	$p=0.037^*$

＊統計学的有意差有り

4．微小転移と臨床病理学的所見との関係

微小転移と臨床病理学的所見について表7に示す．主腫瘍の深達度が筋層以内に留まっている9例中微小転移陽性はわずか1例のみ(11.1%)であったのに対し，筋層をこえる46例では，26例(56.5%)と高率に微小転移を認めた．また微小転移は腫瘍径とも関連していた．

5．予後因子としての微小転移

臨床病理因子の5年生存率への影響を調べると，分化度，静脈侵襲のみが予後因子となる傾向がみられたが，微小転移の有無とは関連性を認めなかった(表8)．これは，stage Ⅰ症例を除いてstage Ⅱ症例だけで検討しても同様であった．

次に微小転移の詳細と予後の関係について検討した．すなわち，微小転移を有するリンパ節の①数，②主腫瘍からの距離，③微小癌細胞の数，および④その様式(なし，single cell, cluster 形成)についてである．このなかで唯一，存在様式に着目した解析で術後再発との関連性が示唆された．N0症例55例中，15例(27.3%)に術後5年以内の再発がみられ，cluster を形成していた5例中3例で再発がみられたのに対し，single cell パターンでは22例中5例，微小転移なし群では28例中7

表8 各因子の5生率への影響

臨床病理学的因子	p値
年齢（<60：≧60）	0.919
性（男性：女性）	0.301
腫瘍占居部位（結腸：直腸）	0.664
深達度（～固有筋層：漿膜下層～）	0.831
腫瘍分化度（高分化：中分化）	0.050
リンパ管侵襲（陰性：陽性）	0.156
静脈侵襲（陰性：陽性）	0.083
腫瘍径（<5.0cm：≧5.0cm）	0.532
術後補助化学療法（なし：あり）	0.557
微小リンパ節転移（陰性：陽性）	0.817

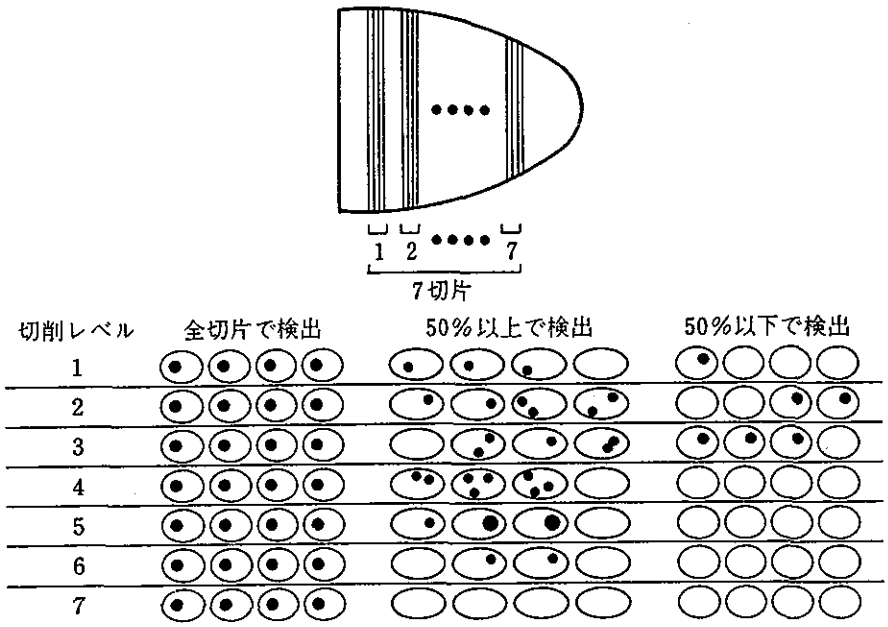

図3　多数切片作製による再現性の検討

例と低率であった．

6．多数切片作製による再現性の検討

微小転移陽性とされた10個のリンパ節について，さらに連続切片4枚を異なる7レベルで作製し計28枚について，微小転移の分布を検討した(図3)．その結果，4個のリンパ節は28切片全てで微小転移が検出されたものの，2個のリンパ節は50%以上の切片で，残り4個のリンパ節では50%以下の切片でのみに微小転移が検出されたにすぎなかった．

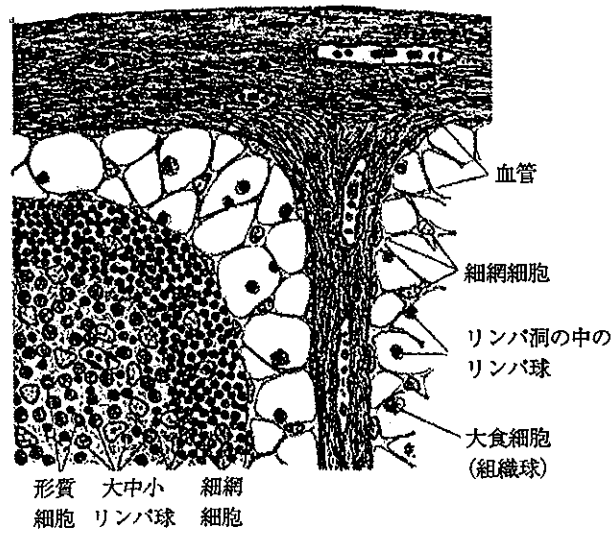

図4　正常リンパ節の構造

III．考　　察

微小癌細胞の検出にあたっては癌細胞で強発現しており，リンパ節の正常な成分では発現がないか，あっても僅かな分子が適当である．これまでの免疫染色を用いた報告の多くはサイトケラチンがマーカーとして利用され，一部でCEAが用いられている．サイトケラチンの検出にはAE1/AE3抗体(DAKO社)が頻用されており，CAM5.2(BectonDickinson社)がときに使用されている．リンパ節を構成する細胞として，リンパ球の他に，細網細胞，大食細胞，形質細胞などがある(図4)[12]．

われわれの検討では，細網細胞が，しばしば弱い染色性を示したが，紡錘形の特徴ある形態から癌細胞と誤認することはない．ときに大食細胞や組織球が染まることがあるが，やはり癌細胞との

識別は容易である．本研究の結果には示していないがpreliminaryにCEA染色も行った．CEAはマクロファージで発現がみられる他，微細構造物が類洞を流れるパターンがしばしばみられた．これは，分泌型のCEA蛋白が類洞内を流れてきたものを捉えているものと考えられる．原発巣では，CEAは腺管形成の内面を中心とする強い染色性がみられたが，微小癌細胞の染色性についてはCEAよりもサイトケラチンの方がむしろ強かったので，本研究ではサイトケラチン抗体(AE1/AE3)を利用することとした．

