再発は906例に認め，再発率は17.1%であった．そのうち，初回再発巣に対して治癒手術を施行しえたのは379例，再発巣治癒切除率は41.8%であった．再発巣治癒切除例の初回再発後5年生存率は42.2%，生存期間中央値は1,293日であり，非治癒切除例(手術非施行例を含む)の生存期間中央値381日に比し，有意に良好であった(図1)．

再発の診断時期別の予後の検討では，術後1年以内の再発例では再発巣治癒切除率が低く，また初回再発後の予後は，術後1年以降に再発した症例に比し，有意に不良であった(図2)．しかし，再発巣が治癒切除できた症例に限って検討すると，再発巣治癒切除後の予後は，診断時期による差はなく，いずれも5年生存率が約40%と，比較的良好であった(図1)．

このことより，一般に予後不良とされている術後早期の再発であっても，再発巣に対し治癒切除を行うことができれば，約40%の5年生存が期待できることが明らかになった．

表1．大腸癌研究会「大腸癌術後再発に関するフォローアップに関する研究プロジェクト」参加施設

施設名	施設代表者
防衛医科大学校外科	望月英隆
弘前大学第二外科	森田隆幸
栃木県立がんセンター外科	固武健二郎
東京医科歯科大学腫瘍外科	杉原健一
東京女子医科大学第二外科	亀岡信悟
都立駒込病院外科	高橋慶一
東邦大学消化器外科	寺本龍生
癌研究会附属有明病院外科	大矢雅敏
自衛隊中央病院外科	長谷和生
国立国際医療センター大腸肛門外科	斉藤幸夫
愛知県がんセンター中央病院 消化器外科	平井　孝
藤田保健衛生大学外科	前田耕太郎
大阪府立成人病センター第一外科	亀山雅男
久留米大学外科	白水和雄

II. 術後サーベイランスは予後の改善に寄与するか

では，術後サーベイランスは再発巣の治癒切除率の向上に貢献し，予後を改善することができるのであろうか？

1990年代後半に，大腸癌術後のサーベイランスに関する代表的な6つのランダム化比較試験(RCT)が行われたが，再発の早期発見および有意な生存率の改善を示した研究は二つのみであっ

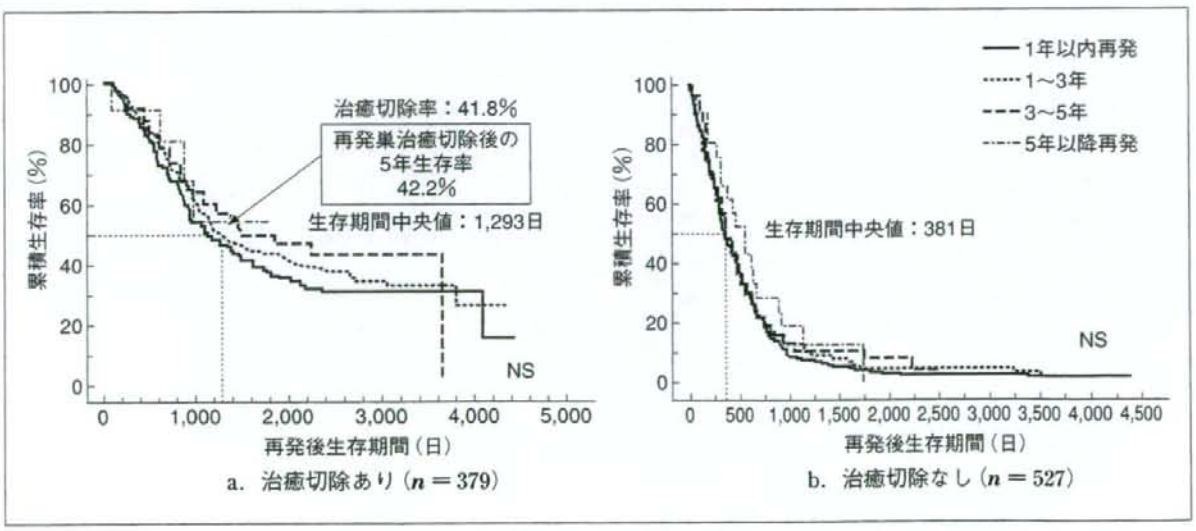


図1．再発巣治癒切除後の生存曲線(初回再発診断時期別)

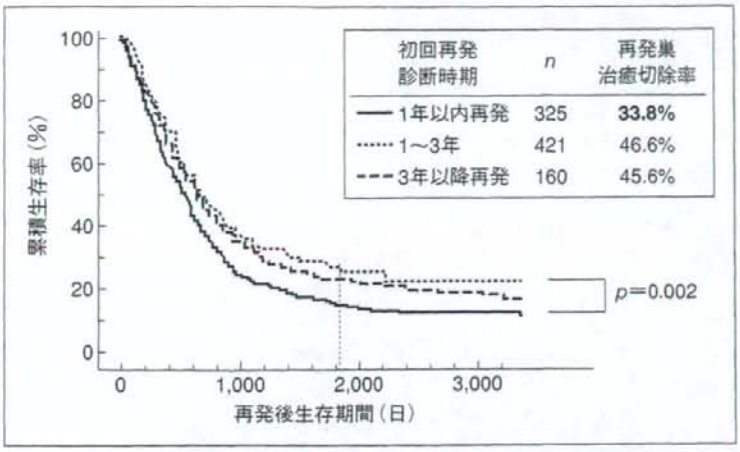


図2. 初回再発診断時期別の再発巣治癒切除率と再発後生存曲線

表2. 大腸癌術後サーベイランスに関するランダム化比較試験

報告者(年)	症例数*	再発率*	再発時期*	再発巣治癒切除率*	5年生存率*
Makela ら[3] フィンランド(1995)	106(52：54)	42%：39% (NS)	10ヵ月：15ヵ月 ($p=0.002$)	22%：14% (NS)	59%：54% (NS)
Ohlsson ら[4] スウェーデン(1995)	107(53：54)	32%：33% (NS)	20ヵ月：24ヵ月 (NS)	29%：17% (NS)	75%：67% (NS)
Kjeldsen ら[5] デンマーク(1997)	597(290：307)	26%：26% (NS)	18ヵ月：27ヵ月 ($p<0.01$)	20%：7% ($p<0.01$)	70%：68% (NS)
Pietra ら[6] イタリア(1998)	207(104：103)	局所再発 25%：19% (NS)	局所再発 10ヵ月：20ヵ月 ($p<0.0003$)	局所再発 65%：10% ($p<0.01$)	73%：58% ($p<0.02$)
Schoemaker ら[7] オーストラリア(1998)	325(167：158)	34%：41% (NS)	—	—	76%：70% (NS)
Secco ら[8] イタリア(2002)	337(192：145)	53%：57% (NS)	—	31%：16% ($p<0.05$)	63%：48% (NS) 再発高危険群 50%：32% ($p<0.05$) 再発低危険群 80%：60% ($p<0.01$)

