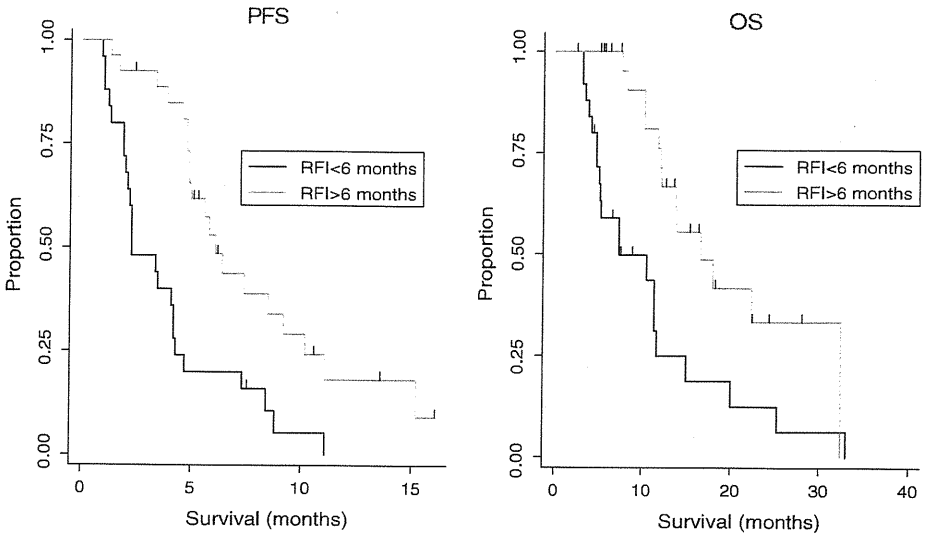

Fig. 2 Progression-free survival (*PFS*) and overall survival (*OS*) according to the length of the recurrence-free interval (*RFI*). Patients with an RFI of ≥6 months had a significantly longer median PFS (6.2 vs. 2.3 months, $P < 0.001$) and OS (16.6 vs. 7.3 months, $P = 0.003$) than patients with an RFI of <6 months. *RFI* recurrence-free interval, PFS progression-free survival, OS overall survival

relatively worse compared with those in the SPIRITS study [4]. However, our results also suggested that patients with an RFI of ≥6 months who received S-1 plus cisplatin had a significantly better response rate, longer PFS, and longer OS compared to patients with an RFI of <6 months. The efficacy of S-1 plus cisplatin for patients with an RFI of ≥6 months in this study was almost compatible with that of patients in the SPIRITS trial in terms of PFS and OS, although these results should be interpreted cautiously due to the heterogeneity of the characteristics of the patients in the two studies. Although no prospective study has evaluated any chemotherapy specifically for patients who have failed adjuvant S-1, Kang and colleagues [15] conducted a phase II study of capecitabine plus cisplatin for 32 patients with gastric cancer that recurred after adjuvant chemotherapy with doxifluridine or 5-FU-containing regimens. They reported a response rate of 28% and a median TTP of 5.8 months, and concluded that capecitabine plus cisplatin was effective as first-line treatment in patients with recurrent gastric cancer after fluoropyrimidine-based adjuvant chemotherapy. In their report, the response rates (21 vs. 39%, $P = 0.427$), TTF (8.3 vs. 5.4 months, $P = 0.072$), and OS (14.1 vs. 9.3 months, $P = 0.075$) tended to be better in patients with an RFI of >6 months ($n = 13$) than in patients with an RFI of ≤6 months ($n = 19$), although the differences did not reach statistical significance [15]. These results were also consistent with those of previous studies in patients with other types of cancer, which suggested the importance of the RFI or treatment-free interval as a predictive marker of responsiveness to similar types of chemotherapy after recurrence [16–18]. Additionally, in the present study, the RFI cut-off value of 6 months was better than that of 12 months for predicting better outcomes and this finding may support the use of the conventional exclusion criteria in clinical trials in the first-line setting, which excluded patients who experienced disease recurrence within 6 months after the last adjuvant chemotherapy [5, 9, 11]. Therefore, selected patients with an RFI of ≥6 months with sufficient organ function may be adequately treated as chemo-naïve patients with standard chemotherapies such as S-1 plus cisplatin.

In contrast to the results for patients with an RFI of ≥6 months, the response rate in patients with an RFI of <6 months in the present study seemed to be worse than that of commonly used second-line chemotherapy regimens such as irinotecan and taxane combinations, which have a reported response rate of approximately 20% for patients with gastric cancer who received prior chemotherapy with fluoropyrimidines alone [18–23]. Based on these results, it may be suggested that the evaluation of chemotherapy regimens other than S-1 plus cisplatin might be warranted for the initial treatment of gastric cancer recurrence after adjuvant S-1. The response rate of 5.0% in our subset of patients with an RFI of <6 months was also lower than that reported previously by Kang et al. for capecitabine plus cisplatin after adjuvant chemotherapy (21%) [15]. The exact reasons for this difference are unknown. One possible reason is that Kang and colleagues did not use the same fluoropyrimidine (capecitabine after doxifluridine or 5-FU), and this choice might have contributed to a higher response in regard to early recurrence, although rechallenge with different types of fluoropyrimidine after the failure of another drug is still controversial in several types of cancer [24–28]. Second, the planned dose intensity of cisplatin as another key drug for gastric cancer was higher in their capecitabine plus cisplatin regimen (60 mg/m^2 every 3 weeks) [15] than that in the S-1 plus cisplatin regimen (60 mg/m^2 every 5 weeks). The efficacy of capecitabine plus cisplatin compared with other

chemotherapy (irinotecan, taxane or irinotecan plus cisplatin) for recurrence after adjuvant S-1 should be evaluated in future clinical trials.

It is important to note the limitations of the present study. First, it was retrospective, and treatment after recurrence was selected by each physician individually. Considering the low proportion of patients who received S-1 plus cisplatin after recurrence (14.0%), the selected population may have been biased toward patients with good performance status (PS) and low tumor burden. Second, toxicity was not evaluated in this study, although the proportion of patients who discontinued S-1 plus cisplatin due to toxicity was low. Third, human epidermal growth factor receptor 2 (HER2) status was not evaluated. Trastuzumab, a humanized monoclonal antibody against HER2, has recently been shown to improve the prognosis of HER2-positive advanced gastric cancer [29], and the HER2 status of all gastric cancer types should be evaluated, even in this setting of recurrent disease. Fourth, the moderate sample size in a single-country study is another limitation; therefore, it would be better to validate the significance of the RFI after adjuvant failure on the PFS in other cohorts as well.

In conclusion, this is the first report to have evaluated the efficacy of chemotherapy with S-1 plus cisplatin in patients with gastric cancer that recurred after adjuvant chemotherapy with S-1. S-1 plus cisplatin was effective in such patients, especially in those with an RFI of $\geq$6 months. Further well-defined, prospective trials in this important patient population are required to identify optimal treatment regimens.

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特集 外科医が行う胃癌化学療法

S-1＋CDDPによる胃癌Neoadjuvant chemotherapyの治療意義
—1コース施行群と2コース以上施行群の比較—

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Significance of Neoadjuvant Chemotherapy with S-1＋CDDP for Gastric Cancer—Comparison between 1 Course Treatment Group and More than 2 Courses Treatment Group—: Takiguchi N[*1], Nagata M[*1], Nabeya Y[*1], Ikeda A[*1], Kainuma O[*1], Hayata H[*1], Cho A[*1], Ohta T[*1], Park S[*1], Iwase T[*1], Yanagihashi H[*1], Arimitsu H[*1] and Yamamoto H[*1] ([*1]Department of Gastroenterological Surgery, Chiba Cancer Center)

Purpose: Gastric cancer with wide serosal invasion or bulky lymph node involvements have been treated by neoadjuvant chemotherapy with S-1＋CDDP (SP). We estimated the significance of neoadjuvant chemotherapy for advanced gastric cancer and compared 1 cycle SP (A group) with more than 2 cycles SP (B group) from the clinicopathological point of view. **Methods:** Sixty seven gastric cancer patients with resection after SP neoadjuvant chemotherapy were examined. Gastric cancer with widespread serosal invasion or bulky node involvements were treated SP neoadjuvant chemotherapy (one cycle is treated for 5 weeks. S-1; 80 mg/m^2×21 days＋CDDP; 30 mg/m^2×2 days (day1, day8) with 14 days rest). They were composed of 52 cases in 1 cycle (A), and 15 cases in more than 2 cycles (B). **Results:** 1) No serious adverse effects were found in both groups. 2) As the histologic response, the ratio of more than Grlb was 50 % in A and 66% in B. 3) Peritoneal lavage cytology positive ratio of gastric cancer with sT3-4 and P0 was 8.8% in A and 0% in B. 4) According to final Stage, the cumulative 4 years survival rate was 88.9% in fStage I-II, and 81.3% in fStage III. **Conclusions:** It is suggested that the 2 cycles SP neoadjuvant chemotherapy for gastric cancer with wide serosal invasion or bulky node involvements is approvable.

