Prognostic Factors after Potentially Curative Resection in Stage II or III Colon Cancer

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Summary: It is important to identify factors that are predictive of outcome after a curative resection in colon cancer in order to optimize adjuvant therapy. To investigate these prognostic factors we conducted a retrospective analysis of our clinicopathological data. A total of 190 patients with a pathological stage II or III colon cancer underwent potentially curative resection with lymphadenectomy at our hospital between 1990 and 1998. These patients received no preoperative chemotherapy, immunotherapy or radiotherapy. Postoperative adjuvant chemotherapy using oral fluoropyrimidines was performed in 127 patients, and the other 63 patients underwent surgery alone. Univariate and multivariate analyses for prognostic factors were carried out. The univariate analysis revealed that invasion to adjacent organs, N1-2, positive mesenteric lymph node metastasis (MLN+), lymphatic permeation (ly)1-3, venous invasion (v)1-3, and v2-3 were each significant factors indicating worse disease-free survival, and that N1-2, MLN+, ly1-3, v1-3 and v2-3 were each significant factors for worse overall survival. In the multivariate analysis, MLN+ and v1-3 were significant factors for worse disease-free survival, and for worse overall survival. In conclusion, stage II or III colon cancer patients positive for mesenteric lymph node metastasis or for venous invasion have a greater risk of recurrence and death after potentially curative resection. Postoperative adjuvant chemotherapy using oral fluoropyrimidines did not significantly reduce the risk of recurrence and death in these patients. More effective adjuvant chemotherapy than oral fluoropyrimidine should be considered, especially in such high-risk patients.

Key words colon cancer, prognostic factor, postoperative adjuvant chemotherapy, oral fluoropyrimidine, metastasis to the mesenteric lymph node

INTRODUCTION

Colon cancers remain one of the leading killers in the world. The mainstay for treatment of colon cancer with curative intent is surgical resection. In node-positive or stage III patients, surgery alone offers a cure to roughly half of the patients treated [1]. Thus, addressing the high risk of recurrence necessarily involves the use of systemic agents such as

chemotherapy and immunotherapy after surgical removal of the primary tumor. Worldwide, intravenous 5-fluorouracil (5-FU) plus leucovorin (LV) combination therapy (5-FU/LV) has been recognized as the standard for stage III colon cancer, for the past decade [2]. However, the current evidence does not support the use of adjuvant chemotherapy for all patients with stage II disease [3,4].

In Japan, since the 1980s oral 5-FU derivatives

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Abbreviations: CEA, carcinoembryonic antigen; 5'-DFUR, 5'-deoxy-5-fluorouridine; 5-FU, 5-fluorouracil; LV, leucovorin; MLN, mesenteric lymph node.

(oral fluoropyrimidines) such as UFT (1: tegafur + 4: uracil) and 5'-deoxy-5-fluorouridine (5'-DFUR), an intermediate of capecitabine, have been used in postoperative adjuvant chemotherapy for colon cancer. Recent meta-analyses have found that the addition of postoperative oral fluoropyrimidines was more effective in patients with colorectal cancer than surgery alone, in particular in stage II disease [5,6]. These findings indicated that there is a difference in efficacy of chemotherapy between the oral fluoropyrimidine regimen and intravenous 5-FU/LV regimen, and that it is important to choose an appropriate chemotherapy regimen for each individual patient. Therefore, it is important to identify which factors are predictive of outcome after a potentially curative resection in colon cancer in order to rationalize adjuvant therapy. In the present study, to investigate these prognostic factors clinicopathological data of stage II or III colon cancer patients who underwent potentially curative resection without preoperative treatment were reviewed retrospectively.

MATERIALS AND METHODS

Clinicopathological data from 190 patients were reviewed in this analysis. The inclusion criteria of this study were pathological stage II or III colon cancer treated by potentially curative resection with lymphadenectomy, including mesenteric lymph nodes, without preoperative chemotherapy, immunotherapy and radiotherapy, between 1990 and 1998. Patients who received intensive adjuvant chemotherapy or who were 80 years of age or older were excluded from this study. The pathological factors and staging for colon cancer were defined according to the International Union against Cancer TNM classification [7]. The grading of lymphatic permeation (ly) and venous invasion (v) was defined according to our previous reports [8,9]. Postoperative adjuvant chemotherapy was performed in 127 patients, and the other 63 patients underwent surgery alone. Most of the patients who received surgery alone declined adjuvant chemotherapy during the process of obtaining informed consent. Fluoropyrimidine s such as UFT and 5'-DUUR were administered perorally for 1 year unless recurrence occurred. The usual oral dosage was 500 mg/m²/day for 5'-DFUR, and 250 mg /m²/day for UFT.

