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

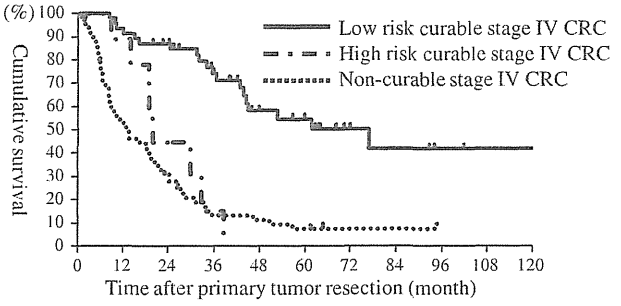

Fig. 2 The OS in patients with noncurable and curable stage IV CRC classified by the independent prognostic factors. For patients with curable stage IV CRC, the OS of the high risk group was significantly poorer than that of the low risk group ($p<0.001$). Furthermore, the OS of this group was as poor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

Acknowledgments We would like to express our gratitude to the staff of our department for their assistance in the collection and registration of patient's data.

References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D (2011) Global cancer statistics. CA Cancer J Clin 61:69–90
2. Mahmoud N, Bullard Dunn K (2010) Metastasectomy for stage IV colorectal cancer. Dis Colon Rectum 53:1080–1092
3. Eadens MJ, Grothey A (2011) Curable metastatic colorectal cancer. Curr Oncol Rep 13:168–176
4. Primrose JN (2010) Surgery for colorectal liver metastases. Br J Cancer 102:1313–1318
5. Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH (1999) Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1,001 consecutive cases. Ann Surg 230:309–318, discussion 318–321
6. Kanemitsu Y, Kato T (2008) Prognostic models for predicting death after hepatectomy in individuals with hepatic metastases from colorectal cancer. World J Surg 32:1097–1107
7. Takakura Y, Miyata Y, Okajima M, Okada M, Ohdan H (2010) Short disease-free interval is a significant risk factor for intrapulmonary recurrence after resection of pulmonary metastases in colorectal cancer. Colorectal Dis 12(7 Online):e68–e75
8. Demmy TL, Dunn KB (2007) Surgical and nonsurgical therapy for lung metastasis: indications and outcomes. Surg Oncol Clin N Am 16:579–605, ix
9. Pfannschmidt J, Dienemann H, Hoffmann H (2007) Surgical resection of pulmonary metastases from colorectal cancer: a systematic review of published series. Ann Thorac Surg 84:324–338
10. Shibata D, Paty PB, Guillem JG, Wong WD, Cohen AM (2002) Surgical management of isolated retroperitoneal recurrences of colorectal carcinoma. Dis Colon Rectum 45:795–801
11. Esquivel J, Elias D, Baratti D, Kusamura S, Deraco M (2008) Consensus statement on the loco regional treatment of colorectal cancer with peritoneal dissemination. J Surg Oncol 98:263–267

12. Huang PP, Weber TK, Mendoza C, Rodriguez-Bigas MA, Petrelli NJ (1998) Long-term survival in patients with ovarian metastases from colorectal carcinoma. Ann Surg Oncol 5:695–698
13. Erroi F, Scarpa M, Angriman I, Cecchetto A, Pasetto L, Mollica E, Bettiol M, Ruffolo C, Polese L, Cillo U et al (2007) Ovarian metastasis from colorectal cancer: prognostic value of radical oophorectomy. J Surg Oncol 96:113–117
14. Lefevre JH, Rondelli F, Mourra N, Bennis M, Tiret E, Parc R, Parc Y (2008) Lumboaortic and iliac lymphadenectomy for lymph node recurrence of colorectal cancer: prognostic value of the MSI phenotype. Ann Surg Oncol 15:2433–2438
15. Min BS, Kim NK, Sohn SK, Cho CH, Lee KY, Baik SH (2008) Isolated paraaortic lymph-node recurrence after the curative resection of colorectal carcinoma. J Surg Oncol 97:136–140
16. Nordlinger B, Guiguet M, Vaillant JC, Balladur P, Boudjema K, Bachellier P, Jaeck D (1996) Surgical resection of colorectal carcinoma metastases to the liver. A prognostic scoring system to improve case selection, based on 1,568 patients. Association Francaise de Chirurgie. Cancer 77:1254–1262
17. Kattan MW, Gonen M, Jarnagin WR, DeMatteo R, D'Angelica M, Weiser M, Blumgart LH, Fong Y (2008) A nomogram for predicting disease-specific survival after hepatic resection for metastatic colorectal cancer. Ann Surg 247:282–287
18. Gomez D, Cameron IC (2010) Prognostic scores for colorectal liver metastasis: clinically important or an academic exercise? HPB (Oxford) 12:227–238
19. Katoh H, Yamashita K, Kokuba Y, Satoh T, Ozawa H, Hatate K, Ihara A, Nakamura T, Onosato W, Watanabe M (2008) Surgical resection of stage IV colorectal cancer and prognosis. World J Surg 32:1130–1137
20. Watkins DJ, Chau I, Cunningham D, Mudan SS, Karanjia N, Brown G, Ashley S, Norman AR, Gillbanks A (2010) Defining patient outcomes in stage IV colorectal cancer: a prospective study with baseline stratification according to disease resectability status. Br J Cancer 102:255–261
21. Japanese Society for Cnacer of the Colon and Rectum (2009) General rules for clinical and pathological studies on cancer of the colon, rectum and anus (The 7th Edition, Revised version). Kanehara shuppan, Tokyo
22. Sobin LHGM, Wittekind C (2003) TNM classification of malignant tumors, 6th edn. Wiley, New York
23. Dindo D, Demartines N (2004) Clavien PA (2004) Classification of surgical complications: a new proposal with evaluation in a cohort of 6,336 patients and results of a survey. Ann Surg 240:205–213
24. Garden OJ, Rees M, Poston GJ, Mirza D, Saunders M, Ledermann J, Primrose JN, Parks RW (2006) Guidelines for resection of colorectal cancer liver metastases. Gut 55(Suppl 3):iii1–iii8
25. Shah SA, Haddad R, Al-Sukhni W, Kim RD, Greig PD, Grant DR, Taylor BR, Langer B, Gallinger S, Wei AC (2006) Surgical resection of hepatic and pulmonary metastases from colorectal carcinoma. J Am Coll Surg 202:468–475
26. Elias D, Ouellet JF, Bellon N, Pignon JP, Pocard M, Lasser P (2003) Extrahepatic disease does not contraindicate hepatectomy for colorectal liver metastases. Br J Surg 90:567–574
27. Bismuth H, Adam R, Levi F, Farabos C, Waechter F, Castaing D, Majno P, Engerran L (1996) Resection of nonresectable liver metastases from colorectal cancer after neoadjuvant chemotherapy. Ann Surg 224:509–520, discussion 520–502
28. Adam R, Pascal G, Castaing D, Azoulay D, Delvart V, Paule B, Levi F, Bismuth H (2004) Tumor progression while on chemotherapy a contraindication to liver resection for multiple colorectal metastases? Ann Surg 240:1052–1061, discussion 1061–1054
29. Poultsides GA, Servais EL, Saltz LB, Patil S, Kemeny NE, Guillem JG, Weiser M, Temple LK, Wong WD, Paty PB (2009) Outcome of primary tumor in patients with synchronous stage IV colorectal cancer receiving combination chemotherapy without surgery as initial treatment. J Clin Oncol 27:3379–3384
30. Stillwell AP, Buettner PG, Ho YH (2010) Meta-analysis of survival of patients with stage IV colorectal cancer managed with surgical resection versus chemotherapy alone. World J Surg 34:797–807
31. de Santibanes E, Fernandez D, Vaccaro C, Quintana GO, Bonadeo F, Pekolj J, Bonofiglio C, Molmenti E (2010) Short-term and long-term outcomes after simultaneous resection of colorectal malignancies and synchronous liver metastases. World J Surg 34:2133–2140
32. Huh JW, Cho CK, Kim HR, Kim YJ (2010) Impact of resection for primary colorectal cancer on outcomes in patients with synchronous colorectal liver metastases. J Gastrointest Surg 14:1258–1264