Key words: Gastric cancer, Neoadjuvant chemotherapy, S-1＋CDDP
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はじめに

新規抗癌剤の開発，なかでもS-1の開発により胃癌化学療法は大きく変化した．治癒切除後の進行胃癌の術後補助化学療法は，ACTS-GCの臨床試験結果により，fStageII，IIIにおける術後補助化学療法の意義が証明された[1]．その結果，S-1が適応薬剤としてガイドラインにも記載され，標準療法となっている．一方，そのSubgroup解析では，fStageIIIの予後は決して満足できるものではない．その原因は，治癒切除された

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としても，肉眼的に確認されない微小な転移が遺残していることにある．そのような症例に対して，術前化学療法を行うことが，予後向上に寄与することが期待されている．

われわれは，漿膜浸潤および高度リンパ節転移性胃癌に対しS-1＋CDDP（SP）療法による胃癌術前化学療法を外来化学療法として施行してきた．今回，1コース群と2コース以上群に分けて組織学的治療効果を中心に臨床病理学的に分析を行ない，進行胃癌に対する術前化学療法の意義を考察した．

1 対象と方法

術前の画像診断で，広範囲なcT3以上またはcN2以上と診断された胃癌に対し，術前化学療法の治療適応としてきた．術前検査としての審査腹腔鏡は実臨床の現場では施行していない．2004年10月より2010年3月までの症例を対象に，modified S-1＋CDDP療法（TS-1; 80 mg/m^2×21 days（day1-21）＋CDDP; 30 mg/m^2×2 days（day1, day8））を1コース施行（A）群52例と2コース以上施行（B）群15例を比較した．

本化学療法では，CDDP 30 mg/m^{2}の投与であり，制吐剤としてカイトリル3 mg，デカドロン8 mg プリンペラン10 mgを点滴投与とし，CDDPを含めて総補液量は約1,700 m*l*となるが，400 m*l*/hrでの点滴投与により約4.5時間の外来化学療法として治療を行なっている．なお，本論文における進行度表記は手術治療および術前治療の判定を明確にするため，第13版胃癌取扱い規約を使用した．

2 結　果

1) 両群間の患者背景

表1に両群間の患者背景を示す．2008年4月を境としてA群は主に前期，B群は主に後期に集積されている．性，年齢に差はなく，切除標本での最大腫瘍径も，平均約80 mmで腫瘍径の大きな症例が多く両群間に差はなかった．肉眼型ではType 3, Type 4が多くを占めていた．cStage Ⅲ，Ⅳが大半を占めていたが，両群間に差は認めなかった．cT, cN, H, P，については両群に差はない．

表1

	A群	B群	P value
性別（男性：女性）	31：21	8：7	0.891
年齢（歳）	61.6±10.9	65.3±9.0	0.217
腫瘍長径（mm）	80.8±42.5	79.8±58.7	0.723
肉眼型 Type 1	0	0	2
Type 2	5　35	5	0.091
Type 3	9	5	
Type 4	3	3	
Type 5			
cStage Ⅱ：Ⅲ：Ⅳ	3：32：17	3：6：6	0.152
H1	3	1	0.647
P1	4	1	1
T-2：3：4	2：45：5	2：12：1	0.382
N 0：1：2：3	1：15：28	2：4：6：3	0.262

2) 術前化学療法の治療完遂率と有害事象

コースが完遂できない症例は10例（15%）で，A群は7例（13.5%）で，B群は3例（20%）であったが，両群間に差はなかった．その原因は，A群では好中球減少；1例，発疹；2例，食欲不振2例，嘔吐2例であった．B群では，好中球減少；1例，発熱；1例，発疹；1例であった（表2）．

しかしながら実際のGrade3以上の副作用が出現した症例は，A群で食欲不振1.9%，好中球減少3.8%，血小板減少1.9%，発熱1.9%であった．B群では，好中球減少6.7%，皮膚反応6.7%，発熱6.7%であった．いずれの群においても，腎障害の出現はなかった（表3）．

3) 術前化学療法による主病巣の組織学的効果

化学療法による主病巣の組織学的効果判定は，Grade 1a以下がA群26例（50%），B群6例（33.3%），Grade 1bがA群14例（26.9%），B群2例（13.3%），Grade 2がA群11例（21.2%），B群6例（40%），Grade 3がA群1例（1.9%），B群2例（13.3%）であった．すなわち，Grade 1b以上の組織学的効果はA群26例

表2

	A群	B群	P value
非完遂理由	7/52(13.5)	3/15(20.0)	0.681
	好中球減少；1	好中球減少；1	
	発疹　；2	発熱　；1	
	食欲不振　；2	発疹　；1	
	嘔吐　；2		

コースが完遂できない症例は10例（15%）で群間差はなかった．

表3

	A群（52例）		B群（15例）	
	Gr 1, 2	3, 4	Gr 1, 2	3, 4
口内炎	1	0	0	0
嘔気/嘔吐	3	0	2	0
食欲不振	2	1(1.9)	2	0
白血球減少，好中球減少	2	2(3.8)	0	1(6.7)
血小板減少	1	1(1.9)	0	0
肝機能障害	0	0	0	0
発疹	3	0	0	1(6.7)
腎機能障害	0	0	0	0
発熱	0	1(1.9)	2	1(6.7)
血栓症	0	0	1	0

（ ）%

(50%)，B群10例（66%）であった（表4）．

4) 術前化学療法による深達度改善

治療対象者の大半が広範な漿膜浸潤陽性胃癌であるので，組織学的深達度を確認することで術前化学療法による深達度の改善効果を推測することができる．術前未治療症例でのsT3症例のpT3正診率は71.9%であるのに対し，A群は48.5%，B群は25%となっており，pSSについてもその比率は，術前未治療群；24.0%，A群；45.5%，B群50%，pMP以浅の比率が，術前未治療群；2.6%，A群；6.1%，B群25%となっており，術前化学療法と未治療群との間には深達度分布に有意な差（p=0.0016）があることが示された．以上の結果は，組織学的深達度の改善を示唆している（表5）．

表4

	A群	B群
Gr 0, 1a	26(50)	5(33.3)
Gr 1b	14(26.9)	2(13.3)
Gr 2	11(21.2)	6(40.0)
Gr 3	1(1.9)	2(13.3)
Total	52	15

（ ）%

Grade 1b以上の組織学的効果はA群26例（50%），B群10例（67%）であった．

表5

	-MP	SS	SE	SI	Total
Control	5	47	141(71.9)	3(1.5)	196
A群	2	15	16(48.5)	0	33
B群	2	4	2(25)	0	8

Neoadjuvant: Control　p=0.0016　（ ）%
A：B　p=0.2013

5) 術前化学療法による洗浄細胞診陽性率低下への寄与

sT3, T4 かつ P0 での Douglas 窩の洗浄細胞診陽性率を示す（表6）．Cy1比率は，未治療群；22.9%に対し，A群；8.8%，B群；0%であった．術前化学療法の有無で有意差を認めた（p=0.020）．以上から，術前化学療法による洗浄細胞診陽性率低下への寄与も示唆される．

6) 術前化学療法のリンパ節転移への効果

cNの判定の正診率は限界があり，組織学的リンパ節転移率の評価は困難であるが，リンパ節の縮小，消失により切除率の向上も考えられる．A群およびB群のリンパ節転移率の現状を示すと，pN0がA群；11.5%，B群；40%であり，pN2はA群；51.9%，B群；20%で深達度の同様にB群の転移率が低かった（表7）．多数例の症例を集積してこの傾向が明確になれば，リンパ節転移率の低下として証明しうると思われる．

7) 生存曲線

術前化学療法症例の生存曲線を示す（図1，2）．B群は，術後観察期間が短いため死亡例は出ていないが，A群においても，4年生存率65.6%

表6

	Cy 0	Cy 1	Total
Control	162	48(22.9)	210
A群	31	3(8.8)	34
B群	9	0	9
Neoadjuvant : Control	p=0.020		( ) %
A : B	p=0.851		