Follow-up investigations were performed through outpatient visits, by letter, or by telephone, and the most recent date of contact for each patient was regarded as the final date of confirmation. The most

recent date in the present series was December 31, 2004. The mean follow-up period was 87 months. The presence or absence of any recurrence was determined by barium enema, physical examination, measurement of serum tumor marker (carcinoembryonic antigen, CEA) level, and by findings on chest radiography, ultrasound, computed tomography, or magnetic resonance imaging.

To evaluate the prognostic factors, univariate analysis and multivariate analysis using Cox's proportional hazard model were carried out. The following were evaluated for their independent contributions to the disease-free survival rate and overall survival rate after operation; histological tumor grade (well vs. others), direct invasion to adjacent organs (yes vs. no), N0 vs. N1-2, positive mesenteric lymph node metastasis (MLN+) vs. negative MLN metastasis (MLN-), ly0 vs. ly1-3, ly0-1 vs. ly2-3, v0 vs. v1-3, v0-1 vs. v2-3, age, male vs. female, and postoperative adjuvant chemotherapy vs. surgery alone. MLN includes the intermediate node and principle node, but not the paracolic node. The factors underwent regression analysis to calculate the risk ratios. All data were compiled and analyzed using Statistical Analysis Software version 6.12, (SAS Institute, Cary, NC, USA).

RESULTS

The background data of the patients are summarized in Table 1. Patients consisted of 106 males and 84 females who ranged in age from 35 to 79 years

TABLE 1.
Background of the Patients

Age (mean $\pm$ sd) / years	64.1 $\pm$ 9.4
Sex (male / female)	106 / 84
N factor	
N0 / N1-2 (stage II / III)	96 / 94
MLN (- / +)	162 / 28
Direct invasion to adjacent organs (- / +)	161 / 29
Tumor histology (well / others)	104 / 86
Lymphatic permeation	
ly0 / ly1-3	101 / 89
ly0-1 / ly2-3	133 / 57
Venous invasion	
v0 / v1-3	122 / 68
v0-1 / v2-3	168 / 22
Adjuvant chemotherapy (- / +)	63 / 127

MLN: mesenteric lymph node metastasis; well: well-differentiated adenocarcinoma

TABLE 2.
Univariate analysis for prognostic factors

Variable	p value	95% CI	Hazard ratio
(Disease-free Survival)			
MLN (+) vs. (–)	0.002	1.504-5.714	2.933
v1-3 vs. v0	0.005	1.603-5.376	2.933
v2-3 vs. v0-1	0.014	1.202-5.236	2.513
ly1-3 vs. ly0	0.005	1.311-4.608	2.451
DI (+) vs. DI (–)	0.027	1.100-4.378	2.183
N1-2 vs. N0	0.043	1.021-3.521	1.898
(Overall Survival)			
MLN (+) vs. (–)	0.002	1.597-7.143	3.378
v1-3 vs. v0	0.002	1.493-6.098	3.012
ly1-3 vs. ly0	0.007	1.337-5.952	2.825
v2-3 vs. v0-1	0.015	1.220-6.536	2.825
N1-2 vs. N0	0.018	1.167-5.208	2.463

CI: confidence interval; MLN: mesenteric lymph node metastasis; ly: lymphatic permeation; v: venous invasion; DI: direct invasion to adjacent organs

TABLE 3.
Multivariate analysis for prognostic factors

Variable	p value	95% CI	Hazard ratio
(Disease-free Survival)			
MLN (+) vs. (–)	0.004	1.372-5.236	2.755
v1-3 vs. v0	0.001	1.515-5.102	2.681
(Overall Survival)			
MLN (+) vs. (–)	0.003	1.493-6.711	3.155
v1-3 vs. v0	0.003	1.418-5.780	2.865

CI: confidence interval; MLN: mesenteric lymph node metastasis; ly: lymphatic permeation