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 79, No. 3, pp. 677–683, 2011

0360-3016/$–see front matter

doi:10.1016/j.ijrobp.2009.11.007

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

TAKEO SATO, M.D.,* HEITA OZAWA, M.D.,* KAZUHIKO HATATE, M.D.,* WATARU ONOSATO, M.D.,* MASANORI NAITO, M.D.,* TAKATOSHI NAKAMURA, M.D.,* ATSUSHI IHARA, M.D.,* WASABURO KOIZUMI, M.D.,† KAZUSHIGE HAYAKAWA, M.D.,‡ ISAO OKAYASU, M.D.,§ KEISHI YAMASHITA, M.D.,* AND MASAHIKO WATANABE, M.D.*

Departments of *Surgery, †Internal Medicine, ‡Radiology, and §Department of Pathology, Kitasato University School of Medicine, Kanagawa, Japan

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

Reprint requests to: Masahiko Watanabe, M.D., Ph.D., Department of Surgery, Kitasato University School of Medicine, 1-15-1, Kitasato, Sagamihara, Kanagawa, 228-8555, Japan. Tel: (+81) 42-778-8735; E-mail: rint@kitasato-u.ac.jp

Supplementary material for this article can be found at www.redjournal.org.

Conflict of interest: none.

Received April 1, 2009, and in revised form Nov 16, 2009. Accepted for publication Nov 18, 2009.

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.

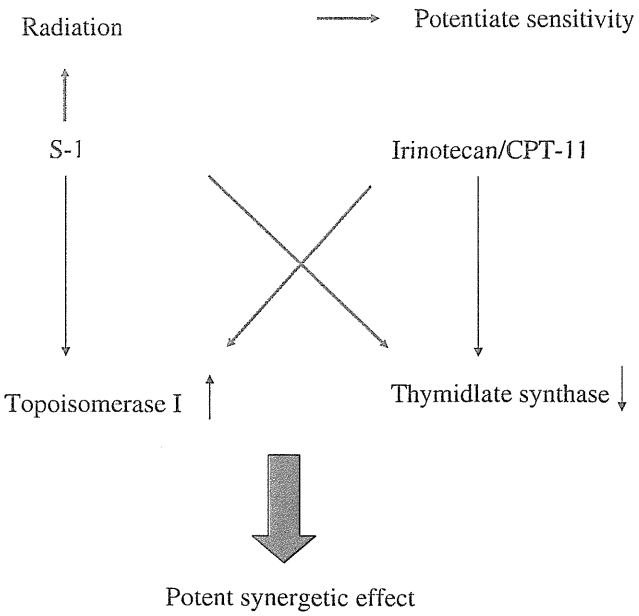

Fig. 1. Interaction of S-1 and irinotecan.

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

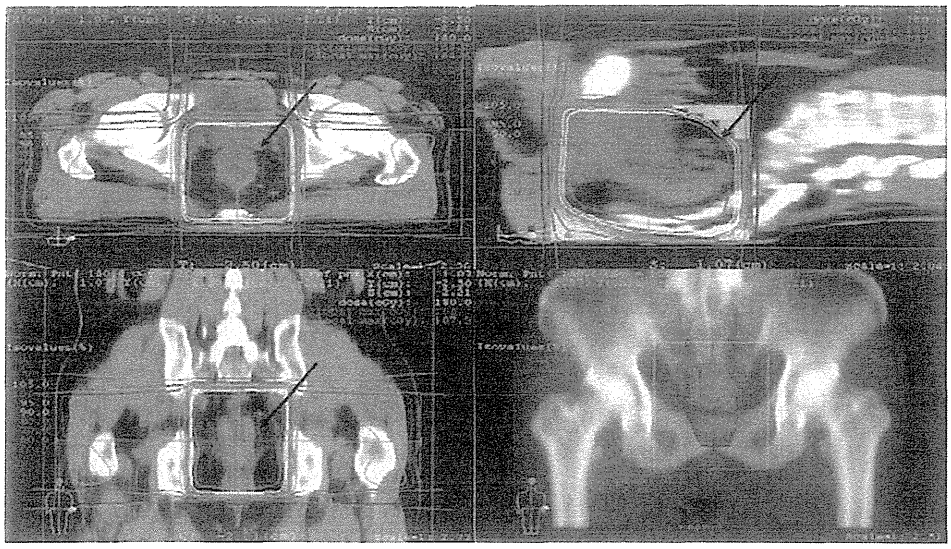

Fig. 2. Treatment field of radiation therapy.

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 $\cdot$ m^{-2} $\cdot$ 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 $\cdot$ m^{-2} $\cdot$ 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

Table 2. Treatment exposure

Relative dose intensity (%)	S-1* (median dose intensity, 80 mg · m^{-2} · d^{-1} × 25 days)		Irinotecan (median dose intensity, 80 mg · m^{-2} · d^{-1} × 4 days)	
	No. of patients	%	No. of patients	%
100	65	97	58	86.6
≥90 to <100	1	1.5	0	0
≥80 to <90	0	0	0	0
≥70 to <80	0	0	8	11.9
Missing	1	1.5	1	1.5

* The maximum dose of S-1 was 120 mg · m^{-2} · d^{-1}.

rate of pathologic CR was 31.6% in the Phase I setting (16), and our result was comparable in this Phase II setting. The total response rate involving both Grade 2 (considerable response) and Grade 3 (CR) was 68.7% (46 of 67 patients), whereas that including even Grade 1a/1b (slight response) reached 100%, if evaluated in the primary cancers (Table 3). Although no cancer cells were found in 54 patients (80.6%) on colonoscopy with biopsy after chemoradiotherapy, more than half of these patients were actually confirmed to have residual disease on histopathologic examination of the resected specimens.