表7

	pN0	pN1	pN2	pN3-
A群 [52]	6(11.5)	11	27	8
B群 [15]	6(40)	5	3	1

組織学的リンパ節転移率は82.1%

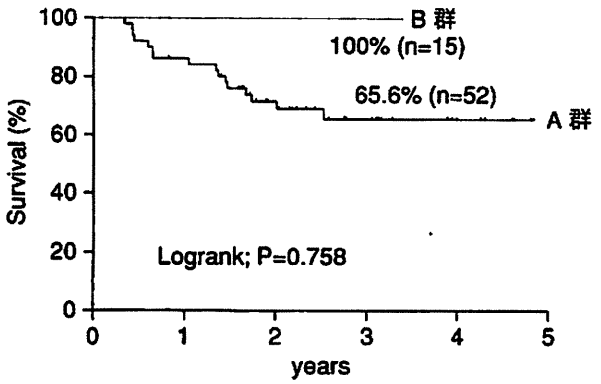

図1

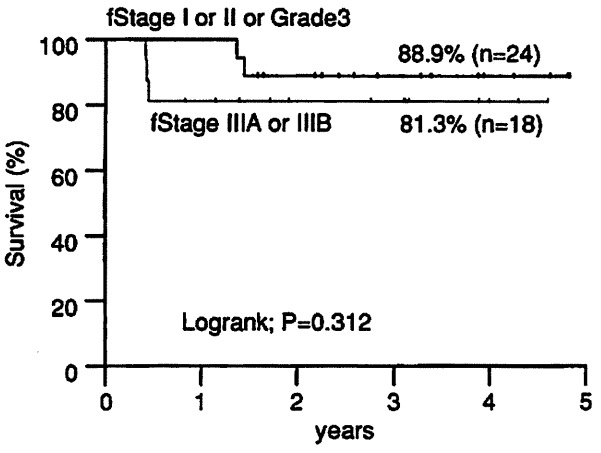

図2

の成績が出ており，さらに，fStageⅡまでの症例は，4年生存率88.9%，fStageⅢ症例でも81.3%の4年生存率であり，術前化学療法による生存率向上の可能性が示された．

3 考察

StageⅡ～Ⅲ進行胃癌に対するD2根治切除後の補助化学療法は，ACTS-GC[1]の結果から，S-1の1年間投与が標準治療となったが，そのSubgroup解析では，fStageⅢの予後は決して満足できるものではない．また，日本胃癌学会の全国統計においてもfStageⅢは5年生存率41.5%である[2]．術前化学療法はcStageⅢa～Ⅲbに対する，あるいは肉眼的根治切除が可能なcStageⅣ胃癌に対する治療として期待されている[3,4]．

術前化学療法の意義は，

1. 術後補助化学療法より高い薬物濃度を維持できる．
2. 腫瘍のdown stagingは，切除率向上につながる．
3. 微小転移の制御．
4. 術後化学療法に対する感受性試験としての位置づけ．
5. 集学的治療としての位置づけ．

とされている．

実際の臨床試験としては，大型3型，4型胃癌に対する術前補助化学療法としてS-1＋CDDPを用いたJCOG0210があるが，治療完遂割合（術前化学療法完遂しかつ根治度A/Bの切除；CYを除く）が70%であった[5]．

われわれの行っているmodified S-1＋CDDP療法（TS-1; 80 mg/m^2×21 days＋CDDP; 30 mg/m^2×2 days（day1, day8））は，Total doseは同一条件として，外来化学療法として実臨床で施行している．術前治療コースは，初期は1コース施行としていたが，現在は2コースを基本としている．今回はその両群の比較を中心に，術前化学療法の意義を検討した．治療コースが完遂できない症例は10例（15%）で，A群は7例（13.5%）で，B群は3例（20%）であったが，食思不振，嘔吐など，胃癌そのものの病状と関係する症例も混在した．そのほかには好中球減少や発疹が原因であった．腎機能障害の出現はなく，外来化学療法として安全に施行された．

化学療法による治療効果は，主病巣の組織学的効果で判定することが基本となるが，その結果は，Grade 1b以上の組織学的効果はA群26例（50%），B群10例（66%）であった．術前化学療法によるpathological CRはA群1.3%，B群13.3%であった．

化学療法によるdown staging効果は，stageⅡ以上の胃癌を対象とし，術前後の化学療法＋手術を手術単独と比較したRCTであるMAGIC trialによって証明されている[6]．すなわち術前化学療法群が，手術単独群に比して病理学的T3以上の割合が62%から48%（p＝0.009），N2以上の割合が29%から16%（p＝0.01）と有意な低下を示した．著者らは，2003年にFP療法による漿膜浸潤胃癌対象の術前化学療法でも，手術単独群に比して病理学的T3以上の割合の減少と洗浄細胞診陽性率の低下の可能性を報告している[7]．今回のmodified S-1＋CDDP術前化学療法からは，術前未治療症例でのsT3症例のpT3正診率は71.9%であるのに対し，A群は48.5%，B群は25%となっており，治療群とくにB群でより浅い深達度比率が増加しており，2コースの術前化学療法意義が示されている．その効果は，洗浄細胞診陽性率でも明確に示されており，実臨床の現場では術前審査腹腔鏡を省略した現状の症例選択が許容されると考えている．リンパ節転移率は，漿膜浸潤胃癌であれば，おおむね80%程度である．リンパ節の術前画像正診率は決して高くないため，cNとpNの関係をみることは困難である．したがって，リンパ節転移率の低下があるかどうか，あるいはリンパ節個数の面から検討する必要があると思われる．A群のリンパ節転移率では，リンパ節のdown stagingはほとんどないと判定されるが，B群ではその可能性に期待したい．B群の症例集積が少ないので，今後の症例集積により判定することが必要と思われる．

生存期間に関しては，4型胃癌を対象にS-1術前補助化学療法2コース後胃切除を行うJCOG0002試験では，病理学的奏効率27.3%で2年生存率59%であった[8]．われわれのデータでは，B群においても，4年生存率65.6%で，fStageⅠ～Ⅱで4年生存率88.9%，fStageⅢで81.3%の4年生存率で，術前化学療法による生存率向上の可能性が示唆された．

臨床試験として治療する場合は，そのプロトコールにしたがって治療しているが，本データは当院における実臨床データであるものの，決して他の臨床試験報告に成績が劣るものではなく，B群の治療集積を行なっている．

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ORIGINAL ARTICLE

Identification of patients likely to benefit from metastasectomy in stage IV colorectal cancer

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Abstract
Purpose The aim of the present study was to determine selection criteria for patients with stage IV colorectal cancer (CRC) who were likely to show survival benefits of metastasectomy.
Methods Clinicopathological data of 119 patients with stage IV CRC who underwent primary CRC resection were retrospectively reviewed. The prognostic factors were analyzed according to the disease resectability status, and patients likely to show survival benefits of metastasectomy were identified.
Results Metastasectomy was performed in 63 patients. Among these patients, R0 resection was reported in 55 patients, who comprised the curable group. The other 64 patients comprised the noncurable group. For the noncurable group, postoperative chemotherapy was identified as the only significant prognostic factor. In the curable group, T stage, histological type, elevated serum carcinoembryonic antigen (CEA) level and the presence of extra hepatic disease were identified as independent prognostic factors. Patients within the curable group were further classified into a low-risk group (zero to two prognostic factors) and a high-risk group (three or more prognostic factors). The overall survival (OS) of the high risk patients in the curable group was as poor as that of the patients in the noncurable group.
Conclusions Stage IV CRC patients consisted of heterogeneous populations who had different prognostic factors, stratified by the disease resectability status. No prognostic benefit of metastasectomy was observed in high-risk patients undergoing curative metastasectomy. These results suggested that patients showing survival benefits of metastasectomy can be identified by considering the prognostic factors in patients undergoing curative metastasectomy.

Keywords Colorectal cancer · Stage IV · Metastasectomy · Selection criteria · Resectability status

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Introduction

Colorectal cancer (CRC) is the third most prevalent cancer and the fourth leading cause of cancer death worldwide [1]. Although the early stage disease of some patients is potentially curable, the detection of distant metastases at the time of presentation is common [2]. Although recent advances in chemotherapeutic regimens, including molecular targeted agents, have led to improved survival in patients with metastatic CRC, patients with stage IV disease have a very poor prognosis, with a 5-year survival of only 10–20 % [3].

Complete surgical resection of both primary CRC and its metastases remains the only potential curative therapy for stage IV CRC patients [2]. An increasing body of data suggests that patients who undergo curative resection of isolated metastases show survival benefits regardless of the metastatic site such as liver [4–6], lung [7–9], peritoneal [10, 11], ovarian metastases [12, 13] and extra regional lymph nodes [14, 15]. Although complete surgical resection of these metastases contributes to long-term survival in selected patients, some patients have early recurrence and very poor prognosis.

To identify the patients with poor prognosis after hepatic or pulmonary resection of metastatic CRC, investigators have proposed several different prognostic scoring systems

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[5, 8, 16, 17]. However, the factors contributing to the identification of patients likely to benefit from resection of metastatic disease have not been defined [18]. The actual indication of metastasectomy depends on the decision of surgeons or oncologists in each institution. The establishment of selection criteria for metastasectomy in patients with stage IV CRC is necessary.