(average age; 64.1 ± 9.4 years). Lymph node metastasis was found in 94 patients, so the tumor stage was classified as stage II in 96 patients, and as stage III in 94 patients. Mesenteric lymph node metastasis was found in 28 patients. Twenty-nine tumors were positive for direct invasion to adjacent organs, and 104 were well-differentiated adenocarcinoma. Lymphatic permeation was found in 89 patients, and 57 of these were grade 2 or 3. Venous invasion was observed in 68 patients, 22 of whom were grade 2 or 3. Postoperative adjuvant chemotherapy using oral fluoropyrimidines was performed in 127 patients, including 14 patients 75 years or older, and the other 63, including 14 patients 75 years or older, underwent surgery alone.

The univariate analysis revealed that positive for direct invasion, N1-2, MLN+, ly1-3, v1-3, and v2-3 were negative prognostic factors indicating a worse

disease-free survival, and that N1-2, MLN+, ly1-3, v1-3, and v2-3 were negative prognostic factors for overall survival (Table 2). The multivariate analyses indicated that MLN+ and v1-3 were each significant factors for worse disease-free survival, and for worse overall survival (Table 3).

DISCUSSION

Since the 1990s, intravenous 5-FU/LV therapy has been adopted worldwide as the standard postoperative adjuvant chemotherapy for colon cancer [2]. In general, chemotherapy using oral fluoropyrimidines, compared to that using intravenous 5-FU/LV, irinotecan [10], oxaliplatin [11] or their combinations [12,13], has been characterized by a lower incidence of adverse effects, and especially infrequent adverse effects of grade 3 or higher [14]. This supports the

continued use of chemotherapy using oral fluoropyrimidines on an outpatient basis without decreasing the patient's quality of life. For patients, the lower incidence of adverse effects and the availability on an outpatient basis are important benefits of oral fluoropyrimidine therapy.

However, the antitumor effects of chemotherapy using UFT without oral LV or 5'-DFUR are thought to be less than those of intravenous 5-FU/LV. In stage III patients, intravenous 5-FU based regimens have consistently been shown to reduce the risks of recurrence and death by up to 30% [2,15,16], which may represent larger benefits than the reduction of 11% in the risk to recurrence and 5% in the risk to death found for oral fluoropyrimidine regimens [6]. Of interest, it has also been reported that the risk reduction benefit of oral fluoropyrimidines for disease-free survival and overall survival was higher in the early stages, for example in Dukes' A or Dukes' B (stage II), as compared with Dukes' C (stage III) colorectal cancers [6]. These findings suggested that oral fluoropyrimidines might be effective in node negative colon cancer, but might be insufficient to reduce the risk of recurrence or death in patients with highly lymphatic-spreading stage III tumors.

It has been shown that lymph node metastasis, including the number of metastatic nodes, was the most reliable prognostic factor in stage II or III colon cancers [17]. Along with the number of metastatic nodes, evaluation of the prognostic significance of the distance or location of lymph node metastasis is also thought to be important. A tumor with mesenteric lymph node involvement (MLN+) represents a tumor that is more highly lymphatic-spreading than one with metastasis to the paracolic lymph node alone. Our univariate and multivariate analyses revealed that mesenteric lymph node involvement had the highest hazard ratio both in recurrence and death among factors including the presence or absence of lymph node metastasis. This result suggested that disease-oriented individual adjuvant chemotherapy might be indicated for stage III colon cancer. Postoperative adjuvant chemotherapy using oral fluoropyrimidines was not a factor for favorable prognosis in our study. In stage III colon cancer with metastasis to the mesenteric lymph nodes, more effective chemotherapy regimens such as oxaliplatin + bolus plus infusion 5-FU/LV (FOLFOX) should be considered [18].

In conclusion, metastasis to the mesenteric lymph node and the presence of venous invasion were each negative prognostic factors after potentially curative

resection in stage II or III colon cancer. Postoperative adjuvant chemotherapy using oral fluoropyrimidines such as UFT and 5'-DFUR did not reduce the risk of recurrence and death. Thus, more effective chemotherapy using intravenous 5-FU/LV combined with oxaliplatin or irinotecan should be considered, especially in patients with metastasis to the mesenteric lymph node or venous invasion.