*intensive 群：対照群

た[3~8](表2)．しかし，これらのRCTをもとに2000年前後に発表された4つのメタアナリシスにおいては，定期的な血清CEA値測定や肝画像検査を含むintensiveなサーベイランスが，再発巣の治癒切除率を高め，生存率を有意に向上させるという結果が示され[9~12](表3)，intensiveなサーベイランスの有用性が認識されるようになった．

元来欧米では，大腸癌の術後サーベイランスとして，定期的な画像検査などは行われてこなかった[13,14]．しかし，これらのメタアナリシスの結果をふまえ，欧米のガイドラインは，定期的な腹部超音波検査やCTを含む，intensiveなサーベイラ

表3. 大腸癌術後サーベイランスに関するメタアナリシス

報告者(年)		症例数*	再発率*	再発時期	再発巣治癒切除率*	予後
Rosen ら[9]	米国 (1998)	2,005(963：1,042)	31%：27% (NS)	—	26%：9%	5年生存率* 62%：48% ($p = 0.003$)
Renehan ら[10]	英国 (2002)	1,342(666：676)	32%：33% (NS)	intensive 群が 8.5ヵ月早い ($p < 0.001$)	—	intensive 群で予後がよい risk ratio：081 ($p = 0.007$)
Jeffery ら[11]	ニュージーランド (2002)	1,342(666：676)	32%：33% (NS)	—	24%：9%	intensive 群で予後がよい risk ratio：0.73 ($p = 0.007$)
Figueredo ら[12]	カナダ (2003)	1,679(858：821)	(NS)	—	—	intensive 群で予後がよい risk ratio：0.80 ($p = 0.0008$)

*intensive 群：対照群

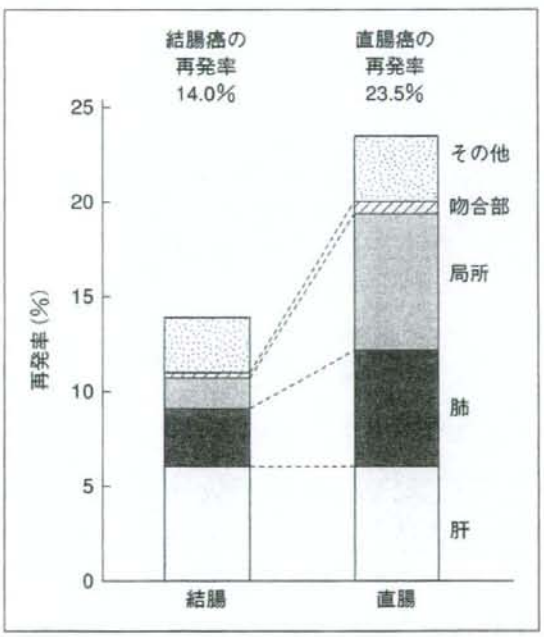
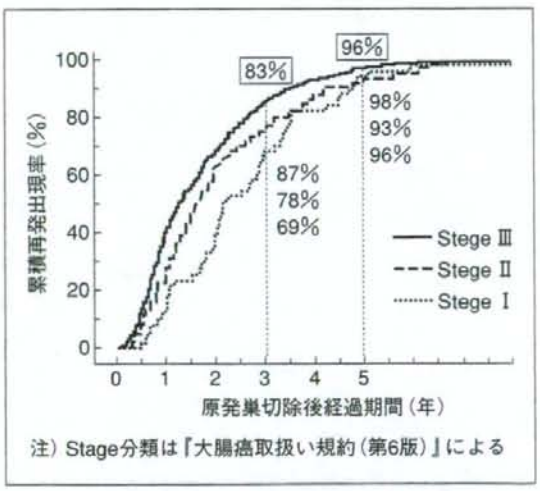


図3. 結腸癌・直腸癌における初回再発部位別再発率の比較(Rsは結腸として集計)



注) Stage分類は『大腸癌取扱い規約(第6版)』による

図4. Stage別累積再発出現率

表4. 欧米のガイドラインにおける大腸癌術後サーベイランスの変化

	ASCO		ESMO	
	2000年[13]	→ 2005年[15]	2001年(結腸癌)[14]	→ 2007年(結腸癌)[16]
診　察	術後3年間は3～6ヵ月ごと 以降は1年ごと	術後3年間は3～6ヵ月ごと 術後4～5年は6ヵ月ごと	術後2年間は6ヵ月ごと	術後2年間は6ヵ月ごと
腫瘍マーカー(CEA)	術後2年間以上は2～3ヵ月ごと (Stage II・III症例)	術後3年以上は3ヵ月ごと (Stage II・III症例)	再発を疑う症状があるとき	術後3年間は3～6ヵ月ごと 術後4～5年は6～12ヵ月ごと
胸部X線検査	CEA上昇時および再発を疑う症状があるとき	—	再発を疑う症状があるとき	術後5年間は1年ごと
腹部超音波検査	—	—	術後3年間は1年ごと	術後3年間は6ヵ月ごと 術後4～5年は1年ごと
CT	—	高リスク群：術後3年間は年1回の胸部・腹部CT 骨盤CT：放射線未照射の直腸癌術後	再発を疑う症状があるとき	高リスク群：術後3年間の胸部・腹部CTを考慮
大腸内視鏡検査	3～5年ごと	術後3年目 正常ならその後5年ごと すべての大腸癌患者は術前にクリーンコロンであることを確認すべきである	5年ごと	術後1年目 その後3年ごと

ASCO：American Society of Clinical Oncology，ESMO：European Society of Medical Oncology

ンスを推奨するように変化した[15,16](表4).

III. 適切な術後サーベイランスとは

では，再発を切除可能な状態で発見するために，どのような間隔で，どれだけの期間，サーベイランスを行うべきであろうか？

術後サーベイランスを行ううえで，再発の特徴(再発の起こりやすい時期，起こりやすい臓器)を認識しておくことはたいへん重要である．前述のプロジェクト研究では，集積した5,317例のうち906例の再発例を詳細に検討し，その結果が『大腸癌治療ガイドライン—医師用(2005年版)』[1,2]に記された．

初回再発臓器のうち，もっとも多いのは肝再発(373例，7.0%)であり，次いで肺再発(251例，4.7%)，局所再発(206例，3.9%)の順であった．直腸癌では結腸癌に比し，有意に再発率が高率であった(23.5%，14.0%，$p<0.001$)．再発臓器では，結腸癌では初回再発の約半数(186例，6.8%)が肝再発であるのに比し，直腸癌では肝再発(96例，7.3%)，肺再発(89例，6.7%)，局所再発(100例，7.6%)がほぼ同数であった(図3)．これより，直腸癌の術後は，結腸癌に比し肺再発・局所再発にも留意すべきである．

また，再発の80%以上が術後3年以内に，95%以上が術後5年以内に診断されていた(図4)．術後5年を超えて診断された再発は，全5,317例のわずか0.6%(33例)のみであった．これより，術後3年までのサーベイランスはintensiveに行い，また少なくとも術後5年間は再発の可能性を念頭におき，サーベイランスを継続すべきであると考える．