Safety includes incidences of adverse reactions and complications, and adverse events as acute toxicities are summarized in Table 5. Adverse events are infrequent, and there was no Grade 4 hematologic or nonhematologic toxicity. Regarding hematologic toxicity, only 3 patients had Grade 3 leukopenia and 3 had Grade 3 neutropenia. One patient with Grade 3 leukopenia concurrently had Grade 3 thrombocytopenia. Regarding nonhematologic toxicity, only 3 patients had Grade 3 diarrhea, which promptly improved after treatment with a continuous intravenous infusion. One patient had Grade 3 anorexia and nausea; treatment was withdrawn before completion at the patient's request. Activity of either dihydropyrimidine dehydrogenase or orotate phosphoribosyl transferase enzyme was not assessed in this study, but such enzyme deficiency might have been involved in the patient with Grade 3 anorexia and nausea.

Surgical procedures and pathologic findings

Of the 67 patients, 50 (74.6%) underwent sphincter-preserving surgery and 17 (25.4%) underwent abdominoperineal resection. A diverting ileostomy was created in all patients who underwent sphincter-preserving surgery. We currently perform ileostomy for patients who had sphincter-preserving surgery in case of anastomotic leakage, because we are afraid that the low anterior resection was done after radiation therapy. Such ileostomy is a transient stoma and usually reversed 6 months to a 1 year later. For patients undergoing abdominoperineal resection, the sigmoid colon was diverted.

The median number of examined lymph nodes was 19 (range, 12 to 52). Among the 67 patients, 26 were found to have lymph node metastasis: 18 (26.9%) had pathologic N1 disease (1–3 metastatic regional lymph nodes) and 8 (11.9%) had pathologic N2 disease (≥4 metastatic regional lymph nodes). The relation between the response of the primary tumor and lymph node metastasis is shown in Table 4. Downstaging of the primary tumor according to clinical T stage was confirmed in 49 patients (73.1%). Of the 37 patients evaluated to have node-positive disease before treatment, 16 (43.2%) had no pathologic evidence of lymph node metastasis. In 1 patient with a Grade 3 response of the primary tumor, 2 metastatic lymph nodes were found in the field of the inferior mesenteric artery.

In 6 of the 26 patients with lymph node metastasis, metastatic lymph nodes along the internal iliac artery and obturator foramen were recognized but were dissected by surgery. These patients all had enlarged lymph nodes in these regions on computed tomography and/or MRI before treatment. Such patients with pathologic evidence of lymph node metastasis also received six courses of postoperative adjuvant chemotherapy with S-1 (80 mg/m^2), given for 14 days, followed by 14 days of rest, and irinotecan (125 mg/m^2), given on Days 1 and 15.

Table 3. Pathologic primary tumor response as secondary endpoint

Grade	Response to treatment	
	No. of patients	%
1a	5	7.5
1b	16	23.9
2	21	31.3
3	25	37.3

The response rate was good in 68.7% of patients, and the response rate was good or slight in 100%.

Table 4. Relation between response to treatment and lymph node metastasis

Grade	Response to treatment		
	No. of patients	No. of patients with lymph node metastasis	%
1a	5	1	20
1b	16	12	75
2	21	12	57.1
3	25	1	4

Table 5. Acute toxicity during treatment course

	Grade 1 [*n* (%)]	Grade 2 [*n* (%)]	Grade 3 [*n* (%)]	Grade 4 [*n* (%)]
Hematologic toxicity				
Leukopenia	0	10 (14.9)	3* (4.5)	0
Neutropenia	0	1 (1.5)	3 (4.5)	0
Thrombocytopenia	0	0	1* (1.5)	0
Nonhematologic toxicity				
Diarrhea	2 (3.0)	2 (3.0)	3 (4.5)	0
Anorexia/nausea	0	0	1 (1.5)	0

* One patient had leukopenia and thrombocytopenia.

Postoperative complications

Postoperative bleeding from a branch of the internal iliac vein required emergency surgery to achieve hemostasis. One patient with intestinal obstruction did not respond to conservative treatment and underwent reoperation (untethering). There were no perioperative or postoperative deaths or postoperative sequelae.

DISCUSSION

Our protocol is considered sufficiently safe, with high rates (86.6%) of completing treatment as compared with the previous studies. There was no Grade 4 toxicity, and all Grade 3 adverse events responded to conservative treatment. In the European Organisation for Research and Treatment of Cancer 22921 study, the rate of completing treatment was 82.0% in the two groups who received preoperative chemoradiotherapy (6). In the CALGB 89901 study, the incidence of Grade 3 or 4 diarrhea was 38% in patients who received preoperative chemotherapy with oxaliplatin plus 5-FU, and the percentage of patients who completed treatment was 72% (17), if we consider completing treatment to have been achieved with at least four cycles of therapy, similar to the definition we used. The recommended dose determined based on a Phase I clinical study of our regimen was thus deemed to be appropriate (16).

The low incidence of complications might be attributed primarily to the fact that the irradiated field was adequately reduced. 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. We have to keep this difference in mind in determining whether we can safely use S-1 and irinotecan along with the more typical larger radiotherapy volumes used compared with the volumes used in this study. Reduced irradiated fields of our protocol can be reasoned for surgical procedures including lateral lymph node dissection, which is one of the standard surgical options in Japan.

The rate of pathologic CR in our study was 34.7%, which was clearly higher than the rates (11%–17%) in the previous studies (8, 18–21) (Table E1). In our study serial sections of tumor tissue were evaluated histopathologically. The reliability of the pathologic evaluation of CR is therefore considered higher than that in previous studies. The median number of dissected lymph nodes was 19 (range, 12–52), considered adequate for lymph node dissection. The addition of another anticancer agent to 5-FU–based chemotherapy plus radiotherapy at a dose of 45 Gy or higher was found to contribute to a higher rate of pathologic CR, consistent with the results of other studies (22, 23). The rate of pathologic CR to 5-FU/leucovorin regimens was 20% or less in most studies. In the CALGB 89901 study, in which patients also received oxaliplatin, the rate of pathologic CR improved to 25%, but serious diarrhea and a low rate of completing treatment were problems (17). With our regimen for chemoradiotherapy, the rates of completing treatment (86.6%) and of pathologic CR (34.7%) reached satisfactory levels. Such good outcomes might be attributed to increased radiosensitivity of tumor cells induced by components of S-1 or to synergism between irinotecan and tegafur (Fig. 1). UGT1A1 nucleotide polymorphisms, which are supposed to determine the sensitivity of irinotecan, were not assessed in our study. However, treatment could be completed safely, perhaps because the dose of irinotecan was lower than that used in folinic acid, 5-FU, and irinotecan regimens (88.9%).