Stage IV CRC encompasses a heterogeneous patient population in which both palliative and curative treatment strategies may be used [19]. The different treatment strategies are determined by the disease resectability status, and wide variation in the outcome has been shown [20]. In the present study, prognostic factors were compared between patients who underwent curative resection and those who did not to determine which patients are likely to benefit from metastasectomy among patients with stage IV CRC. The aim of this study is to establish selection criteria for metastasectomy in patients with stage IV CRC, based on the disease resectability status.

Patients and methods

We identified 131 patients with stage IV CRC disease from a prospective database from January 1992 to December 2008 at the Department of Surgery of Hiroshima University. Among these 131 patients, 119 patients underwent primary CRC resection (90.8 %), regardless of the resection of metastatic disease. These 119 patients were retrospectively analyzed based on the availability of detailed information about tumor-related factors.

Surgical treatment considered resection of the primary CRC when possible, with the exception of patients in poor condition. Determination of treatment strategy did not depend on the presence of tumor-related complications such as small bowel obstruction, bleeding or pain. In all cases with resectable synchronous metastases, simultaneous resection of both the primary and metastatic tumor was performed, regardless of the location of primary tumors and the extent of metastasis. Exceptionally, staged metastasectomy after resection of the primary tumor was performed in patients with lung metastasis or showing complications such as small bowel obstruction. For primary tumor resection, all patients underwent standard resection of colon and rectum with regional lymphadenectomy according to the Japanese general rules for clinical and pathological studies on cancer of the colon, rectum and anus, 7th edition (JGR) [21]. The indications for metastasectomy were the ability of the patient to tolerate the required surgical procedure and surgically controllable disease including primary lesion. For resection of liver metastases, radical operation was possible along with the preservation of at least 30 % of normal parenchyma. These criteria were independent of the number and size of liver tumors. The indications for pulmonary resection were the preservation of adequate postresection respiratory function. Potentially resectable bilateral or multiple lesions were not excluded from the selection criteria [7]. The resection of ovarian, peritoneal and extra regional lymph nodes was performed, if these metastases were isolated and could be completely removed. Curative resection (R0) was defined as microscopically free tumor margins.

Individual demographic and clinicopathological data were collected including age, sex, tumor location, tumor stage (T stage), nodal stage (N stage), tumor histology, presence of lymphovascular invasion, preoperative serum carcinoembryonic antigen (CEA) level, the presence of extra hepatic disease, the extent of hepatic lesions, the presence of lung metastasis, the presence of peritoneal dissemination, the presence of postoperative complications, application of postoperative therapy and survival rate. T stage, N stage and tumor histology were pathologically determined from resected specimens. All patients were staged according to the American Joint Commission for Cancer Staging (AJCC/TNM the sixth edition) system [22]. Survival data were updated until March 2011. Survival was computed from the date of the primary tumor resection. All postoperative complications were reviewed for at least 30 days following surgery. The complications were graded according to the method described by Dindo et al. [23]. Complications with a grade above III were categorized as morbid. Postoperative mortality was defined as any death that occurred within 30 days of surgery.

Statistical analysis

Survival curves were plotted by the Kaplan–Meier method, and univariate analyses of factors thought to influence overall survival (OS) were estimated using the logrank test. The Cox proportional hazard model was used for multivariate analyses. To achieve an optimal cutoff value of serum CEA levels, receiver operating characteristic (ROC) curve analysis for survival was performed to obtain the area under the ROC curve (AUC), and optimal cutoff values were defined as the point on a ROC curve nearest to the point where both sensitivity and specificity were one. In all analyses, statistical significance was set at a p value of less than 0.05. All statistical analyses were performed using JMP 8 software (version 8.02, SAS Institute Inc., Cary, NC, USA).

Results

Clinicopathological features

The clinicopathological features of the 119 patients are summarized in Table 1. Seventy-five male and 44 female

Table 1 Patients' characteristics

	n=119
Male/female	75/44
Age (mean)	61.8 (range, 23–85)
Median follow up time (month)	23.8 (range, 1.0–141.4)
Tumor location	
Colon/rectum	70/49
Number of metastatic organs	
One organ/more than 2 organs	94/25
Metastatic organs	
Liver	88
Lung	9
Extra regional lymph node	22
Peritoneal dissemination	26
Ovary	2
Metastasectomy	63 (52.9 %)
Curative/noncurative	55/8

patients were included in this study, with a median age of 61.8 years (range, 23–85 years). The median follow-up period was 23.8 months (range, 1.0–141.4 months). The distribution of tumor location included 70 colon and 49 rectal cancers. Ninety-four patients had metastatic disease in only one organ, and the other 25 patients had metastasis to more than two organs. The distribution of metastases was 88 in the liver, nine in the lung, 22 in extra regional lymph nodes, 26 with peritoneal dissemination and two in the ovary (including overlapped cases).

Metastasectomy was performed in 63 patients (52.9 %). Synchronous resection of primary and metastatic tumors was performed in 59 patients, and staged resection was performed in four patients. Among these 63 cases, histological tumor-free margin was seen in 55 patients (R0), and histological positive tumor margin was seen in the other eight patients (R1, 2). In the 55 patients with curative resection, the metastatic organ distribution was liver in 47 cases, peritoneal dissemination in four cases, lungs in two cases, extra regional lymph nodes in two cases and ovaries in two cases (including overlapped cases). In cases with liver surgery (n=47), ten cases had more than three subsegments of the liver resected. Postoperative complications were reported in six cases (10.2 %) for patients with only primary CRC resection (n=59) and ten cases (16.7 %) for patients with both primary and metastatic CRC resection (n=60), respectively. There were no reports of mortality in either of the groups.

Overall survival (OS) and classification based on the disease resectability status

The 5-year OS was 24.9 % for all patients combined. The 5-year OS for patients who underwent curative resection (R0), those who underwent noncurative resection (R1, 2) and those who did not undergo metastasectomy were 45.9 %, 12.5 % and 6.7 %, respectively (Fig. 1). The OS of patients who underwent curative resection for both primary and metastatic diseases was significantly better than that of the other two groups (p<0.001, Fig. 1). On the other hand, the OS of patients who could not undergo curative resection of primary or metastatic disease was as poor as that of the patients who did not undergo resection of metastases (p= 0.257, Fig. 1). Therefore, we stratified patients with stage IV CRC into two subgroups according to the disease resectability status: the patients who underwent curative resection for both primary and metastatic diseases (R0) were classified as the 'curable group' (n=55), and the patients who did not undergo curative resection for primary or metastatic diseases (R1, 2) and those who did not undergo resection of the metastatic disease were classified as the 'noncurable group' (n=64). The prognostic factors for both curable and noncurable patient groups were analyzed separately.

Postoperative chemotherapy

Among the patients in the noncurable group (n=64), 52 patients (82.8 %) received postoperative chemotherapy after primary tumor resection. The first-line postoperative therapy regimens were as follows: peroral drug regimen, such as S-1 (n=11) and tegafur-uracil (n=7), 5-FU/leucovorin (n=14), irinotecan-based regimen (n=7), transarterial chemotherapy (n=8) and oxaliplatin-based regimen (n=5).

For patients in the curable group (n=55), postoperative chemotherapy after metastasectomy was administered to 52 patients (94.5 %). The first-line postoperative therapy regimens were as follows: peroral drug regimen, such as S-1 (n=9), tegafur-uracil (n=8), tegafur-uracil/oral leucovorin (n=6) and capecitabine (n=1), transarterial chemotherapy (n=20), 5-FU/leucovorin (n=5) and oxaliplatin-based

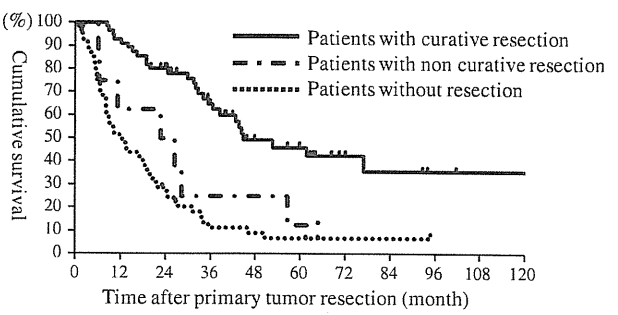

Fig. 1 Overall survival (OS) in patients with stage IV CRC classified by resectability status of the diseases. The OS of patients with curative resection was significantly better than that of the other two groups (p< 0.001). On the other hand, the OS of patients with noncurative resection was as poor as that of the patients without resection of metastases (p=0.257)

regimen (n=3). Before 2001, transarterial chemotherapy with fluorouracil was the main postoperative treatment for colorectal liver metastases. After 2002, peroral drug regimens were included in the treatment. More recently, oxaliplatin-based regimens have been considered as standard therapy in patients with high risk of cancer recurrence.