これまでのほとんどの報告では，微小転移は1枚の切片で診断されている．これは微小転移細胞が広くリンパ節全体に広がっているのではないかという楽観的な見解に基づいているのと，多数のリンパ節を検索するのに複数の切片を調べることは膨大な仕事量となるからである．われわれは，あえて662個のリンパ節について，連続6切片を作製し徹底的に微小転移細胞を探索した．微小転移陽性のリンパ節の頻度は1枚，2枚，5枚と切片数を増やすにつれ，明らかに増加した．その主要因として，1枚では癌の確定診断が困難なことが多いが，両隣の隣接切片を染色してみて初めて大きな核，明瞭な核小体がはっきりと描出され癌細胞と判別できることがあげられる．癌細胞の中央で切片が切られている場合は問題ないが，細胞の端の方をかすめていて僅かに染色性がみとめられる場合は，どのような細胞が染まっているのか形態的に判断できないことをしばしば経験した(図1E)．また，微小転移診断にあたっては，検鏡を2人で行い，サイトケラチンが陽性で，形態的に明らかに癌細胞といえるものだけを陽性とした．このような判定基準の明確化は，検査に普遍性をもたらすうえで重要である．

N0大腸癌の微小転移は実に約半数(49.1%)の例で認められ，この数字は当初のわれわれの想像をはるかに超えるものであった．表4に微小転移リンパ節を解剖学的位置に照らし合わせてみると，1群リンパ節の15.8%，2群，3群リンパ節の7.9%，4.7%と，遠位リンパ節にも少なからずの微小転移が存在した．本邦ではN0でもある程度の予防的リンパ節郭清が行われているが，この結果は多くの微小転移がこれにより除去されていることを示している．

微小転移の有無が，腫瘍の大きさ，ことに深達度と深く関連していたことは，特筆すべきことである．癌が，粘膜下層・筋層に留まるとリンパ節に微小癌細胞が検出される率は10%程度であるが，筋層を越えると微小転移の率は激増する．このことは，免疫染色による微小転移検出が大腸癌の初期進展を的確に表していることを物語っている．本来，免疫染色はたったひとつの癌細胞でも検出する超高感度検査法であり，多数の切片を調べる限りは，きわめて微小な癌細胞をみつけるのに強力な効果を発揮する．例えばセンチネルリンパ節中の微小転移の検索にはRT-PCR法よりもむしろ多数切片検索による免疫染色が有用であると筆者は考えている．

免疫染色で検出される微小転移は予後因子になりえないという多くの報告がある(表1)．一方，GreensonやIsakaらは予後因子となりうるとしている[9][10]．このような意見の相違は，検討症例数や研究デザインの違いなどが関係していると考えられるが，それに加えて，今回の多切片解析の結果は，切片の選び方によって陽性，陰性結果が大きく変わりうることを示しており，このような再現性の不安定性が，これまでのcontroversialな状況と関連しているのかもしれない．

もうひとつ考えられるのは，免疫染色では高感度ゆえに，single cellレベルの微小転移を数多く捉えてしまうことが，予後を予測するうえで問題となるのではないかということである．過去のほとんどの報告は，1枚の検索のみであり，その検出率はN0症例として21.4～39.0%である[5]-[10]．今回われわれは5枚の検索によって，約50%に微小転移を認め，Yasuda[4]らは，やはり5枚の検索で76.2%，Sasaki[3]らは10枚法で100%と報告している．

このように，single cellレベルまで含めると微小転移は非常に高頻度に存在するので，その予後

因子としての意義は，単に存在するか否かではなく，むしろその量が多いか少ないか，あるいは集合体を形成していくかどうかという点がより重要である可能性がある．今回の検討でも，single cell を有する症例に比べて，cluster を形成している症例で高率に再発がみられた．この点についてわれわれは，微小転移といえども n(+)に匹敵する程の癌細胞が存在するものがあることを定量的 RT-PCR 法で確認している[11]．さらに RT-PCR 法で少数ながら prospective に検討すると，微小転移が予後予測に有用であった例を経験した[13]．他に，Liefers らは，同様の結果を報告している[14]．RT-PCR の最大の利点は，リンパ節全体をすりつぶして検索できることであり，免疫染色で問題となった切片のレベルによる結果の再現性についての問題がないことがあげられる．

おわりに

5 枚連続切片を用いた免疫染色は，微小転移診断に確実性を与え有用であった．また single cell を含めると，N0大腸癌の約半数でリンパ節微小転移がみつかった．免疫染色による微小転移は主腫瘍の深達度や腫瘍径とよく相関し，癌の初期進展，すなわち local disease(腸管の限局病変)から expanding disease(周辺のリンパ節に拡がりつつある病変)への移行を的確に反映する．しかし，免疫染色で捉えられる微小転移は cluster 形成例で再発への関連性が示唆されたが，全体としては術後再発の予測因子とはならず，single cell 程度のリンパ節転移は再発の予測因子とならないと考える．

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Sequential Treatment with Irinotecan and Doxifluridine: Optimal Dosing Schedule in Murine Models and in a Phase I Study for Metastatic Colorectal Cancer

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Key Words
Camptothecin · Colorectal cancer · Combination chemotherapy · Doxifluridine

Abstract
Background: Irinotecan (CPT-11) and doxifluridine (5′-DFUR) are active agents against colorectal cancer. Each drug, however, has the possibility of causing diarrhea. ***Methods and Results:*** First, we determined the optimal dosing regimen in murine models. CPT-11 (i.v., q2d × 3) and 5′-DFUR (p.o., qd × 14) were administered to mice bearing a human colorectal cancer xenograft model. Diarrhea was stronger in the simultaneously administered schedule but not much stronger in the sequentially administered schedule compared with monotherapies. Both schedules yielded similar antitumor efficacies. Next, we conducted a phase I study combining CPT-11 on days 1 and 15, and 5′-DFUR on days 3–14 and 17–28 every 5 weeks in 19 patients with metastatic colorectal cancer. The doses of CPT-11 ranged from 80 to 150 mg/m^2 and those of 5′-DFUR from 800 to 1,200 mg. Diarrhea of grade 3/4 developed in only 1 patient at 100 mg/m^2/800-mg doses. Dose-limiting toxicities were hyperbilirubinemia and skipping doses due to fatigue at 150 mg/m^2/1,200-mg doses. ***Conclusion:*** For the phase II study, the recommended dose was set at CPT-11 150 mg/m^2 and 5′-DFUR 800 mg.