Several retrospective studies have reported on the close association between the rate of pathologic CR and long-term outcomes (24, 25), but such a positive correlation between these factors has yet to be clearly shown in a prospective study. In our study overall survival is being followed up as a secondary endpoint. In addition to long-term outcomes, the relation between pathologic CR and the long-term outcome is an interesting issue. Some patients with a pathologic CR may have not required surgery, but postoperative histopathologic examinations are currently required to establish the occurrence of a pathologic CR. More than half of these patients with no cancer cells on colonoscopy with biopsy after chemoradiotherapy were actually confirmed to have residual disease on histopathologic examination of the resected specimens. It is therefore difficult to evaluate the bona fide response rate only on biopsy without surgery. New examination methods other than biopsy will hopefully be established to accurately evaluate pathologic CR before surgery.

Roels *et al.* (26) reported that the rates of recurrence in the pelvic cavity were 49% in the posterior region (presacral region), 21% in the lateral region (internal iliac lymph node region), and 12% in the inferior region (perineal region). Posterior and inferior lymph nodes can be adequately

removed by TME, whereas lateral lymph nodes were not included in the irradiated field in our study and were resected surgically. If these lateral lymph nodes had not been dissected, pelvic recurrence may have occurred. The irradiated field is thus expected to become an important issue in patients with enlarged lateral lymph nodes before treatment. The clinical significance of conventional lateral lymph node dissection has yet to be shown in clinical studies. To determine the optimal irradiated field for patients with lateral lymph node metastasis, we are now closely following local recurrence and outcomes, two other secondary endpoints of this study.

In conclusion, the regimen that we developed for preoperative treatment generated promising results. However, many issues remain unresolved, including the dose (including chemotherapy cycles), duration of chemoradiotherapy, radiation target volumes in patients with lateral lymph node metastasis, optimal concomitant agents, preoperative evaluation methods for response, role of adjuvant chemotherapy, and especially, survival benefit. To assess our regimen for locally advanced rectal adenocarcinoma, the durations of disease-/recurrence-free survival and overall survival should be carefully analyzed prospectively in Phase II trials, and then large Phase III trials might be anticipated.

REFERENCES

1. Marugame T, Matsuda T, Kamo K, *et al.* Cancer incidence and incidence rates in Japan in 2001 based on the data from 10 population-based cancer registries. *Jpn J Clin Oncol* 2007;37:884–891.
2. Heald RJ, Husband EM, Ryall RD, *et al.* The mesorectum in rectal cancer surgery—The clue to pelvic recurrence? *Br J Surg* 1982;69:613–616.
3. MacFarlane JK, Ryall RD, Heald RJ, *et al.* Mesorectal excision for rectal cancer. *Lancet* 1993;341:457–460.
4. Prolongation of the disease-free interval in surgically treated rectal carcinoma. Gastrointestinal Tumor Study Group. *N Engl J Med* 1985;312:1465–1472.
5. NIH consensus conference. Adjuvant therapy for patients with colon and rectal cancer. *JAMA* 1990;264:1444–1450.
6. Skibber J, Hoff P, Minsky B. Cancer of the rectum. In: Devita V, Hellman S, Rosenberg S, editors. Cancer: Principles and practice of oncology. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 1271–1318.
7. Improved survival with preoperative radiotherapy in resectable rectal cancer. Swedish Rectal Cancer Trial. *N Engl J Med* 1997; 336:980–987.
8. Bosset JF, Collette L, Calais G, *et al.* Chemotherapy with preoperative radiotherapy in rectal cancer. *N Engl J Med* 2006; 355:1114–1123.
9. Guillem JG, Chessin DB, Cohen AM, *et al.* Long-term oncologic outcome following preoperative combined modality therapy and total mesorectal excision of locally advanced rectal cancer. *Ann Surg* 2005;241:829–836. discussion 836–828.
10. Nakata E, Fukushima M, Takai Y, *et al.* S-1, an oral fluoropyrimidine, enhances radiation response of DLD-1/FU human colon cancer xenografts resistant to 5-FU. *Oncol Rep* 2006;16: 465–471.
11. Que BG, Ardalan B, Richman S. Camptosar reduced the thymidylate synthase gene expression in 5-FU-resistant cell line [Abstract]. *Proc Am Assoc Cancer Res* 2000;41:749.
12. Guichard S, Hennebelle I, Bugat R, *et al.* Cellular interactions of 5-fluorouracil and the camptothecin analogue CPT-11 (irinotecan) in a human colorectal carcinoma cell line. *Biochem Pharmacol* 1998;55:667–676.
13. Funakoshi S. Enhanced antitumor activity of SN-38, an active metabolite of CPT-11, and 5-fluorouracil combination for human colorectal cancer cell lines [Abstract]. *Proc Am Soc Clin Oncol* 1993;12:563.
14. Ichikawa W, Uetake H, Nihei Z, *et al.* Topoisomerase I expression correlates to thymidylate synthase expression in colorectal cancer [Abstract]. *Proc Am Soc Clin Oncol* 1999;17:946.
15. O'Connell MJ, Martenson JA, Wieand HS, *et al.* Improving adjuvant therapy for rectal cancer by combining protracted-infusion fluorouracil with radiation therapy after curative surgery. *N Engl J Med* 1994;331:502–507.
16. Sato T, Kokuba Y, Koizumi W, *et al.* Phase I trial of neoadjuvant preoperative chemotherapy with S-1 and irinotecan plus radiation in patients with locally advanced rectal cancer. *Int J Radiat Oncol Biol Phys* 2007;69:1442–1447.
17. Ryan DP, Niedzwiecki D, Hollis D, *et al.* Phase I/II study of preoperative oxaliplatin, fluorouracil, and external-beam radiation therapy in patients with locally advanced rectal cancer: Cancer and Leukemia Group B 89901. *J Clin Oncol* 2006;24:2557–2562.
18. Sauer R, Becker H, Hohenberger W, *et al.* Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med* 2004;351:1731–1740.
19. Gerard J-P, Conroy T, Bonnetain F, *et al.* Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: Results of FFCD 9203. *J Clin Oncol* 2006;24:4620–4625.
20. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, *et al.* Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. *Br J Surg* 2006;93: 1215–1223.
21. Roh MS, Colangelo L, Wieand S, *et al.* Response to preoperative multimodality therapy predicts survival in patients with carcinoma of the rectum [Abstract]. *Proc Am Soc Clin Oncol* 2004; 22:3505.
22. Hartley A, Ho KF, McConkey C, *et al.* Pathological complete response following pre-operative chemoradiotherapy in rectal cancer: Analysis of phase II/III trials. *Br J Radiol* 2005;78: 934–938.
23. Sanghera P, Wong DW, McConkey CC, *et al.* Chemoradiotherapy for rectal cancer: An updated analysis of factors affecting pathological response. *Clin Oncol (R Coll Radiol)* 2008;20:176–183.
24. Janjan NA, Crane C, Feig BW, *et al.* Improved overall survival among responders to preoperative chemoradiation for locally advanced rectal cancer. *Am J Clin Oncol* 2001;24:107–112.
25. Capirci C, Valentini V, Cionini L, *et al.* Prognostic value of pathologic complete response after neoadjuvant therapy in locally advanced rectal cancer: long-term analysis of 566 ypCR patients. *Int J Radiat Oncol Biol Phys* 2008;72:99–107.
26. Roels S, Duthoy W, Haustermans K, *et al.* Definition and delineation of the clinical target volume for rectal cancer. *Int J Radiat Oncol Biol Phys* 2006;65:1129–1142.