No patients were treated by molecular-targeted agents as a first line of treatment in either of the two groups, and these agents were applied as a second line of treatment or after the study period. In the noncurable group, one patient was treated with bevacizumab, and another patient was treated with cetuximab. In the curable group, three patients were treated with bevacizumab, and another three patients were treated with cetuximab. In both groups, cetuximab was administrated to the patients without KRAS mutation.

Prognostic factors for patients with noncurable stage IV CRC

To estimate prognostic factors, univariate analysis was performed for the following variables: age (<70 vs. ≥70 years old), sex (male vs. female), primary tumor location (colon vs. rectum), tumor stage (T1–T3 vs. T4), N stage (negative vs. positive), histological type (well-differentiated adenocarcinoma vs. other types), lymphatic invasion (negative vs. positive), venous invasion (negative vs. positive), serum CEA level (<30.0 ng/ml vs. ≥30.0 ng/ml), number of liver metastasis (0–3 vs. ≥4), maximum liver tumor diameter (<5 cm vs. ≥5 cm), lung metastases (absent vs. present), peritoneal dissemination (absent vs. present), extra hepatic disease (absent vs. present), postoperative complications (absent vs. present) and postoperative chemotherapy (no vs. yes). Tumor-related factors were not identified as significant prognostic factors, and only postoperative chemotherapy was identified as a significant prognostic factor (p<0.001, Table 2).

Table 2 Prognostic factors in patients with noncurable stage IV CRC (n=64)

Variables		Number	5-year OS	p value
Age	<70	46	8.0 %	0.281
	≥70	18	5.9 %	
Sex	Male	41	6.1 %	0.681
	Female	23	9.6 %	
Location	Colon	38	3.0 %	0.162
	Rectum	26	14.1 %	
T factor	T1–3	25	8.7 %	0.738
	T4	39	6.4 %	
N factor	Negative	9	0.0 %	0.878
	Positive	55	9.0 %	
Histology	Well	52	0.0 %	0.830
	Other types	12	8.1 %	
Lymphatic invasion	Negative	3	33.3 %	0.153
	Positive	61	6.0 %	
Venous invasion	Negative	19	0.0 %	0.897
	Positive	45	10.2 %	
CEA (ng/ml)	<30	39	9.0 %	0.611
	≥30	25	5.0 %	
Number of liver metastasis	0–3	34	11.5	0.147
	≥4	30	3.5	
Maximum liver tumor diameter (cm)	<5	36	10.2	0.091
	≥5	28	4.3	
Lung metastasis	Absent	55	8.5 %	0.331
	Present	9	0.0 %	
Peritoneal dissemination	Absent	40	8.7 %	0.170
	Present	24	5.9 %	
Extra hepatic disease	Absent	22	5.0 %	0.875
	Present	42	9.7 %	
Postoperative complication	No	57	8.2 %	0.076
	Yes	9	0.0 %	
Postoperative therapy	No	12	0.0 %	<0.001
	Yes	52	9.4 %	

CRC colorectal cancer, *OS* overall survival, *CEA* carcinoembryonic antigen

Prognostic factors for patients with curable stage IV CRC

To estimate prognostic factors, univariate analysis was performed for the same variables as those considered for noncurable disease and extent of liver resection (resection of two or fewer liver subsegments vs. three or more liver subsegments). T stage (T4, p=0.004), N stage (positive, p=0.026), histological type (other types, p=0.026), serum CEA level (≥30.0 ng/ml, p=0.002), peritoneal dissemination (present, p<0.001), extra hepatic disease (present, P<0.001) and postoperative chemotherapy (yes, p=0.036) were identified as significant prognostic factors (Table 3).

In multivariate analysis of selected variables found to be significant in the univariate analysis, T stage (T4, p=0.032), histological type (other types, p=0.043), serum CEA level (≥30.0 ng/ml, p=0.007) and the presence of extra hepatic disease (present, p=0.015) were identified as independent prognostic factors (Table 4).

Risk classification based on the independent prognostic factors for patients with curable stage IV CRC

To identify patients who might show a survival benefit from metastasectomy, we established a risk classification based on the following independent prognostic factors: T stage (T4), histological type (other than well-differentiated adenocarcinoma), serum CEA level (≥30.0 ng/ml) and the presence of extra hepatic disease. We, then, classified patients into two groups, a low-risk group (zero to two risk factors) and a high-risk group (three or more risk factors). Forty-six patients were classified into the low-risk group,

Table 3 Prognostic factors in patients with curable stage IV CRC (n=55)

Variables		Number	5-year OS	p value
Age	<70	45	48.5 %	0.371
	≥70	10	37.5 %	
Sex	Male	34	50.0 %	0.813
	Female	21	39.3 %	
Location	Colon	32	45.7 %	0.898
	Rectum	23	46.7 %	
T factor	T1–3	38	56.5 %	0.004
	T4	17	19.2 %	
N factor	Negative	16	70.2 %	0.026
	Positive	39	35.7 %	
Histology	Well	17	65.7 %	0.026
	Other types	39	37.6 %	
Lymphatic invasion	Negative	11	72.7 %	0.262
	Positive	44	42.5 %	
Venous invasion	Negative	16	45.8 %	0.213
	Positive	39	47.8 %	
CEA (ng/ml)	<30	34	67.5 %	0.002
	≥30	21	16.7 %	
Number of liver metastasis	0–3	46	44.1	0.431
	≥4	9	53.3	
Maximum liver tumor diameter (cm)	<5	48	45.5	0.647
	≥5	7	51.4	
Extent of liver resection	2 or fewer subsegments	44	46.2	0.859
	3 or more subsegments	11	43.8	
Lung metastasis	Absent	53	48.0 %	0.070
	Present	2	0.0 %	
Peritoneal dissemination	Absent	52	48.8 %	<0.001
	Present	3	0.0 %	
Extra hepatic disease	Absent	48	52.0 %	<0.001
	Present	7	0.0 %	
Postoperative complication	No	46	45.1 %	0.843
	Yes	9	48.6 %	
Postoperative therapy	No	3	0.0 %	0.036
	Yes	52	47.4 %	

and nine patients were classified as a high risk group. For patients with curable stage IV CRC, the OS of the high-risk group was significantly poorer than that of the low-risk group (p<0.001, Fig. 2). Furthermore, the OS of this group was as poor as that of patients with noncurable stage IV CRC (p=0.474, Fig. 2).

Discussion

Complete surgical resection of metastases contributes to the long-term survival of patients with stage IV CRC. The present study confirmed that the OS of patients with curative metastasectomy was significantly better than that of patients with noncurative or without metastasectomy. However, there is no consensus regarding the upper limits of operative indications for metastatic tumors. The current guidelines state that the aim of liver resection in patients with colorectal liver metastases is to remove all macroscopic disease, to achieve clear resection margins and to leave a sufficiently functioning liver [4, 18, 24]. These criteria apply to patients with solitary, multiple and bilobar disease as well as extra

Table 4 Prognostic factors in patients with curable stage IV CRC: multivariate analysis

Selected variables	p value	Odds ratio	95 % confidential interval
T factor (T4)	0.032	2.681	1.087–6.623
N factor (positive)	0.272	3.678	0.562–7.752
Histology (other types)	0.043	3.259	1.037–10.242
CEA (≥30 ng/ml)	0.007	3.717	1.443–9.615
Peritoneal dissemination (present)	0.899	1.147	0.137–9.615
Extra hepatic disease (present)	0.015	7.143	1.468–34.483
Postoperative chemotherapy (no)	0.069	5.826	0.875–38.811

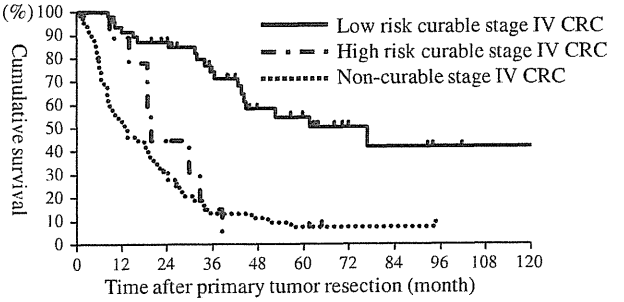

Fig. 2 The OS in patients with noncurable and curable stage IV CRC classified by the independent prognostic factors. For patients with curable stage IV CRC, the OS of the high risk group was significantly poorer than that of the low risk group ($p<0.001$). Furthermore, the OS of this group was as poor as that of patients with noncurable stage IV CRC ($p=0.474$)

hepatic disease that is confirmed in the lungs, ovary, peritoneal dissemination and extra regional lymph nodes [2, 3, 18, 24]. Therefore, the operative indications for metastasectomy are dependent on the decisions of surgeons or oncologists in each institution. Before resecting the metastatic tumor, it is important to recognize who is likely to benefit from the procedure. We, therefore, aimed to identify the patient population who likely benefit from metastasectomy.