おわりに

再発大腸癌を治癒せしめるには，再発を治癒切除可能な状態で発見することが重要であり，術後サーベイランスは，再発大腸癌の診断・治療において，その結果を左右する重要なポイントであるとともに，本邦の良好な治療成績の一端を担っているといえる．

しかし，至適サーベイランス間隔，検査法，費用対効果比など，いまだ解決すべき問題はある．前述したプロジェクト研究の症例集積期間は1991～1996年であり，その後のヘリカルCTの急速な普及に伴い，現在の術後サーベイランスの主流がCTへと変化しているなど，現在とは実情がやや異なっているのも事実である．常に，より新しいデータを集積・検討し，臨床にフィードバックしていくことが望まれる．

症例の集積・検討に多大なご尽力をいただいた「大腸癌術後再発に関するフォローアップに関する研究プロジェクト」参加各施設の先生方に深謝する．

◆◆◆ 文献 ◆◆◆

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お知らせ

◆真菌症フォーラム第10回学術集会

会　　期：2009年2月21日(土)　11：00～18：40(受付：10：00開始)
　　終了後，情報交換会があります．
会　　場：ヒルトン名古屋5階「扇の間」
会　　長：木内哲也(名古屋大学移植外科)
参 加 費：3,000円(抄録集・情報交換会費含む．事前登録はありません)
共　　催：真菌症フォーラム/ファイザー(株)
テ ー マ：「Compromised hostに学ぶ」
プログラム
　招待講演「Compromised hostにおける深在性真菌症―一般臨床への教訓」
　ランチョンセミナー「ハイ・リスクグループにおける深在性真菌症とその対策」
　シンポジウム「Compromised hostにおける深在性真菌症―予防から標的治療まで」
　①Keynote lecture―感染免疫からみた深在性真菌症の病態と対策，②臓器移植領域，③血液領域，④HIV領域，⑤総合討論
演題募集：深在性真菌症全般について，ふるってご応募ください．皮膚科領域の真菌症は対象外とします．
　要望演題(口演発表)：免疫不全下の深在性真菌症の病態・予防・診断・治療に関する演題を募集します．
　一般演題(ポスター発表)：基礎/検査領域，内科系領域，外科系/救急領域
登録期間：2008年8月20日(水)正午～9月25日(木)正午(厳守)
問い合わせ先：〒105-0004 東京都港区新橋2-20 新橋駅前ビル1号館5階
　(株)協和企画コンベンション事業局内
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Surgical Resection of Stage IV Colorectal Cancer and Prognosis

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Abstract
Background Colorectal cancer (CRC) harbors accumulated genetic alterations with cancer progression, which results in uncontrollable disease. To regulate the most malignant CRC, we have to know the most dismal phenotype of stage IV disease.
Methods A retrospective review of the Kitasato University Hospital was performed (from 1990 to 2001) to extract the 162 resected stage IV CRC. Clinical variables were tested for their relationship to survival in a multivariate prognostic analysis and revealed the interaction of the prognostic factors.
Results In stage IV CRC with noncurable resection, the most robust univariate predictors for poor prognosis were preoperative high value of CA19-9, peritoneal dissemination, depth of invasion, age, extent of liver metastases, pathologic lymph node metastasis status, and gender as tumor factors, and postoperative therapy, perioperative transfusion, and lymph node dissection extent as treatment factors. Among these factors, postoperative therapy ($p < 0.0001$), perioperative transfusion (0.0002), CA19-9 (0.001), extent of liver metastases (0.004), and peritoneal dissemination (0.02) were identified as independent prognostic factors by multivariate analysis. Interestingly, among the independent prognostic factors, treatment factors did not depend upon tumor factors and the combination of the three tumor factors (CA19-9, extent of liver metastases, and peritoneal dissemination) can clearly classify the patients into the definite prognostic groups.
Conclusion Our results suggested that the most dismal CRC harbors three definite vectors that may represent the strongest phenotype of putative systemic immune (CA19-9), distant metastasis (extent of liver metastases), and local progression (peritoneal dissemination).

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Introduction

Colorectal cancer (CRC) is the second most prevalent cancer and the fourth leading cause of cancer death worldwide, causing about 530,000 deaths every year [1]. Complete surgical resection of primary CRC and metastases remains the only potentially curative therapy [2]. On the other hand, for stage IV CRC involving synchronous distant metastases or peritoneal dissemination, the prognostic impact of primary tumor resection is not well documented so that both biological behavior and optimal treatment strategy have not been well established so far.

CRC is a genetic disease and accumulated genetic alterations result in cancer progression, leading to uncontrollable disease [3]. Therefore, the identification of genetic alterations in the most dismal prognostic phenotype of CRC would be beneficial for the development of novel diagnostic and treatment options.

Stage IV disease is curatively uncontrollable by any treatment modality, and previous studies suggested that patients with stage IV CRC comprise heterogeneous groups with clinicopathologic predictors that identify subgroups with significantly different prognoses such as lymph node metastasis [4, 5], peritoneal dissemination [4, 5], extent of liver metastases [5–8], depth of primary tumor invasion

[5], age [8], preoperative CA19-9 [9], and preoperative CEA [8, 10].

In this study, we simultaneously validated all such promising clinical parameters reported so far and extracted the excellent combination of prognostic predictors as the most dismal phenotype of CRC. Then we suggested that the three definite vectors may represent the strongest phenotype of putative systemic immune, distant metastasis, and local progression. These prognostic indicators would be the clue for the therapeutic target of CRC.

Patients and methods

Registration and characteristics of patients with stage IV CRC after resection of primary cancer

A total of 1101 patients underwent surgical resection of primary CRC at the Kitasato University Hospital from January 1, 1990, to March 31, 2001, and all were entered into a retrospective database. From this patient source, we identified 946 patients with sporadic CRC, among which we identified 183 patients with stage IV CRC disease (19%) using the JCCC (Japanese Classification of Colorectal Cancer) [11] staging system. Exclusion criteria included operative or other disease-related death, extracolorectal or intracolorectal multiple cancers with previous histologic documentation, and insufficient clinical data such as preoperative tumor marker. The remaining 174 stage IV CRC patients were divided into two groups according to whether they underwent curable operation ($n = 12$) or not ($n = 162$), because as curably resected liver metastasis has been reported as having excellent outcome, hepatic resection has gained wide acceptance as safe and successful treatment [12] (Fig. 1).