Introduction

Two recent large, randomized phase III studies have demonstrated that compared with fluorouracil (5-FU) and leucovorin (LV), the combination of irinotecan (CPT-11), 5-FU and LV improved response rate (RR) and survival in patients with metastatic colorectal cancer [1, 2], and that CPT-11, 5-FU and LV represent one standard option for patients with advanced colorectal carcinoma. However, higher mortality and higher levels of toxicity (particularly diarrhea and neutropenia) were observed in patients treated with a combination of CPT-11 plus 5-FU/LV compared with patients receiving 5-FU/LV [1, 2], necessitating safety precautions [3].

Preclinical and clinical studies have not clarified the optimum combination of CPT-11 and 5-FU. Many preclinical studies have shown schedule-dependent toxicity

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that was more severe when 5-FU was administered after CPT-11 than when CPT-11 was administered after 5-FU [4–7]. One clinical study has shown that the sequence of treatment with CPT-11 and 5-FU affects the tolerability of this combination [8]. In other clinical studies, simultaneous dosing of CPT-11 and 5-FU decreased the area under the concentration curve for SN-38, an active form of CPT-11, and this combination showed low RR (11%, 4 of 36) [9, 10]. These findings have shown that schedule-dependent drug interactions affect the activity and toxicity of the combination of CPT-11 and 5-FU. It would therefore be very useful to determine the optimal dosing regimen for clinical use.

Doxifluridine (5′-DFUR), a 5-FU derivative, is an oral cytostatic that manifests its antitumor effects after being converted to 5-FU by thymidine phosphorylase [11], and it is effective against colorectal cancer [12, 13]. In addition, it is an intermediate of capecitabine [11, 14]. Combination therapy with 5′-DFUR and CPT-11 could therefore be expected to result in a good therapeutic effect together with ease of administration, as this therapy can be administered on an outpatient basis. However, since the primary toxicities of both 5′-DFUR and CPT-11 are gastrointestinal toxicities [12, 15], the combined use of 5′-DFUR and CPT-11 may increase the severity of the gastrointestinal toxicity.

In this study, we first used murine models to determine CPT-11 and 5′-DFUR combination therapy regimens that resulted in a stronger antitumor effect compared with that obtained by monotherapy, while suppressing any augmentation of gastrointestinal toxicity. We then performed a phase I study of CPT-11 and 5′-DFUR in patients with metastatic colorectal cancer to determine the optimal dose. In the phase I combination therapy trial, CPT-11 was administered biweekly for convenience [15], and 5′-DFUR was administered intermittently to prevent gastrointestinal toxicity [16].

Patients and Methods

Animals

Five-week-old male BALB/c nu/nu mice were obtained from Charles River Japan (Yokohama, Japan). They were kept for 1 week in our animal facility before tumor inoculation.

Tumors

The human colon cancer line COLO 205 (ATCC CCL-222) was obtained from Dainippon Pharmaceutical (Osaka, Japan) and was maintained in vitro with RPMI 1640 medium containing 10% FBS.

Human Cancer Xenograft Models

A suspension of COLO 205 cells (5×10^6 viable cells/mouse) was inoculated subcutaneously into male nude mice. The experiment began 11 days after tumor inoculation. The tumor volumes were estimated by using the equation $V = ab^2/2$, where a and b are tumor length and width, respectively. To evaluate the antitumor effect of CPT-11 and 5′-DFUR, tumor size and body weights were measured twice weekly. Gastrointestinal toxicity was estimated by observing the feces and examining them for occult blood. Feces were scored as follows: N = normal feces; L1 = slightly loose feces; L2 = loose feces, and D = diarrhea. The occult blood score was determined using the Shionogi Occult Blood Slide (*o*-toluidine method and guaniac method, Shionogi, Osaka, Japan) and scored as –, ±, +, ++, and +++ in accordance with the instructions in the kit. All animal experiments were conducted in accordance with the 'Guidelines for the Care and Use of Laboratory Animals in the Nippon Roche Research Center'.

Chemicals for Animal Experiments

CPT-11 (irinotecan hydrochloride) was purchased from Daiichi Pharmaceutical (Tokyo, Japan). 5′-DFUR was synthesized at Hoffmann-La Roche (Basel, Switzerland). CPT-11 was diluted with saline and administered intravenously. 5′-DFUR was dissolved in 40 m*M* citrate buffer (pH 6.0) containing 5% gum Arabic as vehicle and orally administered. The maximum tolerated dose (MTD) of 5′-DFUR in the preclinical experiments of this paper was based on the data obtained from nude mice bearing human colon tumor HCT116 in a previous study [17].

Statistical Analysis

For the preclinical experiments, statistical analysis was performed using the Mann-Whitney U test. Differences were considered to be significant at $p < 0.05$.

Patients

The eligibility criteria were as follows: proven unresectable or recurrent colorectal cancer with measurable lesions; age between 20 and 74 years; no major surgery, no radiotherapy or chemotherapy within 4 weeks, Eastern Cooperative Oncology Group performance status of 0–2; predicted life expectancy at least 3 months; adequate baseline organ functions, defined as neutrophil count ≥2,000/μl, platelet count ≥100,000/μl, hemoglobin ≥10.0 g/dl, AST and ALT <3 or less times the upper limit of the institutional reference range; total bilirubin ≤1.5 mg/dl, and serum creatinine ≤1.5 mg/dl. The exclusion criteria included brain metastases, secondary malignancies, severe cardiac disease, history of myocardial infraction within the previous 6 months, severe nausea and vomiting, malabsorption syndrome and serious infection. The trial was initiated after obtaining Institutional Review Board approval for both hospitals, and after obtaining written informed consent from all the patients.

Pretreatment Evaluation and Follow-Up

Pretreatment evaluation included a complete medical history and physical examination, chest X-ray, ECG, and imaging of measurable disease, a complete blood cell count and a biochemical screening profile. During treatment, patient monitoring included the assessment of clinical toxicities, a complete blood cell count, serum chemistry, and physical examination before each biweekly dose of chemotherapy. Adverse events were evaluated according to

the National Cancer Institute Common Toxicity Criteria (version 2.0). Additionally, the target lesion(s) were measured by CT scans performed before each cycle and at the end of treatment. The response was evaluated in accordance with the Response Evaluation Criteria in Solid Tumors.