Previous studies showed a wide variation in outcomes according to the baseline resectability status of metastases for stage IV CRC [20]. For the majority of patients, treatment remains of palliative benefit, with the possibility of cure, were restricted only to those patients who are suitable for surgical resection. Thus, stage IV CRC encompasses a heterogeneous patient population in which both palliative and curative treatment strategies may be used. In the present study, we also showed differences in the prognostic outcome according to the disease resectability status (curable group vs. noncurable group). Furthermore, among patients with noncurable stage IV CRC, tumor-related factors did not reflect the prognosis. Conversely, for patients with curable stage IV CRC, tumor-related factors, such as T stage, histological type, preoperative CEA level and the presence of extra hepatic disease, were indicative of the prognosis. These results implied that stage IV CRC patients consist of heterogeneous populations in which the prognoses and prognostic factors are different and can be stratified by the resectability status of the disease.

To address the controversial topic of patient selection for metastasectomy, various groups have proposed using a prognostic scoring system to stratify patients into different risk categories. Nordlinger et al. [16] and Fong et al. [5] each proposed a prognostic scoring system after hepatic resection using several clinical parameters. Recently, Kattan et al. [17] and Kanemitsu et al. [6] proposed a prognostic nomogram to identify high-risk patient groups. In these systems, age, gender, primary site, primary T and N stage, short disease free interval, the size and number of liver tumors, surgical margin, preoperative CEA level and the presence of extra hepatic disease were found to be prognostic markers. However, there is no ideal prognostic system for the clinical management of patients with colorectal liver metastases [18]. As in liver metastases, a number of prognostic factors have been suggested to predict outcome after pulmonary metastasectomy [7–9]. In general, the number of pulmonary metastases, short disease free survival, preoperative CEA levels and nodal status of perihilar and mediastinal lymph nodes were reported as prognostic factors. However, disagreement exists over which prognostic factors determine who will benefit most from aggressive surgical treatment [25]. In the present study, T4, histological type (other than well-differentiated adenocarcinoma), elevated serum CEA level (≥30 ng/ml) and the presence of extra hepatic disease were identified as independent prognostic factors, considering only the patients with curative metastasectomy. In addition, a patient population likely to show a survival benefit of metastasectomy was identified, stratified by these prognostic factors. To best of our knowledge, the present study is the first to identify a patient population likely to show survival benefits from curative metastasectomy. These present results suggest that the identification of patients who would benefit from metastasectomy is possible, considering the prognostic factors extracted from patients with curative metastasectomy.

Although the presence of extra hepatic disease has long been considered a contraindication for resection, recent reports of long-term survival of patients who undergo resection of both sites suggest that some patients may show long-term benefits [25, 26]. Similar to the management of liver metastases, pulmonary resection for metastatic CRC is increasingly being considered as appropriate and beneficial in selected patients [7, 8]. Resection of metastases in more unusual sites, such as ovary, peritoneal dissemination and extra regional lymph nodes, is more controversial. However, several retrospective studies have suggested that selected patients may be cured with resection of these tumors [2, 10–15]. In the present study, the presence of extra hepatic disease was also selected as an independent prognostic factor in patients with curative metastasectomy. However, our data also showed that the prognostic benefit of resection of extra hepatic disease is limited to patients with two or less other prognostic factors (T4, other than well-differentiated adenocarcinoma and elevated serum CEA level). Our data supported the notion that surgical metastasectomy can be beneficial in well-selected patients with stage IV CRC, despite the number or site of metastatic organs.

Recent advances in chemotherapeutic regimens have produced good results with preoperative chemotherapy; thus, neoadjuvant chemotherapy followed by hepatectomy has

gradually gained acceptance for both initially nonresectable metastases and resectable metastases [2]. The high tumor response rates achieved with modern chemotherapeutics now enable a greater proportion of patients with initially inoperable disease to achieve an operable status and undergo liver resection with curative intent. This type of chemotherapy is termed 'conversion therapy' to differentiate it from 'neoadjuvant therapy' in upfront resectable metastases [27, 28]. The current study did not include so-called 'conversion therapy,' which is aimed at the complete resection after preoperative chemotherapy for patients with unresectable CRC. The present study did not show the prognostic benefit of metastasectomy for the initial treatment of patients with three or more risk factors, even if curative resection of metastases was performed. Although further investigation is required, preoperative chemotherapy may be recommended for such patients.

For the resection of isolated metastases with a curative intent, it is critical that the primary colorectal tumor has been or can be completely resected [2]. In cases with unresectable metastases, the role of primary tumor resection has been controversial, in particular with the improvement in newer chemotherapeutic agents [29]. Although a recent meta-analysis suggested the efficacy of primary CRC resection from a prognostic point of view [30], another study recommended the introduction of chemotherapy without removal of primary tumors in patients without any tumor-related complications [29]. In the present study, our criteria for primary tumor resection did not include the presence of tumor-related complications. However, we recently introduced chemotherapy in patients with asymptomatic and minimally symptomatic tumorus, to avoid the delay of chemotherapy because of the resection of the primary tumors.

The timing of the synchronous resection of metastases and primary tumor has been a subject of debate [2, 4]. Recent studies have demonstrated equivalent outcomes without increased morbidity and mortality in patients who undergo simultaneous resection [31, 32]. In the present study, simultaneous resection of both the primary and metastatic tumors was performed in all cases of resectable synchronous metastases, regardless of the location of primary tumors and the extent of metastasis. The mortality and morbidity rate was low in this study as compared to previous reports [31, 32], which suggested that for well-selected patients, simultaneous resection of primary CRC and abdominal metastases is a safe approach.

This study had several limitations. First, the possible influence of the variable regimen of postoperative therapy cannot be ignored. Second, the current patient cohort included few patients treated with newer chemotherapy agents such as bevacizumab and cetuximab. There were no significant differences in the use of molecular-targeted therapies among the three groups (low-risk curable group, $n=5$; high-risk curable group, $n=1$; and noncurable group, $n=2$; $p=0.221$). Therefore, we can safely assume that the application of these agents would not confound our results.

In conclusion, we demonstrated that stage IV CRC patients consist of a heterogeneous patient population with different prognostic factors, stratified by the disease resectability status. Consideration of the prognostic factors in patients treated with curative metastasectomy (T4, other than well-differentiated adenocarcinoma, elevated serum CEA level and the presence of extra hepatic disease) allowed the identification of patients who would most benefit from this procedure. This study is a retrospective trial with relatively low number of patients, therefore, our data is needed to validate with large series in order to establish universal selection criteria of metastasectomy for stage IV CRC. Regardless of this limitation, however, our data demonstrated the possibility of establishing ideal prognostic models based on the disease resectability status for stage IV CRC.

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A PHASE II TRIAL OF NEOADJUVANT PREOPERATIVE CHEMORADIOTHERAPY WITH S-1 PLUS IRINOTECAN AND RADIATION IN PATIENTS WITH LOCALLY ADVANCED RECTAL CANCER: CLINICAL FEASIBILITY AND RESPONSE RATE

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Purpose: We aimed to validate our hypothesis that a preoperative chemoradiotherapy regimen with S-1 plus irinotecan is feasible, safe, and active for the management of locally advanced rectal cancer in a single-arm Phase II setting.
Methods and Materials: Eligible patients had previously untreated, locally advanced rectal adenocarcinoma. Radiotherapy was administered in fractions of 1.8Gy/d for 25 days. S-1 was administered orally in a fixed daily dose of 80mg/m^2 on Days 1 to 5, 8 to 12, 22 to 26, and 29 to 33. Irinotecan (80mg/m^2) was infused on Days 1, 8, 22, and 29. Four or more weeks after the completion of the treatment, total mesorectal excision with lateral lymph node dissection was performed. The primary endpoint was the rate of completing treatment in terms of feasibility. The secondary endpoints were the response rate and safety.
Results: We enrolled 43 men and 24 women in the study. The number of patients who completed treatment was 58 (86.6%). Overall, 46 patients (68.7%) responded to treatment and 24 (34.7%) had a complete histopathologic response. Three patients had Grade 3 leukopenia, and another three patients had Grade 3 neutropenia. Diarrhea was the most common type of nonhematologic toxicity: 3 patients had Grade 3 diarrhea.
Conclusions: A preoperative regimen of S-1, irinotecan, and radiotherapy to the rectum was feasible, and it appeared safe and effective in this nonrandomized Phase II setting. It exhibited a low incidence of adverse events, a high rate of completion of treatment, and an extremely high rate of pathologic complete response. © 2011 Elsevier Inc.

Chemoradiation, Rectal cancer, S-1, Irinotecan.

INTRODUCTION

In Japan the incidence of colorectal cancer (CRC) is increasing year by year. If this trend continues, forecasts estimate that about 170,000 people will have CRC in 2015. Colorectal cancer will become the most prevalent type of cancer in Japan, surpassing gastric cancer and lung cancer (1). In Europe and North America, CRC is the second leading cause of cancer-related death, behind lung cancer. Globally, the prevention, early diagnosis, and treatment of CRC are urgent tasks.