The clinical parameters of the remaining 162 patients are depicted as noncurable stage IV CRC in Table 1. D2/D3 lymph node dissection was performed in 135 patients

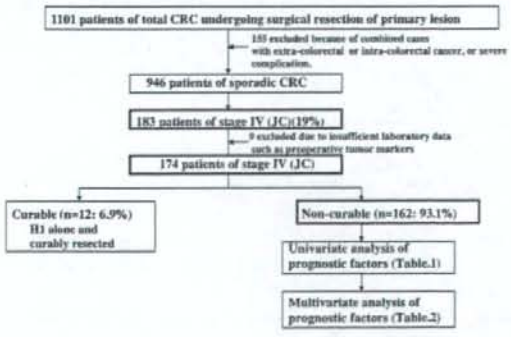

Fig. 1 Flow chart of patient selection. Stage IV CRC cases were 19% of total sporadic CRC cases. JC, Japanese classification

(83%) as the standard therapy, and the remaining 27 patients were restricted to D0/D1 lymph node dissection because of the severe condition of the heart, lung, kidney, or liver. Forty-five operators participated. The average survival was 14.9 months and the 5-year survival rate was 2.6%. All patients were informative for prognosis, namely, death within 5 years or alive at 5 years, and there were four censored cases. These censored cases were four patients who died from organ complications including one from ischemic heart disease, one from chronic renal failure, one from cerebrovascular disease, and one from postoperative complication (pneumonia).

In both the JCCC and the UICC (Unio Internationalis Contra Cancrum) staging system, stage IV CRC includes those patients with distant metastasis and extraregional lymph node metastasis (M in TNM classification). Moreover, in the JCCC staging system, metastasis contains those with peritoneal dissemination, so M is broken down into hepatic metastasis (H), extraregional lymph node metastasis, and peritoneal dissemination (P). For patients with hepatic metastases, hepatic tumor burden was defined according to the JCCC staging system: H1 (up to 4 hepatic metastases and $\leq$5 cm in maximum tumor size), H2 (neither H1 nor H3), and H3 ($\geq$5 hepatic metastases and >5 cm in maximum tumor size). Patients without hepatic metastases were defined as H0 (Table 2). This classification of the H factor was based on the grading of liver metastases that consisted of metastatic tumor size and number in terms of prognostic difference [13]. Because T and N factors are the usual terms used in the TNM classification, we used T and N factors in the Japanese classification, which is the same as the TNM classification except for detailed subdivisions in N. N values were scored by pathologic reports (pN).

Patient demographics, tumor characteristics, and postoperative course were recorded and analyzed. Perioperative transfusion (POT) was defined as allogeneic blood transfusion during the operation or during the first two postoperative days [14]. POT was performed at the discretion of the treating surgeons and anesthesiologists. Postoperative therapy (PTx) included chemo-immunotherapy and radiation therapy; chemo-immunotherapy consisted of various 5-FU-based chemotherapies (e.g., 5-FU alone, 5-FU/mitomycin-C, or 5-FU/leucovorin). In this period, we could not use irinotecan or oxaliplatin. Tumor stage and grade were classified according to the 7th edition (the latest version) of JCCC staging system [11].

Statistical analysis

Statistical computations were performed using SAS StatView version 5.0 (SAS Institute, Cary, NC). A result was considered statistically significant when $p < 5\%$ ($p < 0.05$). The time of follow-up was calculated from the

Table 1 Univariate analysis of 162 stage IV noncurable CRCs

Parameters	No. of patients	%	DSS	
			Average survival (months)	p^*
Gender				
Male	95	59	16.5	0.04
Female	67	41	12.8	
Age				
<60	66	41	18.2	0.01
≥60	96	59	12.6	
Tumor position				
Colon	97	60	15.1	NS
RS	24	15	12.8	
Rectum	41	25	15.9	
Differentiation				
Nonpoor	135	83	15.4	NS
Poor[a]	27	17	12.8	
T factor				
T2,3	149	92	15.6	0.002
T4	13	8	7.5	
pN factor				
pN0, 1, 2	121	75	16.0	0.04
pN3, 4	41	25	11.9	
ND (%)				
<20	56	35	16.7	NS
≥20	106	65	13.8	
H (extent of liver metastasis)				
H0	44	27	16.3	NS
H1, 2, 3	118	73	14.4	
H0, 1	63	39	17.9	0.03
H2, 3	99	61	13.1	
LM				
LM0	128	79	15.2	NS
LM1, 2, 3	34	21	13.8	
P category				
P0	111	69	16.8	0.002
P1, 2, 3	51	31	11.1	
CEA				
Normal	30	19	18.5	NS(0.09)
Elevated	132	81	14.1	
CEA				
<100 (ng/ml)	113	70	17.7	<0.0001
≥100 (ng/ml)	49	30	8.7	
CA19-9				
Normal	76	47	19.9	<0.0001
Elevated	86	53	10.7	
LNDE				
D0, 1	27	17	7.2	<0.0001
D2, 3	135	83	16.4	
Perioperative transfusion (POT)				
Yes	68	42	11.2	0.0005
No	94	58	17.6	
Postoperative therapy (PTx)				
Yes	129	80	17.2	<0.0001
No	33	20	5.6	

DSS = disease speceific survival; NS = not significant; pN = pathologic N factor; ND = lymph node metastatic density; LM = lung metastasis; P = peritoneal dissemination; LNDE = lymph node dissection extent

* Log-rank test

[a] Poor consists of poorly differentiated, mucinous, and undifferentiated types

Table 2 Definition of hepatic metastasis (H) and peritoneal dissemination (P) in Japanese classification

H		P	
X	Hepatic metastasis cannot be assessed	X	Peritoneal metastasis cannot be assessed
0	No hepatic metastasis	0	No peritoneal metastasis
1	Four lesions or less hepatic metastases and ≤5 cm in maximum size	1	Peritoneal metastases to the adjacent but not to the distant peritoneum
2	Hepatic metastasis other than H1 and H3	2	A few metastases to the distant peritoneum
3	Five or more hepatic metastases and >5 cm in maximum size	3	Numerous metastases to the distant peritoneum

date of the first operation. Disease-specific survival (DSS) was estimated according to the Kaplan-Meier method and compared using the log-rank test [15]. A Cox's proportional hazard model was built using the variables that had prognostic potential suggested by univariate analysis ($p < 0.1$) [16]. On the other hand, multivariate logistic regression analyses were performed for the significant univariate prognostic predictors of tumor factors and treatment factors to reveal the interaction.

Results

Univariate prognostic analysis in 162 noncurable stage IV CRCs

Table 1 shows the univariate prognostic factors on disease-specific-survival (DSS). Preoperative CA19-9 ($p < 0.0001$), H factor (H0, 1 or H2, 3) (0.03), P factor (0.002), T factor (0.002), age (0.01), gender (0.04), pathologic N (pN) factor (0.04), lymph node dissection extent (LNDE) (<0.0001), perioperative transfusion (POT) (0.0005), and postoperative therapy (PTx) (<0.0001) were associated with a poor outcome in noncurable stage IV CRC, and Kaplan-Meier curves are shown in Fig. 2 (A: CA19-9, B: H factor, C: P factor). On the other hand, preoperative CEA did not show significant association with prognosis (0.09).

Multivariate characterization of prognostic factors

The attempt at building a multivariate model for DSS was done using Cox's proportional hazard model analysis. Included were all factors that had prognostic potential as suggested by the univariate analysis ($p < 0.1$). The model defined preoperative CA19-9 ($p = 0.001$), H factor (0.004), and P factor (0.02) as independent prognostic tumor factors, and postoperative therapy (PTx) (<0.0001) and perioperative transfusion (POT) (0.0002) as independent prognostic treatment factors (Table 3). Preoperative CEA, pN factor, T factor, and gender were eliminated after multivariate analysis.