Plan of Sequential Treatment

Patients received treatment every 5 weeks. CPT-11 was administered in 500 ml of normal saline or dextrose as 90-min intravenous infusions on days 1 and 15. 5'-DFUR was supplied as capsules in two dose strengths (100 and 200 mg), and two or three capsules were administered orally per day after meals on days 3–12 and 17–28 (sequential treatment). The prophylactic use of granulocyte colony-stimulating factor was not allowed. In the case of intolerable toxicity, disease progression, or patient refusal, the study treatment was discontinued.

Treatment was delayed until the granulocyte count had recovered to $\geq 2{,}000/\mu l$, the platelet count to $\geq 100{,}000/\mu l$, serum bilirubin to ≤ 1.5 mg/dl, serum creatinine to ≤ 1.5 mg/dl, and when there was no $\geq$ grade 2 diarrhea or infection. If toxicity required a dosing delay of more than 3 weeks, the patient was withdrawn from the study due to toxicity. If patients experienced dose-limiting toxicity (DLT) or patients required a dosing delay of more than 2 weeks, the CPT-11 dose given was 1 level lower than the original dose. If patients experienced DLTs after this dose reduction, the protocol treatment was stopped. DLT was defined as any grade 3 or 4 nonhematologic toxicity (except nausea, vomiting, or fatigue), grade 4 neutropenia/leukopenia for more than 4 days, grade 4 neutropenia/leukopenia with fever (temperature $\geq 38°C$), grade 4 hematologic toxicity (except neutropenia or leukopenia), or discontinuation of treatment due to treatment-related toxicity during the first treatment cycle.

Dose-Escalation Schedule

The dose of 5'-DFUR was initially fixed at 800 mg, and CPT-11 doses of 80, 100, 120 and 150 mg/m^2 were studied. When the 150 mg/m^2 dose of CPT-11 was tolerable, the 5'-DFUR was escalated to 1,200 mg. Cohorts of 3 patients were to be entered at each dose level, starting at dose level 1. If any DLT was observed in any of the first 3 patients, an additional 3 patients were enrolled at the same dose level. If 2 or more patients at any dose level experienced the same DLT, the MTD was determined to have been reached, and the dose level below the MTD was considered to be the recommended dose for further studies.

Results

Gastrointestinal Toxicity Induced by CPT-11 Alone and 5'-DFUR Alone in the Human Colon Tumor Xenograft Model (COLO 205)

We first examined a monotherapy dosing regimen with CPT-11, which can induce a delayed-type gastrointestinal toxicity in mice bearing the COLO 205 human colon tumor xenograft. A single intravenous injection of CPT-11 at a dose of 150 mg/kg resulted in death immediately after the injection due to the acute toxicity of CPT-11. In contrast, at a dose of 120 mg/kg (MTD), the intravenous CPT-11 injection induced neither death nor gastrointestinal toxicity as assessed by fecal observation and the occult blood test (data not shown). We therefore examined the use of multiple injections of CPT-11 on the induction of delayed-type intestinal toxicity. Intravenous CPT-11 injection at a dose of 100 mg/kg/day (5/6 MTD), administered on days 1, 3 and 5 (q2d × 3), induced intestinal toxicity. The median toxicity levels observed were N–L1 for the fecal form (on days 7–10) and ± for occult blood (on days 7–10). When 5'-DFUR was administered per os daily for 14 days at a dose of 154 mg/kg/day (5/6 MTD) [17], gastrointestinal toxicity, evidenced by slightly loose feces N–L1 and occult blood – to ± was detected on days 15 and 16.

Gastrointestinal Toxicity of Three Different Dosing Regimens in the Human Colon Tumor Xenograft Model (COLO 205)

We compared the gastrointestinal toxicity and antitumor activity of three different combination dosing regimens in mice bearing the human colon tumor COLO 205. CPT-11 was injected at a dose of 100 mg/kg/day i.v. three times every other day (on days 1, 3 and 5), whereas 5'-DFUR was administered at 154 mg/kg/day p.o. for 14 days. 5'-DFUR was given from days 9 to 22 in regimen 1, days 7–20 in regimen 2, and days 1–14 in regimen 3.

In the simultaneously administered dose regimen (regimen 3), the gastrointestinal toxicity observed in the combination therapy group appeared to be higher than that found in the CPT-11 or 5'-DFUR monotherapy treatment groups (fig. 1). In regimen 2, which had 1-day treatment intervals after the CPT-11 injections, the toxicity was slightly higher than that in the monotherapy treatment groups. The occult blood score for the combination group was significantly higher than that for the CPT-11 treatment group on the following days ($p < 0.05$): on day 12 in regimen 2 and from days 7–13 in regimen 3. In regimen 1, however, which had 3-day intervals after the CPT-11 injections, there was no augmentation of either the fecal observation or occult blood score (fig. 1).

Antitumor Activity of Three Different Dosing Regimens in the Human Colon Tumor Xenograft Model (COLO 205)

We also examined antitumor activity in the experiment described above. The antitumor activity was additive in the combination therapy groups for each of the dosing regimens (fig. 2). The combination therapy group exhibited significantly better efficacy than the vehicle and