ANTICANCER RESEARCH *31*: 3073-3078 (2011)

Neoadjuvant Chemoradiotherapy for Clinical Stage II-III Esophageal Squamous Cell Carcinoma

HIROSHI SAEKI, MASARU MORITA, YUICHIRO NAKASHIMA, HIDETO SONODA, KENKICHI HASHIMOTO, AKINORI EGASHIRA, EIJI OKI, TAKEFUMI OHGA, YOSHIHIRO KAKEJI and YOSHIHIKO MAEHARA

Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

Abstract. *Background: The clinical significance of neoadjuvant chemoradiotherapy (NACRT) for potentially resectable esophageal squamous cell carcinoma (ESCC) is unclear. Patients and Methods: Patients with clinical stage II-III ESCC were classified into an NACRT group (n=76) and surgery alone group (n=92). The prognosis and the incidence of postoperative complications were retrospectively investigated. The pathological response to NACRT and patient prognosis were also analyzed. Results: The 5-year survival rate was 47.7% in the surgery alone group and 56.5% in the NACRT group (p=0.4831). The 5-year survival rates of patients in whom NACRT was markedly effective was clearly better than that of the other patients (ineffective/slightly effective: 36.9%, moderately effective: 53.8%, markedly effective: 100%). The incidence of postoperative complications was 31.5% in the surgery alone group and 40.8% in the NACRT group (p=0.2121). Conclusion: A pathological complete response to NACRT is critical for improving the survival of patients with clinical stageII-III ESCC.*

Since the majority of patients with esophageal cancer still tend to have widespread disease at the time of detection, esophageal cancer remains one of the most difficult malignancies in the digestive tract to control by surgery alone (1). Neoadjuvant chemoradiotherapy (NACRT) has been applied for esophageal cancer, mainly at advanced stages, for the purpose of reducing the main tumor and control of microscopic metastases. However, the clinical usefulness of NACRT for potentially resectable esophageal cancer still remains controversial. Some randomized studies and meta-analyses have emphasized the superiority of the clinical results in NACRT plus surgery to those of surgery alone (2, 3), whereas other reports have shown that the difference was not significant (4-6). With regard to postoperative complications, NACRT for esophageal cancer was reported to increase their incidence (7, 8). However, others have reported that the incidence of complications was similar to that in the patients who received surgery without NACRT (9-11).

In Japan, the clinical significance of NACRT for resectable advanced esophageal squamous cell carcinoma (ESCC) still remains controversial. In this study, we retrospectively evaluated the usefulness of NACRT for clinical stage II-III (cStageII-III) ESCC. We also examined the relationship between NACRT and the development of postoperative complications.

Correspondence to: Hiroshi Saeki, MD, Ph.D., Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan. Fax: +81 926425482, Tel: +81 926425466, e-mail: h-saeki@surg2.med.kyushu-u.ac.jp

Key Words: Esophageal squamous cell carcinoma, neoadjuvant chemoradiotherapy, pathological response, complication, prognosis.

Patients and Methods

Patients. An esophagectomy was performed in 168 patients with cStageII-III ESCC between 1998 and 2007 in the Department of Surgery and Science at Kyushu University, Japan. Among these patients, NACRT had been performed for 76 patients, while surgery alone was indicated for 92 patients. For cStageII-III patients, NACRT was principally administered between 1998 and 2002. However, since NACRT was found to demonstrate no substantial survival benefit, surgery without neoadjuvant therapy was performed between 2003 and 2007. Therefore, this study is retrospective, without randomization, but is based on historical controls.

The clinicopathological backgrounds according to the administration of NACRT are shown in Table I. There were some differences in the clinical backgrounds between the two groups: the incidence of clinical T1b was significantly lower in the NACRT group than in the surgery alone group ($p<0.05$). The incidence of pathological T1 and pathological N (+) was also significantly lower in the NACRT group than in that of surgery alone ($p<0.05$ and $p<0.0005$, respectively). The pathological stage (pStage) was significantly more advanced in the NACRT group than in that of surgery alone ($p<0.05$). There were no differences in factors such as age, gender, location of the tumor, clinical N factor, cStage and curability.

0250-7005/2011 $2.00+.40

Table I. *Clinicopathological background according to NACRT.*

Factor		NACRT, n (%)		*p*-Value
		No (n=92)	Yes (n=76)	
Gender	Male	80 (87.0)	62 (81.6)	0.3375
	Female	12 (13.0)	14 (18.4)	
Age, years (mean)		63.6	62.6	0.5165
Location of tumor	Upper	12 (13.0)	14 (18.4)	0.4012
	Middle	40 (43.5)	36 (47.4)	
	Lower	40 (43.5)	26 (34.2)	
Clinical T factor	cT1b	10 (10.9)	1 (1.3)	0.0183*
	cT2	30 (32.6)	20 (26.3)	
	cT3	52 (56.5)	55 (72.4)	
Clinical N factor	cN (–)	38 (41.3)	36 (47.4)	0.4307
	cN (+)	54 (58.7)	40 (52.6)	
Clinical stage	II	53 (57.6)	41 (53.9)	0.6342
	III	39 (42.4)	35 (46.1)	
Pathological T factor	pT1	22 (23.9)	3 (3.9)	0.0010*
	pT2, 3	65 (70.7)	70 (92.1)	
	pT4	5 (5.4)	3 (3.9)	
Pathological N factor	pN (–)	27 (29.3)	44 (57.9)	0.0002*
	pN (+)	65 (70.7)	32 (42.1)	
Pathological stage	I	12 (13.0)	2 (2.6)	0.0469*
	II, III	73 (79.3)	69 (90.8)	
	IV	7 (7.6)	5 (6.6)	
Curability	Curative	77 (83.7)	67 (88.2)	0.4107
	Non-curative	15 (16.3)	9 (11.8)	

*A significant difference was observed between the two groups.

For NACRT, 30-42 Gy of radiation for the primary tumor and metastatic lymph nodes was administered preoperatively. The chemotherapy regimen was low-dose cisplatin and 5-fluorouracil (5-FU) (cisplatin: 5 mg/m^2/day, 5-FU: 250 mg/m^2/day, administered on weekdays, repeated every 3-4 weeks).

Staging of the tumor and pathological effectiveness of NACRT. The staging of the tumor and the effects of NACRT were assessed based on the criteria in the Guidelines for the Clinical and Pathologic Studies on Carcinoma of the Esophagus by the Japanese Society for Esophageal Diseases (12). The details of pathological evaluations are as follows: markedly effective (grade 3), all cancer cells were destroyed with no evidence of viable cancer cells; moderately effective (grade 2), most (more than two-thirds) of the cancer cells were damaged, despite the continued presence of viable cancer cells. In this study, slightly effective cases (grade 1) and ineffective cases (grade 0) were regarded as ineffective. The pStage was determined not only based on the viable cancer cells but also on the scar tissue affected by NACRT.