To reveal the interaction between both independent and dependent prognostic factors, multivariate logistic regression analyses were also performed. For example, the results of multivariate logistic regression analyses of tumor factors (preoperative CA19-9, H factor, and P factor) and treatment factors (PTx, POT, and LNDE) are given in Tables 4 and 5, respectively. H factor was significantly related to preoperative CA19-9 and P factor. Preoperative CEA was a predictor for preoperative CA19-9 and H factor. Similarly, pN factor, over 20% of lymph node metastasis density (ND20), T factor, and gender were involved in P factor. PTx and LNDE were significantly correlated with each other and both were associated with age. Unexpectedly, LNDE was related to preoperative CA19-9. Multivariate logistic regression analysis revealed the interrelationship of the univariate prognostic factors as shown in Fig. 3. Among tumor factors, three independent prognostic factors were CA19-9, H factor, and P factor, where CA19-9 and H factor are interrelated and H factor and P factor are also mutually associated. Intriguingly, P factor was related to T factor, pN factor, and ND20, suggesting that it represents the most dismal phenotype of local progression. As treatment factors, PTx and POT remained independent prognostic factors, but these could not be associated with the three independent prognostic tumor factors (Fig. 3), suggesting that treatment factors were not affected by the independent tumor prognostic factors.

Combination of the independent prognostic tumor factors and prognosis in noncurable stage IV CRC

We believe that tumor factors are constant and treatment factor could be affected by a physician's judgment. We then focused on remnant-independent prognostic tumor factors (CA19-9, H factor, and P factor) and examined whether a combination of them could actually predict the definite patient prognosis at staging (Fig. 4). We assigned positivity of 0 factor ($n = 23$), 1 or 2 factors ($n = 122$), and 3 factors ($n = 17$) among the three independent prognostic tumor factors to the staging group A, B, and C, respectively. Group A showed the best prognosis (average survival = 25.1 months), followed by group B (14.4 months) and the most dismal group C (5.4 months) (A vs B, $p = 0.002$; B vs C, $p < 0.0001$).

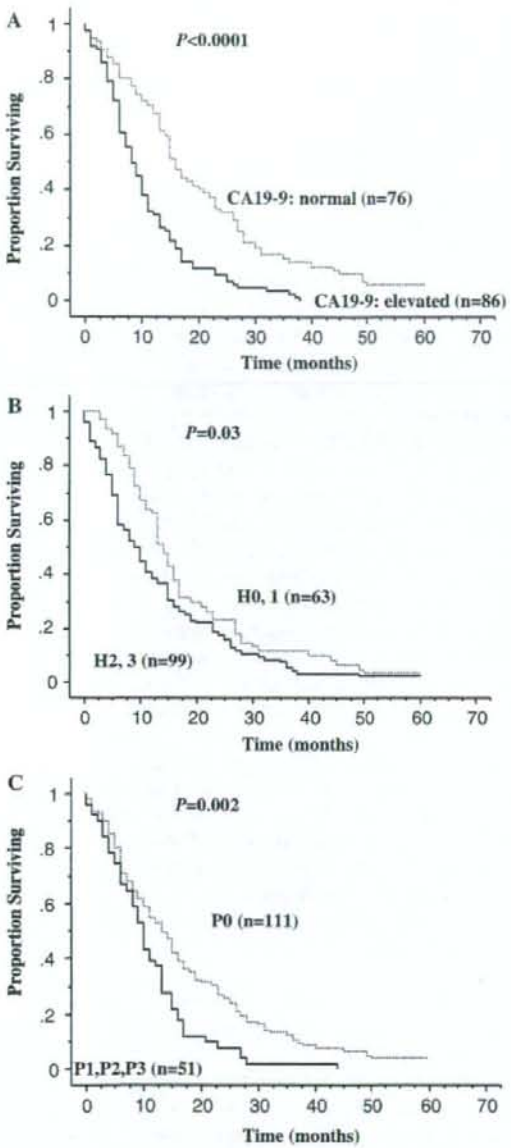

Fig. 2 Disease-specific survival of noncurable stage IV CRC after resection of primary lesion by Kaplan-Meier analysis. (**A**) Preoperative CA19-9; (**B**) H factor; and (**C**) P factor

Discussion

Our primary goal was to identify tumor factors reflecting the most dismal phenotype of CRC in order to know the therapeutic target. Our multivariate analysis revealed high-hazard risks for preoperative CA19-9 (1.93), H factor (1.78), and P factor (1.69), which were identified as the most potent independent prognostic factors in noncurable stage IV CRC among tumor factors (Table 3), and the combination was proven to be an excellent predictor of definite survival (Fig. 4). Interestingly, these three tumor factors are independent of treatment factors (Fig. 3). Previous multivariate analysis of stage IV CRC revealed that the independent prognostic tumor factor was preoperative CA19-9, where H factor was classified as solitary or not and eliminated by multivariate analysis; moreover, P factor was not included in the patient's characteristics [9]. Hotta et al. [4] also reported that lymph node metastasis and peritoneal dissemination were final remnant prognostic

Table 3 Multivariate analysis of factors associated with disease-specific survival of stage IV noncurable CRC

Variable	HR	95%CI	*p* value
CA19-9	1.93	1.29–2.89	0.001
H factor (H0, 1 or H2, 3)	1.78	1.20–2.63	0.004
P factor	1.69	1.11–2.59	0.02
Age	1.25	0.87–1.81	NS
pN factor	1.29	0.85–1.96	NS
T factor	1.57	0.80–3.08	NS
Gender	1.24	0.86–1.79	NS
CEA	0.96	0.60–1.53	NS
PTx	2.89	1.76–4.77	<0.0001
POT	1.98	1.38–2.86	0.0002
LNDE	1.62	0.97–2.70	NS

HR = hazard ratio; CI = confidence interval; P = peritoneal dissemination; pN = pathologic N factor; PTx = postoperative therapy; POT = perioperative transfusion; LNDE = lymph node dissection extent

Table 4 Multivariate logistic regression analysis of tumor factors

	Preoperative CA19-9		H factor		P factor	
	OR	*p*	OR	*p*	OR	*p*
Preoperative CA19-9	–	–	2.72	0.003	1.78	NS
H factor	2.72	0.003	–	–	0.26	0.0002
P factor	1.78	NS	0.26	0.0002	–	–
Age	1.23	NS	1.15	NS	0.87	NS
Differentiation	0.89	NS	1.58	NS	0.42	NS (0.05)
pN factor	1.03	NS	0.58	NS	2.77	0.007
ND20	0.58	NS	1.38	NS	0.30	0.0008
T factor	2.10	NS	0.72	NS	3.94	0.02
Gender	0.51	0.04	1.70	NS	0.35	0.003
Preoperative CEA	7.94	<0.0001	6.10	<0.0001	0.53	NS