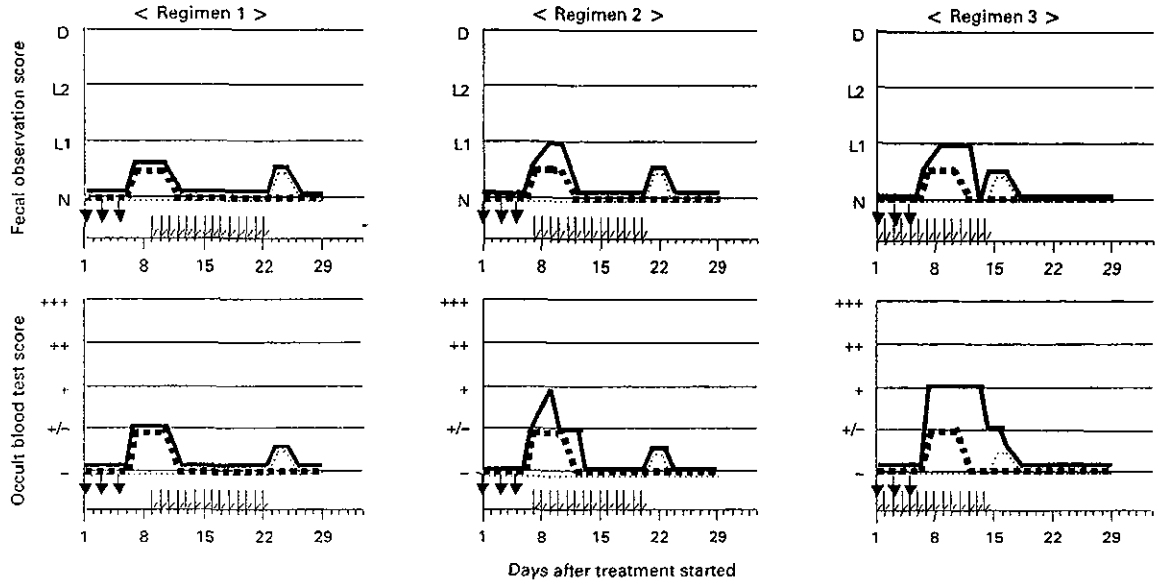

Fig. 1. Gastrointestinal toxicity of three different CPT-11 and 5'-DFUR combination therapy schedules in human colon tumor xenografts (COLO 205). Mice bearing COLO 205 tumors were randomized into groups of 6 mice each. CPT-11 was injected intravenously three times (days 1, 3 and 5) at 100 mg/kg beginning 11 days after the tumor inoculation. 5'-DFUR was administered per os for 14 days at 154 mg/kg/day (schedule 1, days 9–22; schedule 2, days 7–20; and schedule 3, days 1–14). Data are medians of fecal observation scores and occult blood test scores. N = Normal feces; L1 = slightly loose feces; L2 = loose feces; D = diarrhea. The occult blood test score was determined using the Shionogi Occult Blood Slide kit. Thick arrows indicate the timing of CPT-11 injection, and thin arrows the timing of 5'-DFUR administration. ■■■■ = CPT-11 alone; ····· = 5'-DFUR alone; ▬▬ = CPT-11 + 5'-DFUR in combination.

the CPT-11 and the 5'-DFUR monotherapy groups for all three dosing regimens ($p < 0.05$, on day 29). The efficacy for the sequential dosing regimens was similar to that for the simultaneous dosing regimens. These results suggest that a sequential administration regimen of CPT-11 and 5'-DFUR would be more tolerable than and equally efficacious to a simultaneous administration regimen in the mouse COLO 205 xenograft model.

Phase I Study of Sequential Treatment for Metastatic Colorectal Cancer

From May 2001 to July 2002, 19 patients with metastatic colorectal cancer were enrolled in this trial at the Departments of Surgery of the Osaka National Hospital and the Minoh City Hospital. The patients' characteristics are listed in table 1. Of these 19 patients, 14 (74%) had received one or more prior chemotherapy regimens including 13 patients (68%) with previous fluoropyrimidine-based treatment and 6 patients (32%) with previous CPT-11-based treatment. All patients received at least one complete cycle of the trial chemotherapy, and a total of 51 cycles (median 2.0, range 1.0–7.5) were administered.

The total number of patients, courses of treatment administered, and patients with DLT are listed in table 2. DLTs were observed in 3 patients. One patient experienced grade 3 diarrhea during the first treatment cycle (dose level 2), but this patient continued with the chemotherapy after a 4-week rest and a dose reduction of CPT-11 to 80 mg/m^2. At this dose, only 1 of the 6 patients developed DLT. One patient who experienced grade 3 hyperbilirubinemia during the first treatment cycle (dose level 5) discontinued the study treatment. One patient experienced skipping doses owing to grade 2 fatigue, diarrhea and vomiting during the first treatment cycle (dose level 5), and discontinued the study treatment. At dose level 5, 2 of the 4 patients developed DLT; therefore, this dose was determined to be the MTD. At dose level 4, nei-