We compared the clinicopathological features, as well as the prognosis, of the patients according to the effects of NACRT. We divided the patients into two groups, those whose pathological effects were grade 3 (n=16) and those who were grade 0-2 (n=60), because the outcome of the patients was clearly different between the groups.

Statistical analysis. The differences in distribution frequencies among the groups were evaluated using Fisher's exact test or unpaired *t*-test. The survival curves were plotted according to the Kaplan-Meier method and any differences were analyzed using the log-rank test. Differences were considered to be significant if the *p*-value was less than 0.05.

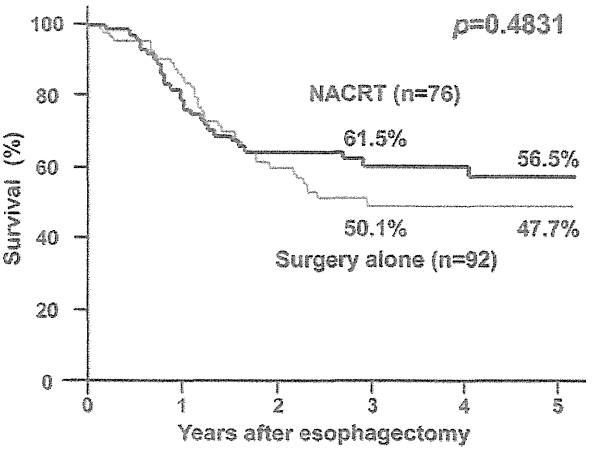

Figure 1. *The survival curves of cStageII-III ESCC patients in the surgery alone group and in the NACRT group. The 5-year survival rate was 56.5% in the NACRT group and 47.7% in the surgery alone group, which was not significantly different (p=0.4831).*

Results

Outcome of NACRT in patients with cStageII-III ESCC. The survival curves of cStageII-III ESCC patients in the surgery alone group and the NACRT group are shown in Figure 1. The 3-year and 5-year survival rate was 61.5% and 56.5% in the NACRT group and 50.1% and 47.7% in the surgery alone group (p=0.4831). As shown in Figure 2, there were no significant differences in the prognosis between the patients in the surgery alone group and the NACRT group, regardless of disease stage (cStageII, p=0.7387, cStageIII, p=0.4370).

Pathological effects of NACRT and prognosis. Among the 76 patients who received NACRT, grade 3 and grade 2 responses were observed in 16 (21.1%) and 26 patients (34.2%), respectively. In the other 34 (44.7%) patients, the pathological effects of NACRT were grade 0/1.

No significant differences were observed with regard to clinical background between the patients with grade 0-2 and grade 3 responses (Table II). The survival of patients whose pathological effects were grade 3 was clearly better than those with grade 2 or grade 0/1: the 5-year survival rate was 100%, 53.8% and 36.9%, respectively (Figure 3). The log-rank test was inapplicable because no events were observed in the patients with grade 3 responses.

NACRT and postoperative complications. Table III shows the postoperative complications and hospital mortality of each

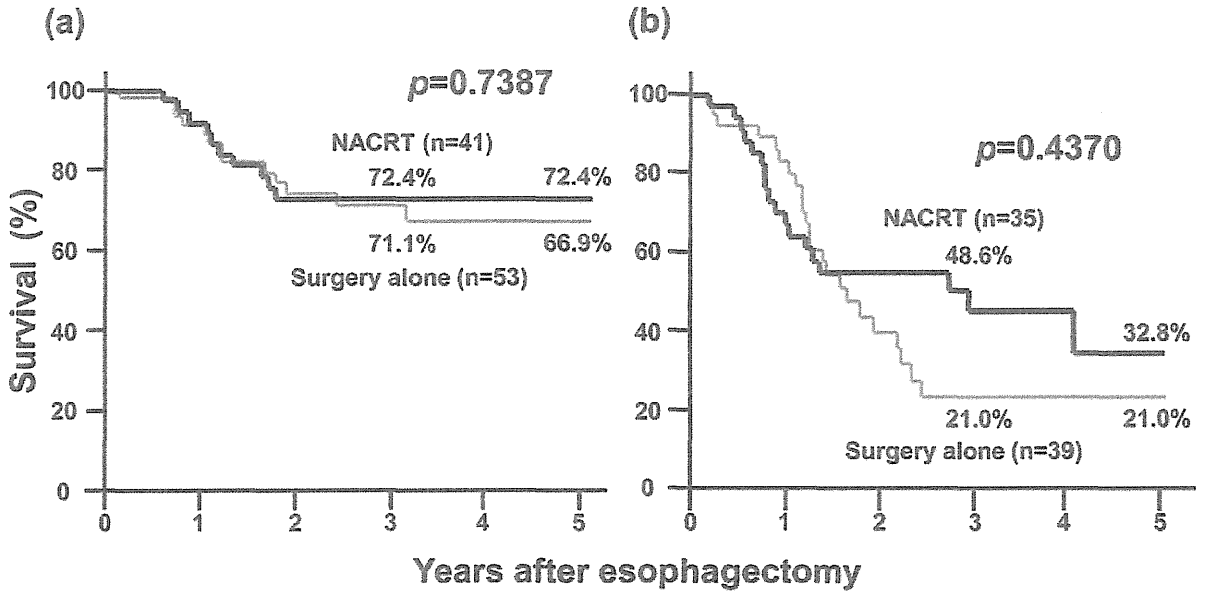

Figure 2. *The survival curves of cStageII (a) and cStageIII (b) ESCC patients in the surgery alone group and the NACRT group. The 5-year survival rates were not significantly different (cStageII: p=0.7387, cStageIII: p=0.4370).*

group. The incidence of postoperative complications was 31.5% in the surgery alone group and 40.8% in the NACRT group (p=0.2121). Pulmonary complications developed in 12.0% of patients in the surgery alone group and in 19.7% of patients in the NACRT group (p=0.1621). Anastomotic leakage developed in 17.4% of the surgery alone patients and in 25.0% of the NACRT patients (p=0.2268). Regarding in-hospital mortality, there were no significant differences between the groups: the incidence was 3.3% in the surgery alone group and 0% in the NACRT group (p=0.1122).