Advanced rectal cancer carries a poorer prognosis than advanced colon cancer. The control of local recurrence, a unique characteristic of rectal cancer, and improved overall survival are important goals of treatment. Total mesorectal excision (TME) has recently been shown to decrease the rate of local recurrence and is performed throughout the world as a standard procedure (2, 3). In the mid 1980s the Gastrointestinal Tumor Study Group showed that postoperative chemoradiotherapy improves the rate of recurrence-free survival (4). On the basis of these results, the National Institutes of Health in the United States has recommended resection plus postoperative chemoradiotherapy as standard therapy for pathologic Stage II and III rectal cancer since 1990 (5). Five controlled studies comparing preoperative radiotherapy followed by surgery with surgery alone subsequently showed that the rate of local recurrence is significantly lower in patients who receive preoperative radiotherapy than in those who receive surgery alone (6). Moreover, the Swedish Rectal Cancer Trial showed that preoperative radiotherapy significantly improves overall and disease-free survival (7). On the other hand, European Organisation for Research and

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Treatment of Cancer Trial 22921, a large Phase III study, failed to prove that chemoradiotherapy improves survival rates, but the control of local recurrence at 5 years was significantly better in patients who received chemoradiotherapy than in those who received radiotherapy alone if chemotherapy was given at any time during the course of treatment (8). On the basis of these results, preoperative chemoradiotherapy was acknowledged to be standard treatment for locally advanced rectal cancer. However, the dose, duration, and radiation target volumes, as well as optimal concomitant agents, remain controversial. Recently, Guillem *et al.* (9) reported that patients with a complete response (CR) or nearly complete response to preoperative chemoradiotherapy have good long-term outcomes. Attention has thus focused on the relation between CR ratio (tumor downstaging) and survival outcome by preoperative chemoradiotherapy.

In Japan, however, few clinical trials of adjuvant radiotherapy have been conducted because the rate of local recurrence after the Japanese standard therapy (TME plus lateral lymph node dissection without neoadjuvant radiotherapy) is comparable to that including neoadjuvant chemoradiotherapy in Europe and North America. Because surgery alone has reached the most optimal outcome for decreasing local recurrence or improving survival of advanced rectal cancers in Japan at present, we wondered whether it is really necessary to evaluate chemotherapy combined with radiotherapy to improve clinical outcomes.

S-1 is an oral anticancer drug that combines tegafur, which is finally converted to the active agent of 5-fluorouracil (5-FU), with gimeracil and oteracil potassium. Gimeracil was added to increase the blood 5-FU concentration by inhibiting metabolism of 5-FU by dihydropyrimidine dehydrogenase mainly in the liver. On the other hand, oteracil potassium is widely distributed to gastrointestinal tissues and antagonizes orotate phosphoribosyl transferase, resulting in inhibition of 5-fluoronucleorides (active metabolites) generated from 5-FU, as well as reduced toxicity of 5-FU. Moreover, we also focused on the recently proven fact that components of S-1 markedly increase the radiosensitivity of cancer cells (even 5-FU–resistant cells) to radiotherapy in CRC (10). In addition, irinotecan hydrochloride decreases messenger ribonucleic acid levels of thymidylate synthase as a target enzyme of 5-FU (11), thereby augmenting its inhibition (12). Several studies have also shown that 5-FU induces topoisomerase I and that cancer cells overexpressing topoisomerase I increased chemosensitivity against irinotecan (13, 14). Such *in vitro* mechanisms provide a theoretic basis for combining S-1 and irinotecan plus radiation therapy (Fig. 1). At present, 5-FU–based chemoradiotherapy is used as a standard treatment for rectal cancer (4, 15); however, our 5-FU–based chemoradiotherapy was considered worthy of investigation.

A Phase I clinical study was performed to determine the maximum tolerated doses and recommended doses of S-1 and irinotecan. The pathologic response rate to the recommended dose, though not the primary endpoint in the Phase I study, however, was 94.7%, and the pathologic CR rate was surprisingly 31.6%, indicating that treatment with S-1 and irinotecan plus radiation was very active for locally advanced rectal cancer (16). In this Phase II clinical trial, we aimed to validate our hypothesis that a preoperative chemoradiotherapy regimen with S-1 plus irinotecan is feasible, safe, and effective for the management of locally advanced rectal cancer.

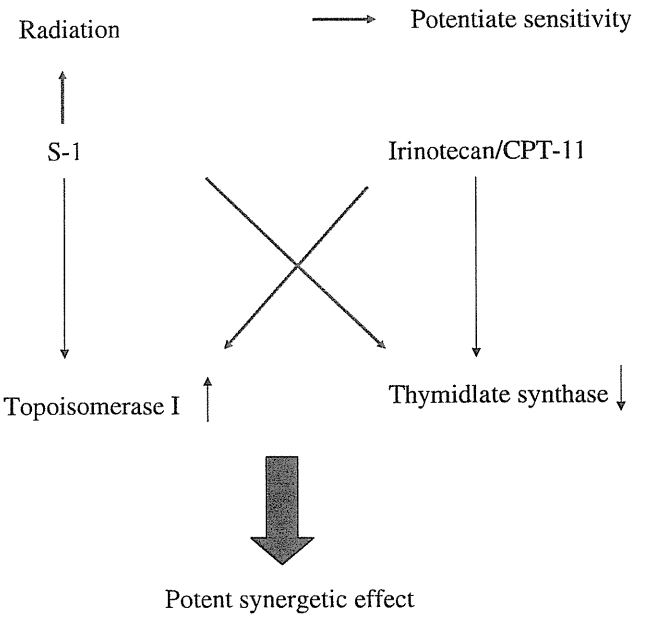

Fig. 1. Interaction of S-1 and irinotecan.

METHODS AND MATERIALS

This study was performed according to the guidelines of the Declaration of Helsinki, as amended in Edinburgh, Scotland, in October 2000. The protocol was approved by the Institutional Review Board of Kitasato University Hospital (Kanagawa, Japan). All patients gave written informed consent before study entry.

Eligibility criteria

Eligible patients had previously untreated clinical T3 or T4, N0 to N2, M0 locally advanced rectal cancer as confirmed histopathologically as adenocarcinoma in the rectum from August 2005 through December 2007, as well as an Eastern Cooperative Oncology Group performance status of 0 to 2. We used the International Union Against Cancer staging system. We described rectal cancer as involving the portion of the rectum above the peritoneal reflection and the portion of the rectum below the peritoneal reflection and ruled out other portions using the Japanese classification of CRC, and our definition of the rectum is thus the same as that of the International Union Against Cancer. Other eligibility criteria were as follows: age 20 to 80 years at enrollment; no severe disturbances of main organ functions (including bone marrow, heart, lung, liver, and kidney); no severe hematologic or blood chemical abnormalities such as leukocyte count of 4,000 to 12,000/mm^3, neutrophil count of 2,000/mm^3 or greater, platelet count of 100,000/μL or greater, hemoglobin concentration of 9.0 g/dL or greater, total bilirubin concentration of 1.5 mg/dL or less, serum aspartate aminotransferase and alanine aminotransferase levels less than twice the upper limit of normal, serum creatinine concentration less than the upper limit of the normal; normal electrocardiographic findings; and the ability

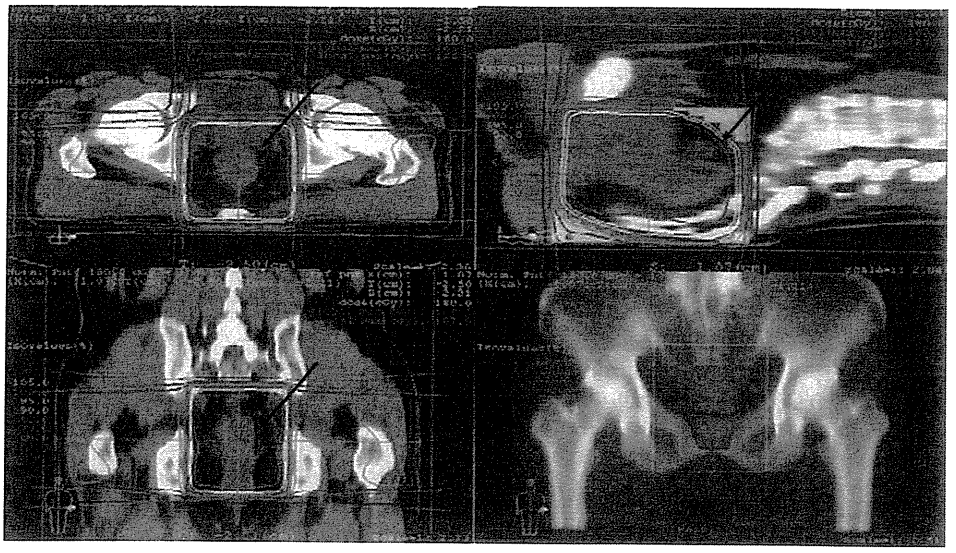

Fig. 2. Treatment field of radiation therapy.

to ingest solid foods and drugs orally. The eligible patients could not be transfused with red cells to meet these criteria.