OR = odds ratio; ND20 = node density 20%; CEA = carcinoembryonic antigen

Table 5 Multivariate logistic regression analysis of treatment factors

	Postoperative therapy		Perioperative transfusion		LNDE	
	OR	*p*	OR	*p*	OR	*p*
CA19-9	2.03	NS	0.89	NS	4.88	0.003
H factor	1.92	NS	1.05	NS	2.03	NS
P	1.32	NS	1.35	NS	0.90	NS
Age	3.91	0.01	0.79	NS	4.88	0.01
pN factor	1.97	NS	2.16	0.04	1.04	NS
T factor	1.19	NS	2.37	NS	0.90	NS
Gender	1.30	NS	0.74	NS	1.24	NS
CEA	2.65	NS	1.11	NS	3.27	NS
PTx	–	–	3.05	0.006	8.13	<0.0001
POT	3.05	0.006	–	–	0.78	NS
LNDE	8.13	<0.0001	0.78	NS	–	–

OR = odds ratio; CEA = carcinoembryonic antigen; PTx = postoperative therapy; POT = perioperative transfusion; LNDE = lymph node dissection extent

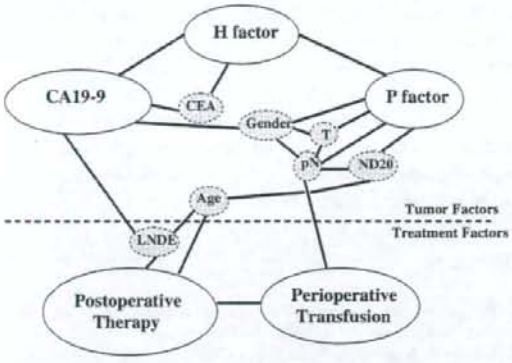

Fig. 3 Interrelationship of independent prognostic factors according to logistic regression analyses. White boxes are independent prognostic factors. Gray boxes are dependent prognostic factors. These factors reflect associated independent prognostic factors

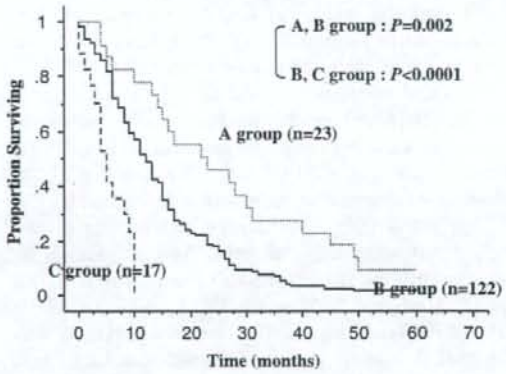

Fig. 4 Combination of independent prognostic tumor factors extracted from multivariate analysis. Preoperative CA19-9, H factor, and P factor were combined to predict patient survival of noncurable stage IV CRC. Definitions of groups A, B, and C were given in the Results section. The statistical difference was found between groups A and B ($p = 0.002$), and between groups B and C ($p < 0.0001$)

factors, where H factor (classified as solitary or not) was eliminated and CA19-9 was not informative for the analysis. The present study is the first multivariate analysis that examined all the possible tumor factors to predict stage IV CRC patient outcome.

In this study, when patients were divided into H0, 1 group and H2, 3 group, H factor (H0, 1 or H2, 3) was the independent prognostic tumor factor in noncurable stage IV CRC (Table 3), whereas H factor would not be univariate prognostic factor when divided into H0 or not (Table 1). Using this criterion, we could extract H factor as the independent prognostic factor, which is different from the literature [4, 9]. Classification of H0, 1 vs. H2, 3 may represent multiple metastasis-prone phenotype (H2, 3) and other phenotypes (H0, 1). There have been numerous reports about identification of the molecules that differentiated liver metastasis from localized primary CRC by means of the microarray method [17] or SAGE analysis [18]. However, there have not been any reports that compared the two phenotypes H0, 1 and H2, 3 in the JCCC staging system. Hereafter, we plan to identify oncogenes and tumor suppressor genes that explain rigorous growth of multiple liver metastasis [19, 20].

As to P factor, T factor, ND, gender, and pN factor were predictors in our multivariate logistic regression analysis (Table 4, Fig. 3). It is quite intriguing that these predictors for P factor represent local progression and were eliminated after multivariate analysis. Finally, we may insist that P factor could be one of the most robust phenotypes of local progression in CRC. Tanaka et al. [21] reported a correlation between extranodal invasion of lymph nodes and peritoneal dissemination in gastric cancer. In the present study, lymphatic progression significantly correlated with P factor, supporting this hypothesis in CRC, too.

It is surprising that only one glycoform, serum CA19-9, predicts prognosis more strongly than the powerful prognostic phenotypes of H factor (H2, 3) and P factor. In our multivariate logistic regression analysis, H factor was significantly correlated with preoperative CA19-9 (Table 4), but both were involved in prognosis independently. These findings could support the intriguing hypothesis that CA19-9 makes the oncogenic disease more systemic through something different than tumor-bearing metastatic ability, and its inhibition is promising as a metastatic controller. Matsumoto et al. [22, 23] showed that blocking CA19-9 by cimetidine is beneficial to CRC patient outcome. This could also allow for the classical hypothesis that CA19-9 enhances extravasation and metastasis by interaction with E-selectin expressed on endothelium [24].

From the earlier publications, we may propose the following three mechanisms of CA19-9 involving systemic dissemination of cancer cells: (1) There was a report that described tumor-produced mucins expressing CA19-9 (sialyl Le^a) lead the immune status to Th2 dominance [25]. For tumor rejection by the immune system, appropriate Th1 dominance is believed to be more critical [26, 27]. (2) Mucins expressing CA19-9 were associated with the induction of inflammatory molecules in human cancers [25, 28], suggesting chronic stimulation of E-selectin expression on systemic endothelial cells. Such preparation for metastasis may be associated with systemic metastasis. (3) Finally, P-selectin, another specific ligand for CA19-9, may be involved in promoting tumor aggregation with platelet [29], leading to cancer cell metastasis [30]. These studies suggest that CA19-9 could facilitate systemic metastasis not only by the mechanisms of selectin-related progression but also by immune evasion, which may be the reason why only one glycoform, CA19-9, predicted prognosis more significantly than the phenotypes of H factor and P factor.

Preoperative CEA was not an independent prognostic factor in this study (Table 3), which is different from that found in other reports [8, 10]. Lack of predictive effect of CEA might be affected by the fact that not all patients would be CEA producers. However, we would rather consider that the reason was because preoperative CEA was strongly correlated with preoperative CA19-9, and preoperative CA19-9 was a more robust prognostic predictor than preoperative CEA (Table 4). When using a cutoff level for preoperative CEA at 100 ng/ml, CEA was in fact the most robust independent prognostic factor instead of preoperative CA19-9 (hazard ratio = 1.99, $p = 0.001$). The cutoff level of CEA (100 ng/ml) may be of clinical and biological importance; however, use of this cutoff level is unusual in practical medicine, so we did not use it in the present model. In our study, CEA was the predictor for H factor, because published articles reported an association of CEA with liver metastasis [31, 32], and preoperative CEA did not predict P factor (Fig. 3, Table 4).