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REFERENCES

1. Greenlee RT, Murray T, Bolden S, and Wingo PA. Cancer Statistics, 2000. *CA Cancer J Clin* 2000; 50:7-33.
2. International Multicentric Pooled Analysis of Colon Cancer Trials (IMPACT) investigators. Efficacy of adjuvant fluorouracil and folinic acid in colon cancer. *Lancet* 1995; 345:939-944.
3. International Multicentric Pooled Analysis of B2 Colon Cancer Trials (IMPACT B2) investigators. Efficacy of adjuvant fluorouracil and folinic acid in B2 colon cancer. *J Clin Oncol* 1999; 17:1356-1363.
4. Van Cutsem E, Dicato M, Wils J, Cunningham D, Diaz-Rubio E et al. Adjuvant treatment of colorectal cancer (current expert opinion derived from the Third International Conference: Perspectives in Colorectal Cancer, Dublin, 2001). *Eur J Cancer* 2002; 38:1429-1436.
5. Sakamoto J, Hamada C, Kodaira S, Nakazato H, and Ohashi Y. Adjuvant therapy with oral fluoropyrimidines as main chemotherapeutic agents after curative resection for colorectal cancer: individual patient data meta-analysis of randomized trials. *Jpn J Clin Oncol* 1999; 29:78-86.
6. Meta-Analysis Group of the Japanese Society for Cancer of the Colon and Rectum and the Meta-Analysis Group in Cancer. Efficacy of oral adjuvant therapy after resection of colorectal cancer: 5-year results from three randomized trials. *J Clin Oncol* 2004; 22:484-492.
7. International Union Against Cancer (UICC) TNM Classification of Malignant Tumors, 6th edn, Edited by Sobin LH, Wittekind Ch WILEY-liss, New York, 2002.
8. Shirouzu K, Isomoto H, Morodomi T, and Kakegawa T. Carcinomatous lymphatic permeation: prognostic significance in patients with rectal carcinoma a long term prospective study. *Cancer* 1995; 75: 4-10.
9. Shirouzu K, Isomoto H, Kakegawa T, and Morimatsu M. (1991) A prospective clinicopathologic study of venous invasion in colorectal cancer. *Am J Surg* 1991; 162:216-222.
10. Shimada Y, Yoshino M, Wakui A, Nakao I, Futatsuki K et al. Phase II study of CPT-11, a new camptothecin derivative, in metastatic colorectal cancer. *J Clin Oncol* 1993; 11:909-913.
11. Becouarn Y, Ychou M, Ducreux M, Borel C, Bertheault-Cvitkovic F et al. Phase II trial of oxaliplatin as first-line

- chemotherapy in metastatic colorectal cancer patients. *J Clin Oncol* 1998; 16:2739-2744.
12. Saltz LB, Cox JV, Blanke C, Rosen LS, Rosen LS et al. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2000; 343:905-914.
 13. de Gramont A, Figer A, Seymour M, Homerin M, Hmissi A et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol* 2000; 18:2938-2947.
 14. Scheithauer W, McKendrick J, Begbie S, Borner M, Burns WI et al. Oral capecitabine as an alternative to i.v. 5-fluorouracil-based adjuvant therapy for colon cancer: safety results of a randomized, phase III trial. *Ann Oncol* 2003; 14:1735-1743.
 15. Wolmark N, Rockette H, Mamounas E, Jones J, Wieand S et al. Clinical trial to assess the relative efficacy of fluorouracil and leucovorin, fluorouracil and levamisole, and fluorouracil leucovorin, and levamisole in patients with Dukes' B and C carcinoma of the colon: results from National Surgical Adjuvant Breast and Bowel Project C-04. *J Clin Oncol* 1999; 17:3553-3559.
 16. O'Connell MJ, Mailliard JA, Kahn MJ, Macdonald JS, Haller DG et al. Controlled trial of fluorouracil and low-dose leucovorin given for 6 months as postoperative adjuvant therapy for colon cancer. *J Clin Oncol* 1997; 15:246-250.
 17. Park YJ, Park KJ, Park JG, Lee KU, Choe KJ et al. Prognostic factors in 2230 Korean colorectal cancer patients: analysis of consecutive operated cases. *World J Surg* 1999; 23:721-726.
 18. Andre T, Boni C, Mounedji-Boudiaf L, Navarro M, Tabernero J et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *N Engl J Med* 2004; 350:2343-2351.