Before enrollment in the study, we reviewed the histories of past and present disease and the general condition of all patients, assessed based on interview, physical examination, and blood tests. Locally advanced rectal cancer (clinical T3 or T4) without distant metastasis was confirmed by barium enema; colonoscopy including histopathologic evaluation; computed tomographic scans of the chest, abdomen, and pelvis; and magnetic resonance imaging (MRI) of the pelvis. Magnetic resonance imaging of the pelvis is useful to differentiate the clinical diagnosis of T3 and T4 and lymph node metastasis adjacent to the rectum. Differential diagnostic standards of MRI dictate that clinical T3 indicates a breach of the outer layer of the longitudinal muscle on T2 intensity imaging and T4 indicates irregular invasion to the extracorporeal region of the rectum on T1 intensity imaging.

Radiotherapy and chemotherapy

The treatment field of radiotherapy has been published previously (16). In brief, radiotherapy was administered in fractions of 1.8 Gy/d, given 5 days per week for 5 weeks. The total dose of radiation was 45 Gy. Patients were treated in the prone position, by use of a dedicated device (lead board) to minimize exposure of the small bowel. A computed tomography–based treatment planning system was mandatory to define the planned target volume (PTV), which allowed for setup error, organ movement, and a 1-cm circumference (clinical target volume) around both the primary tumors including regions invading surrounding organs or tissues and the adjacent swollen lymph nodes (gross tumor volume) (Fig. 2). The PTV was treated with radiation from a 10-MV linear accelerator, and we used a four-field box technique. The clinical target volume for the primary tumor used in this study typically included the perirectal lymph nodes. The target volumes used for radiotherapy in this study are far smaller in comparison to those usually described in North American and European practice, where the internal iliac nodes and often the external iliac nodes are electively irradiated. Thirty-eight patients had swollen lymph nodes included in the gross tumor volume preoperatively, and none was outside the PTV for radiotherapy. The response rate of the primary tumor was graded, but that of lymph nodes was not assessed.

S-1 (80 mg · m^{-2} · d^{-1}) was given orally after breakfast and dinner on Days 1 to 5, 8 to 12, 22 to 26, and 29 to 33. Irinotecan (80 mg · m^{-2} · d^{-1}) was given as an intravenous infusion over a period of 90 minutes on Days 1, 8, 22, and 29. The relative dose of irinotecan between the folinic acid, 5-FU, and irinotecan regimen and that used in this study is 180 mg/m^2 biweekly vs. 80 mg/m^2 weekly (180/160 = 1.125). The rationale for using a 1-week interval for chemoradiotherapy was to allow recovery of the patient's fatigue. It was our impression that a shorter interval duration would lead to several patients discontinuing the regimen before its completion.

Surgery

Total mesorectal excision with bilateral autonomic nerve preservation was performed, and lymph nodes were dissected from the middle rectal, internal iliac, and obturator lymph node regions. For sphincter-preserving surgery, the anorectal side of the rectum was divided, leaving a margin of at least 2 cm from the inferior border of the tumor. Abdominoperineal resection was done if the distal margin was insufficient.

Criteria for modification of treatment schedule and dosage

Our protocol specified that the regimens may be suspended for Grade 3 or worse diarrhea and nausea/vomiting, and we prospectively assessed hematologic, urinary, and dermatologic toxicities every 7 days by blood, urine, and dermatologic assessment. Toxicities were evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 2. If toxicity necessitated a dose reduction within a course of treatment, the dose could be decreased by one step (20%) of irinotecan and treatment resumed. If toxicity requiring a further dose reduction recurred after the dose was decreased by one step, the study was terminated in the patient, with no further decrease in dosage.

Method for calculating rate of completing treatment

The ratios of the total administered dose to the total scheduled dose up to the date of surgery were calculated for radiotherapy,

S-1, and irinotecan by the following formula: Administered dose/Scheduled dose × 100 (%). We defined completing treatment as administered dose equal to or over 75% of full dose, and such cases actually coincided with the patients who were given 100% of the dose of chemotherapy.

Method for calculating rate of response

After surgery, the responses of tumors to chemoradiotherapy were histopathologically evaluated by examining serial sections of the resected specimens. Responses were evaluated based on the degree of degeneration or necrosis and fusion of cancer cells. No response was assigned a grade of 0, and a CR was assigned a grade of 3. The criteria for histopathologically evaluating the response to preoperative chemoradiotherapy, according to the Histopathological Response Criteria of the General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus edited by the Japanese Society for Cancer of the Colon and Rectum, have been previously described (16). In brief, complete, considerable, and slight responses coincide with Grade 3, Grade 2, and Grade 1, respectively.

Endpoints and statistical considerations

The primary endpoint was the rate of completing treatment in terms of feasibility. The secondary endpoints were the response rate, safety (incidences of adverse reactions and complications), local recurrence rate, and overall survival. The response rate is determined based on pathologic CR, as well as incidences of adverse reactions including hematologic, urologic, dermatologic, and symptomatic complications. Data on local recurrence and overall survival are not presented in this report, because follow-up is not sufficient to allow conclusions regarding survival outcome.

We calculated the required sample size for this study based on a target rate of treatment completion of 70% and a minimum completion rate of 50%, with an α error of 0.05 (1-sided) and a β error of 0.1. The required number of patients was estimated to be 50. In anticipation of 10% of patients being ineligible, we planned to enroll 55 patients. Ineligible patients were those who did not provide informed consent or who had rectal cancer located in portions other than those above the peritoneal reflection or below the peritoneal reflection. Patient enrollment was discontinued at the end of the month when the target number of 55 subjects had been reached. The final number of enrolled patients was 67. The final number was higher than the target number of 55 by 12, but less than 1 month had elapsed between the dates of enrollment of Patient 55 and Patient 67. Moreover, Patient 67 started treatment before the results for Patient 55 were analyzed. We therefore decided that the histopathologic findings from all enrolled patients should be included in this analysis and considered this a valid procedure. The final number of enrolled patients was therefore higher than the initially planned target number.

RESULTS

Table 1 shows the demographic characteristics of the 67 patients with locally advanced rectal cancer who were eligible for the study and received preoperative chemoradiotherapy at our hospital. Median follow-up was 26 months (range, 11 to 51 months).

Table 1. Clinical characteristics of patients with locally advanced rectal cancer who received preoperative chemoradiotherapy

Clinical characteristic	Data	%
Sex		
Male	43	64.2
Female	24	35.8
Age (y)		
Median	63	
Range	32–79	
ECOG performance status		
0	67	100
1	0	0
Tumor site		
Ra	23	34.3
Rab	7	10.5
Rb	37	55.2
Depth of invasion		
T3	56	83.6
T4	11	16.4
Preoperative chemoradiotherapy		
Lymph nodes		
N0	30	44.8
N1	36	53.7
N2	1	1.5

Abbreviations: ECOG = Eastern Cooperative Oncology Group; Ra = rectum above peritoneal reflection; Rab = rectum above and below peritoneal reflection; Rb = rectum below peritoneal reflection.

Data are presented as No. of patients, unless otherwise indicated.

Primary endpoint

Of the 67 patients, 66 (98.5%) completed treatment based on our definition of completing treatment. The dose of irinotecan was reduced by 20%, and the radiation and S-1 protocols were not changed (except in 1 patient, who forgot to take S-1 for several days and in whom final S-1 compliance was equal to or over 90% but less than 100%, as shown in Table 2). Eight patients exhibited irinotecan compliance equal to or over 70% but less than 80% (Table 2). Finally, 1 patient who did not complete treatment had Grade 3 anorexia, nausea, and vomiting, and these symptoms responded to treatment with fluid therapy; however, treatment was discontinued at the patient's request. On the other hand, the rate of completing treatment reached 86.6% (58 of 67) per the protocol according to the criteria of the Cancer and Leukemia Group B (CALGB) study (17), where rates of completing treatment were determined in two categories of patients—those having completed six cycles of oxaliplatin (56%) and those having completed at least four cycles of therapy (72%). In our study 58 patients completed treatment with 100% of the dosage (including four cycles of chemotherapy).

Secondary endpoints

The pathologic response was Grade 3 (pathologic CR in the primary cancer) in 25 (37.3%) of 67 patients (Table 3). Because we included 1 case with lymph node metastasis, the number of bona fide cases exhibiting pathologic CR was therefore 24 patients (34.7% [24 of 67]) (Table 4). The