Discussion

For surgically resectable esophageal cancer, whether or not NACRT actually increases long-term survival remains controversial. Urba *et al.* (4) reported that in randomized trial, NACRT *versus* surgery alone for patients with potentially resectable esophageal carcinoma did not demonstrate a statistically significant survival difference. Burmeister *et al.* (5) reported that NACRT with cisplatin and 5-FU did not significantly improve progression-free or overall survival for patients with resectable esophageal cancer compared with surgery alone, however, the subgroup analysis showed that patients with ESCC had better progression-free survival with NACRT than did those with non-squamous carcinomas. In randomized trials in Western countries, the patients usually have different pathological types (*i.e.* adenocarcinoma and ESCC). No clearly recommended protocols have so far been established regarding either the radiation dose and field, or the chemotherapy regimen for the treatment of surgically resectable esophageal cancer. We therefore need to pay careful attention when we introduce new treatments based on evidence from Western countries to our practice in Japan. In this study, there was no significant difference between the patients with and without NACRT, thus suggesting that

Table II. *Clinical background according to the pathological effect of NACRT.*

Factor		Effect of NACRT, n (%) Grade 0-2 (n=60)	Grade 3 (n=16)	*p*-Value
Gender	Male	49 (81.7)	13 (81.3)	>0.9999
	Female	11 (18.3)	3 (18.8)	
Age, years (mean)		61.7	66.2	0.1009
Location of tumor	Upper	10 (16.7)	4 (25.0)	0.6197
	Middle	30 (50.0)	6 (37.5)	
	Lower	20 (33.3)	6 (37.5)	
Clinical T factor	cT1b	1 (1.7)	0 (0)	0.7824
	cT2	15 (25.0)	5 (31.3)	
	cT3	44 (73.3)	11 (68.8)	
Clinical N factor	cN (-)	28 (46.7)	8 (50.0)	>0.9999
	cN (+)	32 (53.3)	8 (50.0)	
Clinical stage	II	30 (50.0)	11 (68.8)	0.2602
	III	30 (50.0)	5 (31.3)	
Curability	Curative	51 (85.0)	16 (100.0)	0.1906
	Non-curative	9 (15.0)	0 (0)	

No significant differences were observed between the two groups.

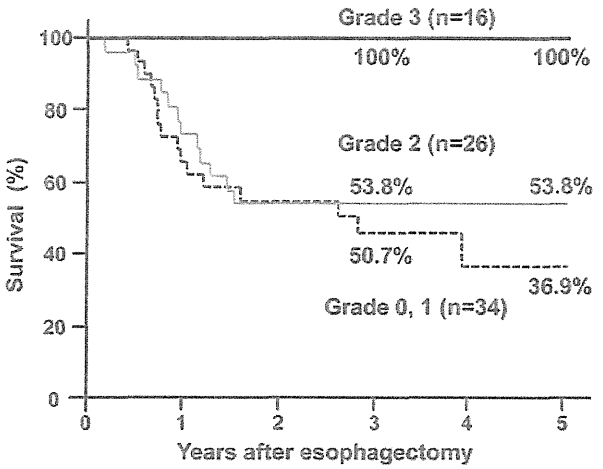

Figure 3. *Overall survival after esophagectomy according to the pathological effectiveness of NACRT in patients with ESCC who underwent NACRT. Each grade indicates the pathological effectiveness (grade 0, 1: ineffective or slightly effective; grade 2: moderately effective; and grade 3: markedly effective). The 5-year survival rate of patients in whom the response to NACRT was grade 3 (100%) was clearly better than that of patients whose pathological response was grade 2 (53.8%), or grade 0/1 (36.9%).*

Table III. *Mortality and morbidity according to NACRT.*

Factor		NACRT, n (%) No (n=92)	NACRT, n (%) Yes (n=76)	*p*-Value
Morbidity	(–)	63 (68.5)	45 (59.2)	0.2121
	(+)	29 (31.5)	31 (40.8)	
Pulmonary complication	(–)	81 (88.0)	61 (80.3)	0.1621
	(+)	11 (12.0)	15 (19.7)	
Anastomotic leakage	(–)	76 (82.6)	57 (75.0)	0.2268
	(+)	16 (17.4)	19 (25.0)	
Mortality	(–)	89 (96.7)	76 (100)	0.1122
	(+)	3 (3.3)	0 (0)	

No significant differences were observed between the two groups.

NACRT has no clinical significance for patients with cStageII-III ESCC. However, the incidence of clinical T1b was significantly lower in the NACRT group than in the surgery alone group. As a result, this incidence may have affected the clinical results of NACRT in this study.

In Japan, a recent randomized trial of postoperative adjuvant chemotherapy with cisplatin and 5-FU *versus* neoadjuvant chemotherapy for cStageII-III ESCC (JCOG 9907) rendered a dramatic change in the daily practice of esophageal surgery (13). Preoperative chemotherapy with cisplatin and 5-FU followed by surgery improved overall survival without additional serious adverse events in the treatment for cStage II-III ESCC. Preoperative chemotherapy with cisplatin and 5-FU is, therefore, regarded as a new standard treatment for cStage II-III ESCC. However, preoperative cisplatin and 5-FU-induced down-staging and R0 resection were reported to be less beneficial in cStage III than in cStage II disease. This suggests that a more powerful preoperative treatment than the cisplatin and 5-FU regimen may be necessary for patients with cStage III ESCC. We retrospectively evaluated the effectiveness of NACRT as a treatment for cStage II-III ESCC in this study. However, we need to make efforts to conduct further prospective randomized trials including NACRT in order to clarify its usefulness.

In terms of the long-term survival after NACRT followed by surgery for esophageal cancer, the response to NACRT has been reported to be the most important factor. Swisher *et al.* (14) emphasized that pathologic response is an independent risk factor for survival and proposed revision of the esophageal cancer staging system to accommodate pathologic response following NACRT. However, factors associated with pathological complete response are still unclear. We had previously performed a multivariate analysis, and the depth of invasion was found to be an independent factor associated with the clinical response to NACRT (15). In this study, no differences were observed in the background between the patients with grade 3 and those with grade 0-2 responses. It is thought to be clinically difficult to predict the effect of NACRT before treatment.

Regarding anticancer drugs, combination chemotherapy using cisplatin and 5-FU with radiation has been proven to be superior to radiation alone according to the RTOG 85-01 study (16). Our previous study supported the idea that pre-operative cisplatin and 5-FU administration improved patient prognosis, as well as the response to NACRT (15). Thus, in this study, we focused on the patients who received cisplatin and 5-FU regimens as NACRT in order to avoid a mixture of subjects having different treatment backgrounds.

The current study examining NACRT did not reveal NACRT to be associated with postoperative complications, including pulmonary complications. However, we have reported the clinical results of esophagectomy for 1,000 cases with esophageal cancer in our institute, and we found preoperative radiotherapy to be an independent risk factor for postoperative pulmonary complications (1). Regarding the mechanism of this increase in postoperative complications, suppression of immune function has been reported to be significant (17). In our previous report, multiple immunological measures in patients with esophageal cancer revealed that preoperative treatment induced significant reductions in the total lymphocyte count, phytohemagglutinin response, and natural killer cell activity, as well as a significant gradual decrease in the CD^{4+}/CD^{8+} ratio (18). It has also been reported that NACRT for patients with ESCC results in the suppression of T-lymphocyte functions (19). Since NACRT

induces a pronounced influence on the immune function, perioperative immunonutritional management might play a key role in reducing postoperative complications after NACRT.