In this study, PTx and POT were the most robust independent treatment prognostic indicators (Table 3). Nevertheless, we do not conclude that treatment factors are significant effectors against stage IV CRC. Because such factors contained a variety of therapies and were affected by surgeon intuition, they could not be constant, which is different than tumor factors. We would need further prospective study under unified eligibility, on condition of the same treatment, in order to validate the prognostic effect of tumor factors which we identified in this study.

In conclusion, we propose the hypothesis that the most dismal phenotypes of noncurable CRC may be determined by three definite vectors: putative immunologic indicator, CA19-9; metastatic indicator, H factor; and local progression indicator, P factor. However, these three factors are collinear in the present study, with the exception of the interaction of CA19-9 and P factor, although they are independent prognostic predictors. Therefore, in the near future we plan to assess these three tumor factors by prospective validation to see whether they are bona fide prognostic determinants in a multivariate analysis adjusted for the collinear factors.

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Phase II Trial to Evaluate Laparoscopic Surgery for Stage 0/I Rectal Carcinoma

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Clinical Trial Notes

Phase II Trial to Evaluate Laparoscopic Surgery for Stage 0/I Rectal Carcinoma

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Recently reported randomized controlled trials demonstrated that laparoscopic surgery (LS) was comparable or superior to open surgery with regard to the long-term outcome for colon and rectosigmoidal carcinoma; however, controversy persists with regard to the appropriateness of LS for patients with rectal carcinoma. To examine the technical and oncological feasibility of LS for rectal carcinoma, a phase II trial was started in patients with a preoperative diagnosis of Stage 0/I rectal carcinoma, under the direction of the Japan Society of Laparoscopic Colorectal Surgery. Surgeons in 39 specialized institutions will recruit 350 patients. The primary end-point in the first stage is the anastomotic leakage rate by double-stapling technique and that in the second stage is overall survival. Secondary end-points are relapse-free survival, short-term clinical outcome, adverse events, the rate of histologically curative operation, the proportion of completion of LS and the conversion rate.

Key words: laparoscopic surgery – rectal carcinoma – phase II trial

INTRODUCTION

Recently reported randomized controlled trials (RCTs) demonstrated that laparoscopic surgery (LS) was comparable or superior to open surgery with regard to the long-term outcome for colon and rectosigmoidal carcinoma (1–6); however, controversy persists with regard to the appropriateness of LS for patients with rectal carcinoma because of the uncertainty of the long-term outcome, and of concerns over the safety of the procedure (7–10).

Despite many reports of LS for advanced rectal carcinoma in Western countries, advanced rectal carcinoma is seldom treated laparoscopically in Japan. Lateral lymph node dissection combined with total mesorectal excision remains the standard surgical procedure for patients with advanced lower rectal carcinoma in Japan, and lateral lymph node dissection by laparoscopy is still an unexplored frontier (11–13). Moreover, LS for rectal carcinoma remains controversial because of concerns over the safety of the procedure, especially in low anterior resections for lower rectal carcinoma.

With regard to the complications of LS for rectal carcinoma, the most difficult complication is anastomotic leakage. In rectal carcinoma, anastomotic leakage requires not only prolonged hospitalization, but also a temporary or permanent stoma in some patients, thereby resulting in unavoidable deterioration in their quality of life. Moreover, anastomotic leakage may cause fatal peritonitis, or may promote intrapelvic recurrence in some cases. To examine the technical and oncological feasibility of LS for rectal carcinoma, a phase II trial has started in patients with a preoperative diagnosis of Stage I rectal carcinoma, under the direction of the Japan Society of Laparoscopic Colorectal Surgery, of which leading hospitals in LS for colorectal carcinoma in Japan are members.

The study protocol was approved by the Ethics Committee of the Japanese Society for Cancer of the Colon and Rectum

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(JSCCR) on 2 August 2007, and the study was started on February 2008.

PROTOCOL DIGEST OF THE STUDY

Purpose

The purpose of this study is to evaluate short- and long-term outcomes of LS for clinical stage 0/I rectal carcinoma.

Study Setting

A multi-institutional (39 specialized centers), non-randomized and one-arm (laparoscopic) trial (phase II).

Resources

Research grant from JSCCR.

End-points

The primary end-point in the first stage is the anastomotic leakage rate by double-stapling technique (DST) and that in the second stage is overall survival. Secondary end-points are relapse-free survival, operative mortality rate, the rate of histologically curative operation, the proportion of completion of LS, conversion rate, intraoperative and postoperative complication rate, re-operation rate and postoperative hospital stay.

All laparoscopic cases, which require skin incision >8 cm, are counted as a conversion, except for those in which retrieval of the resected specimen alone requires this length of incision. The completion of LS is defined as the completion of the curative operation without conversion.

Eligibility Criteria

Tumors are staged according to the TNM classification system. Tumor location was defined according to the JSCCR General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus (14). When the tumor was located between the inferior margin of the second sacral vertebra and the peritoneal reflection, the location was recorded as the upper rectum. When the tumor was located below the peritoneal reflection, its location was recorded as the lower rectum. The location of the tumor was determined by pelvic CT scan, colonoscopy and/or barium enema preoperatively and confirmed during surgery.

Inclusion Criteria

For inclusion in the study, patients must fulfill the following requirements preoperatively:

(i) Histologically proven rectal adenocarcinoma.
(ii) Tumor located in the rectum.
(iii) Clinical Tis-T2/N0/M0.
(iv) Without multiple lesions other than carcinoma *in situ*
(v) Tumor size ≤ 8 cm.
(vi) Age ≥ 20 and ≤ 75 years.
(vii) No bowel obstruction.
(viii) No history of major colorectal surgery.
(ix) No prior chemotherapy or radiotherapy for any malignancy.
(x) Sufficient organ function.
(xi) Written informed consent.

Exclusion Criteria

Exclusion criteria are as follows:

(i) Synchronous or metachronous (within 5 years) malignancy other than carcinoma *in situ*.
(ii) Pregnant or lactating women.
(iii) Severe mental disease.
(iv) History of acute myocardinal infarction within 6 months before registration, or unstable angina.
(v) Severe pulmonary emphysema, interstitial pneumonitis or ischemic heart disease.
(vi) Continuous systemic steroid therapy.

Registration

Eligible patients are registered by calling the registration office at Kitasato University after confirmation of the inclusion/exclusion criteria. An eligibility report form is sent to the Data Center at the Clinical Trial Coordinating Office at the National Cancer Center Hospital.

Quality Control of Surgery

Surgeons with experience of more than 30 laparoscopic and 30 open operations for rectal carcinoma are accredited by the study chair. To control the quality of the operation, only accredited surgeons participated in this study. We perform a central review of the surgical procedure by photographing all patients and by videotape of arbitrarily selected patients.