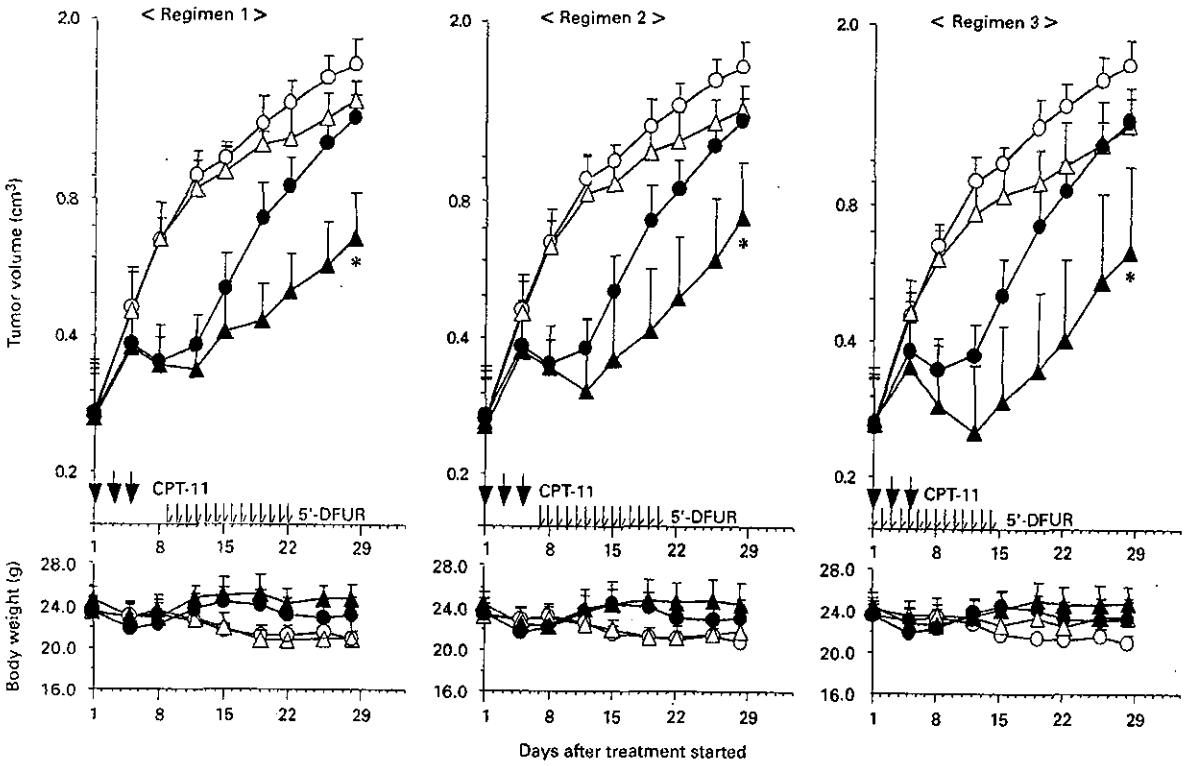

Fig. 2. Antitumor activity of three different CPT-11 and 5'-DFUR combination therapy schedules in human colon tumor xenografts (COLO 205). Mice bearing COLO 205 tumors were randomized into groups of 6 mice each. CPT-11 was injected intravenously three times (days 1, 3 and 5) at 100 mg/kg beginning 11 days after the tumor inoculation. 5'-DFUR was administered per os for 14 days at 154 mg/kg/day (schedule 1, days 9–22; schedule 2, days 7–20; schedule 3, days 1–14). Data are means ± SD (vertical bars) of tumor volume and body weight. Thick arrows indicate the timing of CPT-11 injection, and thin arrows the timing of 5'-DFUR administration. ○ = Vehicle; ● = CPT-11 alone; Λ = 5'-DFUR alone; ▲ = CPT-11 + 5'-DFUR in combination; * $p < 0.05$ vs. vehicle, CPT-11, 5'-DFUR.

ther DLT nor grade 3 or 4 toxicity were observed. Therefore, dose level 4 is the recommended dose for the phase II trial of the combination therapy using the regimen used in this study.

The major adverse events per each dose level are shown in table 3, and all adverse events for the 19 patients are shown in table 4. The most common adverse events, fatigue (89%), nausea/vomiting (74%) and alopecia (47%; 26% of grade 2), were mild and did not exceed grade 2. There were only 2 (11%) grade 3 or 4 adverse events, namely grade 3 hyperbilirubinemia and grade 3 diarrhea. Grade 3 or 4 diarrhea, which may be the greatest concern for safety, developed in only 1 (5%) patient at dose level 2. Common hematologic adverse events were neutropenia (58%) and leukopenia (32%), which were also mild and did not exceed grade 2.

Tumor response was not the primary end point of this phase I study; however, evidence of antitumor activity was observed. Seventeen of 19 patients were assessable for tumor response; a partial response (PR) was achieved in 3 patients. One and 2 PR were observed at dose levels 1 and 2, respectively. With respect to the characteristics of the individual patients who showed a PR, 1 patient experienced DLT (grade 3 diarrhea) at 100 mg/m^2 of CPT-11, but continued treatment for 12 months after a dose reduction to 80 mg/m^2, resulting in a 12-month re-

Table 1. Patient characteristics

Characteristics	Patients	Median (range)	%
Total patients	19		100
Males/females	13/6		68/32
Age, years		58 (46–71)	
ECOG performance status		0 (0–1)	
Primary tumor site			
Colon	5		26
Rectum	14		74
Reason for prior chemotherapy			
Adjuvant	7		37
Metastatic	9		47
Prior chemotherapy	14		74
Fluoropyrimidine based	13		68
CPT-11 based	6		32
Courses of prior chemotherapy		1 (0–4)	
Sites of metastases			
Lung	9		47
Liver	8		42
Lymph nodes	8		42
Other	4		21

ECOG = Eastern Cooperative Oncology Group.

Table 2. Dose escalation scheme and incidence of DLT

Dose level	CPT-11 mg/m^2/day	5'-DFUR mg/day	Patients n	Courses n	Patients with DLT n[1]
1	80	800	3	10	0
2	100	800	6	20	1
3	120	800	3	7	0
4	150	800	3	9	0
5	150	1,200	4	5	2
Total			19	51	3

[1] During the first treatment cycle.

sponse duration. Two of the 19 patients received only one cycle of the study treatment owing to DLT at dose level 5 and were not assessable. However, 1 of these patients discontinued the study treatment and received the CPT-11 monotherapy at the dose of 100 mg/m^2 for 2 weeks and achieved a PR soon after the cessation of the study treatment.

Discussion

The CPT-11 and 5-FU/LV combination therapy has resulted in improved anti-tumor activity and clinical efficacy in the treatment of metastatic colorectal cancer in comparison to 5-FU/LV therapy. This combination therapy, however, also results in increased toxicity as evidenced by diarrhea and neutropenia [1, 2]. In addition, there is need for vigilance against the use of the CPT-11/5-FU/LV combination therapy [3]. Further investigation of the clinical safety and efficacy of this combination therapy was therefore warranted.

5'-DFUR, a prodrug of 5-FU, is an intermediate form of capecitabine [11, 14], and it is therefore expected to be efficacious when administered in combination with CPT-11. In addition, as it may be orally administered, it is convenient to use on an outpatient basis resulting in an improved quality of life. The primary toxicity of 5'-DFUR is gastrointestinal [12], which is the same as that for CPT-11 [15]. However, there is no report on the safety of its combined use with CPT-11, and the combined use may result in augmentation of gastrointestinal toxicity.

In this study on COLO205-tumor-bearing murine models, we first examined the CPT-11 and 5'-DFUR combination dosing regimens that did not result in gastrointestinal toxicity but did result in a stronger antitumor effect compared with that observed after monotherapy with either drug. Three different treatment regimens were compared in which CPT-11 was injected three times every other day (days 1, 3 and 5) in each of the regimens, whereas 5'-DFUR was given daily for 2 weeks as follows: (1) at 3-day treatment intervals after the CPT-11 injections, (2) at a 1-day treatment interval after the CPT-11 injections, and (3) simultaneously with CPT-11. The antitumor effect for all three regimens was significantly stronger compared with the results achieved by monotherapy with CPT-11 or 5'-DFUR. Similar antitumor effects were observed in each of the three dosing regimens. In contrast, when 5'-DFUR was administered after 3- or 1-day intervals following the CPT-11 injections, the augmentation of gastrointestinal toxicity was mild compared with that for the simultaneous dosing regimen. This lack of augmentation of gastrointestinal toxicity was most pronounced for the regimen in which 5'-DFUR administration started 3 days after the CPT-11 injections.