NACRT for esophageal cancer must be associated with improvement in patient survival. Our current study strongly supports the notion that the patients who achieve pathological complete response show a better prognosis than non-responders, suggesting that strict determination of the indications for NACRT is important in order to avoid performing unnecessary NACRT. One approach to improving the outcome after NACRT is the use of molecular biological assessment of particular characteristics of the tumor. To identify biomarkers that predict the response of esophageal cancer to NACRT, gene expression analysis of pretreatment cancer biopsies from patients with esophageal cancer has been demonstrated to be significant (20).

The current study confirms that achievement of a pathological complete response is the most significant factor underlying the efficacy of NACRT. It is important not only to clarify the most useful diagnostic strategy for prediction of the effectiveness of NACRT, but also to identify the molecular markers associated with the effects of NACRT.

Acknowledgements

We thank Brian Quinn for assisting with the preparation of the manuscript.

References

1 Morita M, Yoshida R, Ikeda K, Egashira A, Oki E, Sadanaga N, Kakeji Y, Yamanaka T and Maehara Y: Advances in esophageal cancer surgery in Japan: An analysis of 1,000 consecutive patients treated at a single institute. Surgery *143*: 499-508, 2008.

2 Gebski V, Burmeister B, Smithers BM, Foo K, Zalcberg J and Simes J: Survival benefits from neoadjuvant chemoradiotherapy or chemotherapy in oesophageal carcinoma: a meta-analysis. Lancet Oncol *8*: 226-234, 2007.

3 Fiorica F, Di Bona D, Schepis F, Licata A, Shahied L, Venturi A, Falchi AM, Craxì A and Cammà C: Preoperatrive chemoradiotherapy for oesophageal cancer: a systematic review and meta-analysis. Gut *53*: 925-930, 2004.

4 Urba S, Orringer M, Turrisi A, Iannettoni M, Forastiere A and Strawderman M: Randomized trial of preoperative chemoradiation *versus* surgery alone in patients with locoregional esophageal carcinoma. J Clin Oncol *19*: 305-313, 2001.

5 Burmeister BH, Smithers BM, Gebski V, Fitzgerald L, Simes RJ, Devitt P, Ackland S, Gotley DC, Joseph D, Millar J, North J, Walpole ET and Denham JW: Surgery alone *versus* chemoradiotherapy followed by surgery for resectable cancer of the oesophagus: a randomized controlled phase III trial. Lancet Oncol *6*: 659-668, 2005.

6 Greer SE, Goodney PP, Sutton JE and Birkmeyer JD: Neoadjuvant chemoradiotherapy for esophageal carcinoma: A meta-analysis. Surgery *137*: 172-177, 2005.

7 Avendano CE, Flume PA, Silvesri GA, King LB and Reed CE: Pulmonary complications after esophagectomy. Ann Thorac Surg *73*: 922-926, 2002.

8 Fink U, Stein HJ and Wilke H: Multimodal treatment for squamous cell esophageal cancer. World J Surg *19*: 198-204, 1995.

9 Law S, Wong K, Kwak K, Chu K and Wong J: Predictive factors for postoperateive pulmonary complications and mortality after esophagectomy for cancer. Ann Surg *240*: 791-800, 2004.

10 Kelley ST, Coppola D and Karl RC: Neoadjuvant chemoradiotherapy is not associated with a higher complication rate *vs*. surgery alone in patients undergoing esophagectomy. J Gastrointest Surg *8*: 227-232, 2004.

11 Lin FC, Durkin AE and Ferguson MK: Induction therapy does not increase surgical morbidity after esophagectomy for cancer. Ann Thorac Surg *78*: 1783-1789, 2004.

12 Japanese Society for Esophageal Disease. Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus, ninth edition: Preface, General Principles, part II. Esophagus *1*: 107-125, 2004.

13 Igaki H, Ando N, Kato H, Shinoda M, Shimizu H, Nakamura T, Ozawa S and Yabusaki H, Aoyama N, Kurita A, Fukuda H. A randomized trial of postoperative adjuvant chemotherapy with cisplatin and 5-fluorouracil *versus* neoadjuvant chemotherapy for clinical Stage II/III squamous cell carcinoma of the thoracic esophagus (JCOG 9907). ASCO abstract #4510, 2008.

14 Swisher SG, Hofstetter W, Wu TT, Correa AM, Ajani JA, Komaki RR, Chirieac L, Hunt KK, Liao Z, Phan A, Rice DC, Vaporciyan AA, Walsh GL and Roth JA: Proposed revision of the esophageal cancer staging system to accommodate pathologic response (pP) following preoperative chemoradiation (CRT). Ann Surg *241*: 810-820, 2005.

15 Morita M, Masuda T, Okada S, Yoshinaga K, Saeki H, Tokunaga E, Endo K, Emi Y, Kakeji Y and Maehara Y: Preoperative chemoradiotherapy for squamous cell carcinoma of the esophageal cancer: special reference to factors associated with clinical response and postoperative complications. Anticancer Res *29*: 2555-2562, 2009.

16 Herskovic A, Martz K, al-Sarraf M, Leichman L, Brindle J, Vaitkevicius V, Cooper J, Byhardt R, Davis L and Emami B: Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. N Engl J Med *326*: 1593-1598, 1992.

17 Saeki H, Masuda T, Okada S, Ando K, Sugiyama M, Yoshinaga K, Endo K, Sadanaga N, Emi Y, Kakeji Y, Morita M, Yamashita N and Maehara Y: Impact of perioperative peripheral blood values on postoperative complications after esophageal surgery. Surg Today *40*: 626-631, 2010.

18 Tsutsui S, Morita M, Kuwano H, Matsuda H, Mori M, Okamura S and Sugimachi K: Influence of preoperative treatment and surgical operation on immune function of patients with esophageal carcinoma. J Surg Oncol *49*: 176-181, 1992.

19 Heidecke CD, Weighardt H, Feith M, Fink U, Zimmermann F, Stein HJ, Siewert JR and Holzmann B: Neoadjuvant treatment of esophageal cancer: Immunosuppression following combined radiochemotherapy. Surgery *132*: 495-501, 2002.

20 Luthra R, Luthra MG, Izzo J, Wu TT, Lopez-Alvarez E, Malhotra U, Choi IS, Zhang L and Ajani JA: Biomarkers of response to preoperative chemoradiation in esophageal cancers. Semin Oncol *33*: S2-5, 2006.

Received May 5, 2011
Revised June 14, 2011
Accepted June 15, 2011

厚生労働科学研究費補助金

医療技術実用化総合研究事業

大腸癌におけるオキサリプラチンの末梢神経障害に対する漢方薬：

牛車腎気丸の有用性に関する多施設共同二重盲検ランダム化

比較検証試験（臨床第Ⅲ相試験）

平成22年度～24年度　総合研究報告書（4/5冊）

研究代表者　掛地　吉弘

平成25（2013）年　４月

目次

Ⅰ．研究成果の刊行物・別刷 ---------- 1