Treatment Method

Laparoscopic resection of the rectum with adequate lymphadenectomy is performed according to the JSCCR General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus (14). The extent of lymphadenectomy and site of ligation and division of the inferior mesenteric vessels were decided by the surgeon in charge. Pneumoperitoneal approaches are used to explore the abdomen, mobilize the left-side colon, identify critical structures and ligate the vascular pedicle. Mobilization of the rectum, excision of the mesorectum, rectal transection, removal of the specimen and reconstruction are performed

by the pneumoperitoneal approach or the extracorporeal approach via a small incision (<8 cm). For sphincter-preserving operations, the decision to make a protective ileostomy is based on the surgeon's technical evaluation of the quality of the anastomosis. Hand-assisted LS is permitted when required for the control of intraoperative complications, but sliding window and moving window methods are not permitted. When an incision longer than 8 cm is required for the control of intraoperative complications or tumor extension, the operation is counted as a conversion.

Additional Treatment

When pathological stage III, assessed by histological examination of the resected specimen, is reached three cycles of adjuvant chemotherapy with fluorouracil (500 mg/m^2 by bolus infusion on Days 1, 8, 15, 22, 39 and 36) and L-leucovorin (250 mg/m^2 by 2 h drip infusion on Days 1, 8, 15, 22, 39 and 36) are recommended.

Follow-up

For surveillance after curative surgery, patients are observed periodically by their surgeon: every 12 months for 5 years for pathological stage 0/I patients; every 4 months for the first 2 years and then every 6 months for 3 years for pathological stage II/III patients. Blood tests, abdominal and pelvic computed tomography and plain chest X-ray are carried out at each visit.

Study Design and Statistical Method

This trial has been designed to evaluate the feasibility of LS for rectal carcinoma in terms of short- and long-term outcome.

In the first stage, the expected anastomotic leakage rate by DST is 12% and the threshold value is 20%. The sample size has been calculated as 160 DSTs (one-sided $\alpha = 0.05$ and $\beta = 0.1$). If the anastomotic leakage rate is higher than the permitted rate, LS for rectal surgery is not accepted. If the leakage rate is within the permitted rate, we move on to the second stage to evaluate oncological safety. In the second stage, the expected 5-year overall survival rate is 88% and the threshold value is 83%. The sample size has been calculated as 350 (one-sided $\alpha = 0.05$ and $\beta = 0.2$). The planned accrual period is 3 years, and the follow-up period has been set as 5 years after completion of accrual.

Interim Analysis and Monitoring

The Data and Safety Monitoring Committee (DSMC) independently review the trial monitoring report with regard to efficacy and safety data from the present study. Based on this monitoring, DSMC can consider early termination of a treatment regimen during the study and modification of the study protocol, including increasing the sample size if no definitive selection is possible at the end of study. Protocol compliance, safety and on-schedule study progress are also monitored by the DSMC.

ClinicalTrials.gov Registration

This study protocol was registered in the ClinicalTrials.gov (NCT00635466), a service of the United States National Institute of Health, on 14 March 2008 (http://clinicaltrials.gov/ct2/show/NCT00635466).

PARTICIPATING INSTITUTIONS

Sapporo Medical University, Iwate Medical University, Sendai City Medical Center, Sendai Open Hospital, Jichi Medical University, Jichi Medical University Saitama Medical Center, Saitama Medical University International Medical Center, National Cancer Center Hospital East, Juntendo University Urayasu Hospital, Juntendo University Hospital, Cancer Institute Hospital of Japanese Foundation for Cancer Research, National Cancer Center Hospital, Keio University Hospital, Tokyo Medical and Dental University Hospital, Toho University School of Medicine Ohashi Medical Center, Kitasato University Hospital, Showa University Northern Yokohama Hospital, Yokohama City University Medical Center, St Marianna University Hospital, Ishikawa Prefectural Central Hospital, Fukui Prefecture Saiseikai Hospital, Nagano Municipal Hospital, Fujita Health University, Kyoto Prefectural University of Medicine, Kyoto Medical Center, Kyoto University, Osaka Red-cross Hospital, Osaka University, Osaka Medical College, Minoh City Hospital, Suita Municipal Hospital, Nishinomiya Municipal Hospital, Fukuyama City Hospital, Hiroshima University Hospital, Yamaguchi University Graduate School of Medicine, Shikoku Cancer Center Hospital, Kochi Medical School, Kochi Health Sciences Center, Oita University Faculty of Medicine.

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Conflict of interest statement
None declared.

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本邦における直腸癌に対する腹腔鏡下手術の現況
—腹腔鏡下大腸切除研究会多施設共同研究—

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Key words◆腹腔鏡下手術，進行直腸癌，腹腔鏡大腸切除研究会

◆要旨：腹腔鏡下手術は，骨盤内操作において開腹手術では得られない良好な視野展開が可能である．骨盤内の解剖を熟知し，手術手技に習熟することで，徐々に本法の適応を拡大していくことが肝要である．しかし，腫瘍学的要因から，すべての直腸癌が腹腔鏡下手術の適応となるわけではない．特に直腸癌手術には，根治性の向上と機能温存が求められている．進行癌では，現在もなお標準的治療が確立されていないのが現状で，無作為臨床試験の結果が得られた後に，標準治療が確立される段階である．これまで，腹腔鏡下大腸切除研究会が中心となり，cT1，cT2直腸癌に対する腹腔鏡下手術の第Ⅱ相臨床試験が予定されている．この結果をふまえ，進行直腸癌に対する腹腔鏡下手術の適応を再考することになろう．進行直腸癌に腹腔鏡下手術を適応拡大していく際は，自律神経を温存し局所再発を制御する安全な手術手技の確立が重要である．側方郭清に関する臨床試験結果や術前化学放射線治療を併用することなども視野に入れて，慎重に検討していく必要がある．

はじめに

腹腔鏡下大腸切除術の適応は，早期癌から進行癌に徐々に拡大されてきた．特に直腸癌に対しては，骨盤内の解剖を熟知したうえで，確実な視野展開が行われれば，本法の拡大視効果のもと安全な手術が施行可能である．大腸癌治療ガイドライン[1]では，腹腔鏡下手術の適応は，結腸癌および直腸S状結腸移行部（Rs）癌のうちstage 0およびstage Ⅰとされている．一方，2004年から開始された日本臨床腫瘍研究グループ（JCOG）による，盲腸，上行結腸，S状結腸，Rs癌で，術前診断がstage Ⅱ，stage Ⅲ症例に対する開腹と腹腔鏡下手術の治療成績を検討する大規模無作為比較試験（JCOG 0404）[2]の結果に基づく適応拡大が期待されている．ただし，直腸癌に対する腹腔鏡下手術に関しては，ガイドラインには記載されていないのが現状であり，また進行直腸癌については標準治療も各施設により異なることも多い．

本稿では，腹腔鏡下大腸切除研究会が中心となり，国内で大腸癌に対して積極的に腹腔鏡下手術を施行している24施設に腹腔鏡下直腸癌手術に

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