The results of this study in the murine models suggested that a stronger antitumor effect can be achieved, compared with monotherapy, without augmenting the in-

Table 3. Major adverse events for each dose level

Dose level	Patients[1]	Grading according to NCI-CTC (patients)																			
		fatigue				nausea/vomiting				alopecia				diarrhea				neutropenia			
		1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
1	3	3	0	0	0	2	0	0	0	1	1	0	0	0	0	0	0	2	0	0	0
2	6	4	1	0	0	4	0	0	0	1	2	0	0	0	1	1	0	1	1	0	0
3	3	1	2	0	0	0	3	0	0	2	0	0	0	0	0	0	0	1	0	0	0
4	3	1	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	2	1	0	0
5	4	2	2	0	0	1	3	0	0	0	2	0	0	1	2	0	0	2	1	0	0

NCI-CTC = National Cancer Institute Common Toxicity Criteria.
[1] Number of patients assessable for adverse events for each dose level.

Table 4. Adverse events in 19 patients treated with CPT-11 and 5′-DFUR

Adverse events	Patients		Grade				Grade 3 or 4 %
	n	%	1	2	3	4	
Hematologic							
Neutropenia	11	58	8	3	0	0	0
Leukopenia	6	32	5	1	0	0	0
Hemoglobinemia	2	11	2	0	0	0	0
Nonhematologic							
Fatigue	17	89	11	6	0	0	0
Nausea/vomiting	14	74	7	7	0	0	0
Alopecia	9	47	4	5	0	0	0
Diarrhea	5	26	1	3	1	0	5
Headache	1	5	1	0	0	0	0
Stomatitis	1	5	0	1	0	0	0
Hyperbilirubinemia	1	5	0	0	1	0	5

Adverse events are reported for all courses.

testinal toxicity, when 5′-DFUR is administered a few days after the administration of CPT-11.

Based on the rationale of the preclinical study, we conducted a phase I study using the regimen in which 5′-DFUR was administered 1 day after CPT-11. Although augmentation of gastrointestinal toxicity was mildest when 5′-DFUR was administered at 3-day intervals after CPT-11 in the preclinical study, we chose the combination dosing regimen in which 5′-DFUR was administered 2 days after the administration of CPT-11. This choice was based on the following reasoning: namely, augmentation of gastrointestinal toxicity was mild enough even after a 1-day interval, compliance with 5′-DFUR treatment is likely to improve, and some clinical reports have already shown that drug interaction was avoided when 5-FU was administered 2 days following administration of CPT-11 [9, 10].

During the phase I study, 19 patients with metastatic colorectal cancer received CPT-11 on days 1 and 15 and 5′-DFUR on days 3–14 and 17–28, every 5 weeks. The results of this study showed that the MTDs of CPT-11 and 5′-DFUR were 150 mg/m^2 and 1,200 mg, respectively, and that DLT was observed in 3 cases: grade 3 diarrhea at dose level 2, grade 3 hyperbilirubinemia, and discontinuation of treatment due to grade 2 fatigue, diarrhea and vomiting at dose level 5. The recommended doses for CPT-11 and 5′-DFUR were 150 mg/m^2 and 800 mg (dose level 4), respectively. No adverse drug reactions of grade 3 and above were observed at this dose level. A biweekly dose of 150 mg/m^2 is the maximum dose of CPT-11 that is permitted in Japan.

The most common adverse drug reactions were neutropenia (58%), leukopenia (32%), fatigue (89%), nausea/vomiting (74%) and alopecia (47%). There were only two incidents (11%) of serious adverse drug reactions of grade 3 or 4, which were diarrhea and hyperbilirubinemia. There was only 1 case (5%) of grade 3 or 4 diarrhea, which is considered to be the most serious toxicity associated with this treatment. This incidence was similar to that (5%) reported for 800 mg 5′-DFUR alone [16] and slightly lower than that (13%) reported for 150 mg/m^2 CPT-11 q2w alone [15]. The most commonly used concomitant treatments were propulsives (such as metoclopramide) and serotonin ($5HT_3$) antagonists (such as granisetron). Most patients preferred granisetron for prevention of chemotherapy-induced nausea or vomiting as already reported [18]. The only patient who experienced this grade 3 diarrhea had

been receiving 100 mg/m^2 of CPT-11 and 800 mg of 5′-DFUR. Although administration was discontinued for 4 weeks after grade 3 diarrhea was observed during the first cycle of treatment, CPT-11 administration was resumed at 80 mg/m^2 as antitumor effects were being observed. From that point on, this patient received 80 mg/m^2 CPT-11 and 800 mg 5′-DFUR and had no incident of serious diarrhea for 12 months while exhibiting a tumor response. This particular patient seemed to be very sensitive to CPT-11 with regard to both its efficacy and toxicity. No grade 3 or 4 diarrhea was observed at the 150 mg/m^2 CPT-11 dose level (level 4 or 5). The incidence of severe diarrhea does not seem to be increased by the combination therapy. Therefore, we considered that sequential treatment improved the tolerability of CPT-11 and 5′-DFUR. This enhanced tolerability may be due to the differential timing of CPT-11- and 5′-DFUR-induced diarrhea.

Tumor response was not the primary end point of this phase I study; however, evidence of antitumor activity was observed in previously treated patients. One and 2 PR were observed at dose levels 1 and 2, respectively. Response to CPT-11 may be independent of its dose as already reported [19].

Thus, sequential combination therapy with CPT-11 and 5′-DFUR may be very safe; however, further clinical studies are needed to confirm their safety and efficacy. Therefore, a phase II study in metastatic colorectal cancer patients using sequential combination therapy of CPT-11 150 mg/m^2 on days 1 and 15 and 5′-DFUR 800 mg on days 3–14 and 17–28 every 5 weeks is warranted.

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大腸癌肝転移切除後長期生存例の検討

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The Long-Term Results of Hepatic Resection for Metastatic Lesions from Colorectal Cancer: Minoru Tanada, Yoshiro Kubo, Masahiro Ishizaki, Kengiro Aogi, Akira Kurita and Shigemitsu Takashima (*Dept. of Surgery, National Shikoku Cancer Center Hospital*)

Summary

We reviewed the clinical course of 51 patients who underwent hepatic resection for metastatic lesions from colorectal cancer between January 1984 and December 1997. The cumulative survival rate at 3 and 5 years were 57% and 43%, respectively. Sex, age, chronology of liver metastases (LM), number of LM, maximum diameter of LM, macroscopic surgical resection margin, type of hepatic resection, chemotherapy after hepatic resection, and site of primary tumor were not found to be statistically significant prognostic factors. The presence of lymph node metastases for the primary tumor was a predictor of shorter survival duration by univariate analysis ($p=0.03$).

Recurrence was not observed in 15 patients. However, recurrence was observed in 36 patients, of which 4 were in remission by undergoing repeated resection for recurrence sites (2 were in lung, 2 were in liver). Although the long term survival of the 19 patients with no significant remarks to be noted, but no one survived with more than 4 hepatic metastases among the long term survivors. Key words: Colorectal cancer, Liver metastases, Hepatic resection

要旨 1984年1月より1997年12月までに51例の大腸癌肝転移に対し肝切除を行った。51例の3，5年生存率はそれぞれ57，43%であった。予後因子の検討では，性別，年齢，再発時期，肝再発腫瘍径，肝再発個数，肝切除術式，肝切除断端，肝切除後の補助化学療法の有無，原発巣の部位の各因子では予後に差を認めず，原発巣のリンパ節転移陽性例は有意に予後不良であった($p=0.03$)。15例は無再発生存中であり，再発36例中再発巣を切除した4例が無病生存中である。長期生存19例に特徴的所見は認められなかったが，肝転移個数4個以上に長期生存例は認められなかった。

はじめに

大腸癌肝転移に対して積極的に切除が行われ，各施設で良好な成績が報告されている[1-3]。

今回われわれは，当院での大腸癌肝転移切除例の長期フォローアップより，長期生存例について検討した。

I. 対象と方法

1984年1月から1997年12月までに当院外科で切除し，5年以上経過観察できた大腸癌肝転移51例を対象とした。再発例は36例で，36例中4例が再発巣の切除により長期無病生存中である(肝転移2例，肺転移2例)。この4例と無再発生存中の15例の，計19例の臨床病理学的特長について検討した。

累積生存率はKaplan-Meier法にて算出し，logrank testで検定，危険率5%未満($p<0.05$)を有意とした。

II. 結 果

1. 肝転移切除例

大腸癌肝転移切除51例の背景因子は，男性33例，女性18例，平均年齢62歳(40～83歳)，同時性27例，異時性24例，平均腫瘍径3.7 cm (0.5～9.6 cm)，肝転移個数は，1個31例，2個8例，3個6例，4個4例，5個1例，6個1例，切除術式は，部分切除34例，1区域切除7例，2区域切除9例，3区域切除1例，切除断端1 cm未満23例，1 cm以上28例，術後補助化学療法施

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行例は18例で，原発巣は結腸26例，直腸25例，原発巣のリンパ節転移陽性例は34例であった。

2．肝転移切除後の予後

3，5年生存率はそれぞれ57，43%で，3，5年無再発生存率はそれぞれ31，29%であった(平均観察期間71か月)（図1)。

性別，年齢，転移時期，転移個数，転移腫瘍径，切除断端，切除術式，切除後の補助化学療法，原発巣の部位，原発巣のリンパ節転移の有無の各因子での予後の検討では，原発巣のリンパ節転移陽性例は有意に予後不良であった（p=0.03）（表1)。

3．再　　発

肝切除後の再発は36例に認められ，再発部位は肝22例，肺16例，腹膜2例，原発巣局所1例，骨1例，皮下1例で，再発治療は切除6例，化学療法18例，放射線療法3例，無治療9例であった。

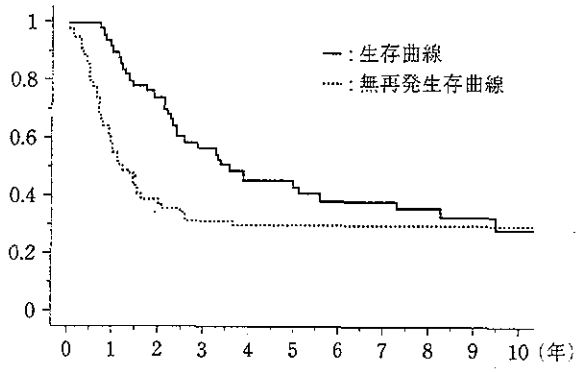

図 1　大腸癌肝転移切除例の予後

4．再発後長期生存例

再発後長期生存例は4例である（表2)。症例1は，肝転移切除後10か月目に肝再発し，再肝切除，初回肝切除後127か月無病生存中，症例2は肝転移切除後44か月目に肺再発し，切除，初回肝切除後112か月無病生存中，症例3は肝転移切除後31か月目，47か月目に肺再発し，それぞれ切除，初回肝切除後70か月無病生存中，症例4は肝転移切除後8か月目に肝再発し，再肝切除，初回肝切除後67か月無病生存中である。

5．長期生存例

無再発例15例と再発後長期生存例の4例を合わせた19例の背景因子は表のごとくであった（表3)。

III．考　　察

当院における大腸癌肝転移切除51例中5年以上無病生存中の症例は19例であった。これら長期生存例に特徴的な所見は認められなかった。15例は肝転移切除後無再発で生存しているが，再発例でも再発巣が切除により完全にコントロールされている4症例で長期生存例が認められている。長期生存例の平均観察期間は107か月で，肝転移切除後4年以降に再発を認めた症例はなかった。予後因子の検討では，原発巣のリンパ節転移陽性例は有意に予後不良であったが，長期生存例でも19例中9例に原

表 1　大腸癌肝転移切除例の予後因子

因　子		症例数	5年生存率（%）	p値
性別	男性：女性	33：18	45：39	0.91
年齢	59≧：60≦	21：30	48：40	0.29
転移時期	同時性：異時性	27：24	37：50	0.08
転移個数	単発：多発	31：20	51：30	0.12
腫瘍径	2 cm>：2 cm≦	15：36	27：50	0.14
切除断端	1 cm>：1 cm≦	28：23	39：46	0.76
切除術式	部切：区域切除	34：17	38：53	0.83
補助化学療法	あり：なし	23：28	43：43	0.90
原発巣	結腸：直腸	26：25	39：48	0.32
原発巣のリンパ節転移	(−)：(+)	17：34	64：32	0.03

表 2　大腸癌肝転移切除後再発例で長期生存中の症例

症例	年齢/性別（歳）	再発時期	肝転移個数	腫瘍径（cm）	切除術式	切除断端（mm）	補助療法	原発巣	リンパ節転移	再発部位	無病期間
1	58歳/男性	同時性	3	2.7	部分切除	10	−	結腸	+	肝	10か月
2	66歳/男性	異時性	1	0.8	部分切除	5	+	直腸	−	肺	44か月
3	54歳/男性	異時性	1	3.5	1区域切除	8	+	直腸	+	肺	31か月
4	76歳/男性	異時性	1	1.5	部分切除	5	−	直腸	−	肝	8か月