Association Between Time (Initiation and Length) and Oncological Outcomes for the Patients with Colon Cancer Treated with Adjuvant Chemotherapy

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Abstract Adjuvant chemotherapy is benefit for high-risk stage II and stage III colon cancer after curative resection. But, the optimal time between surgical and initiation of adjuvant chemotherapy remains unclear. Moreover, no study of efficacy with different lengths of adjuvant chemotherapy has appeared. This study was aimed to identify association between time (initiation and length) and oncological outcomes of adjuvant chemotherapy on the stages II and III colon cancer patients. A total of 406 high-risk stages II and III colon cancer patients were retrospectively enrolled in prospectively collected data. They were categorized into three groups representing chemotherapy initiation time: less than 4 weeks (group 1), 4 to 6 weeks (group 2), and more than 6 weeks (group 3). They were categorized into two groups representing chemotherapy length time : less than 200 days (group 1a) and more than 200 days (group 2a). The 5-year disease-free survival (DFS) rates were 74.97 % in group 1, 76.94 % in group 2, and 63.97 % in group 3 ($p>0.05$). The 5-year DFS rates were 75.49 % in the group that received adjuvant chemotherapy within 6 weeks and 63.97 % in the group that received

adjuvant chemotherapy >6 weeks ($p=0.0539$). The 5-year DFS rates were 77.21 % in group 1a and 81.82 % in group 2a ($p>0.05$). Adjuvant chemotherapy should be safely offered within 6 weeks after surgical excision in patients with colon cancer after considering the patient's general physical condition and hematological factors, even if the chemotherapy length is prolonged.

Keywords Colon cancer · Adjuvant chemotherapy · Oncological outcome · Time

Introduction

Colorectal cancer is the second most common cancer in Korean men and the third most common in women [1]. The mainstay of colon cancer treatment is surgical resection. However, 40–50 % of patients eventually develop recurrence or die from metastasis [2, 3]. Several large, randomized clinical trials have reported that patients who undergo adjuvant chemotherapy after curative resection of colorectal cancer have better prognoses than those who undergo surgical treatment only [4, 5]. Stage II with high-risk factor and stage III colon cancer patients are routinely recommended to undergo adjuvant chemotherapy after surgical resection [6, 7]. However, the optimal time between surgical and initiation of adjuvant chemotherapy remains unclear. Some studies have reported that adjuvant chemotherapy commenced within 8 weeks after surgical resection results in a better prognosis than chemotherapy commenced after 8 weeks [8–12]. Thus, most surgical oncologists tend to start adjuvant chemotherapy as soon as possible, no later than 6–8 weeks after surgery.

No difference was observed in the efficacies of 6- and 12-month chemotherapy durations in a 5-fluorouracil (5-FU)/

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levamisole adjuvant chemotherapy study [13]. In addition, no difference was found between 6- and 9-month chemotherapy durations in the GERCOR C96.1 trial [14]. The current recommendation for the duration of adjuvant chemotherapy in patients with colon cancer is 6 months, which is 12 cycles of the FOLFOX regimen and 6 cycles of the 5-FU/leucovorin (FL) regimen. Nevertheless, for various reasons (side effects and patient- and hospital-specific factors), regular chemotherapy cycles are often completed after more than 6 months. No study of efficacy with different lengths of adjuvant chemotherapy has appeared.

Thus, we evaluated the efficacy of adjuvant chemotherapy in terms of initiation time and length.

Materials and Methods

Subjects

This retrospective study included 406 patients with colon cancer who were given FOLFOX4 or FL chemotherapy after radical surgery in the Department of Surgery, Busan Paik Hospital, Inje University College of Medicine between January 2005 and December 2010. The patients were classified using the 6th edition of the American Joint Committee on Cancer TNM staging system. We enrolled stage II with high-risk factor and stage III colon cancer patients and based on the 2013 National Comprehensive Cancer Network (NCCN) guidelines.

Colon cancer was defined as cancer in which the lower tumor margin was located in the upper part of the peritoneum, and the high-risk stage II group had to have at least one of the following features: T4a/4b stage; tumor perforation; bowel obstruction; a poorly differentiated tumor; or venous, perineural, or lymphatic invasion.

Chemotherapy Methods and Follow-Up Observations

FOLFOX4 Chemotherapy

Leucovorin (LV; 200 mg/m²/day) was administered intravenously (IV) for 2 h. Then, a bolus IV infusion of 400 mg/m² 5-FU was administered, followed by IV administration of 600 mg/m² 5-FU continuously for 22 h. This regimen was continued for 2 days. Oxaliplatin (85 mg/m²) was infused for 2 h only on day 1. A prophylactic antiemetic agent and adequate fluid were infused on chemotherapy days 1 and 2. This regimen was administered every 2 weeks for a total of 12 cycles.

FL Chemotherapy

A bolus IV of 20 mg/m² LV was administered, followed by IV continuous administration of 425 mg/m² 5-FU for 2 h. This

regimen was continued daily for 5 days, every 4 weeks for a total of 6 cycles.

Follow-Up

Patients were followed up every 3 months for the first 2 years after surgery and every 6 months thereafter for 3 years. History, physical features, and serum carcinoembryonic antigen level were checked at each follow-up visit. Chest X-ray and abdominopelvic computed tomography scans were performed to assess chemotherapy efficacy every 3 months and every 6 months (respectively) after completion of chemotherapy. Colonoscopy was performed annually. Recurrence was identified by imaging studies and colonoscopy and was confirmed by colonoscopic or percutaneous biopsy. Radiologically identified tumor growth at the operative site was considered to indicate recurrence when histological confirmation was not possible.

Patient Categorization

Chemotherapy Initiation Time After Surgery

- Group 1: within 4 weeks after surgery
- Group 2: 4–6 weeks after surgery
- Group 3: >6 weeks after surgery

Chemotherapy Length (Only Patients Who Completed Adjuvant Chemotherapy)

- Group 1a: <200 days
- Group 2a: >200 days

Statistical Analysis

Statistical analysis was performed using Cox's proportional hazards models for univariate and multivariate analyses of factors affecting the prognosis and the 5-year disease-free survival (DFS) rate. The Kaplan–Meier method and the log-rank test were used to compare DFS rates among risk groups. A *p* value <0.05 was considered significant. SAS version 9.3 (SAS Institute, Cary, NC, USA) was used for statistical analysis.

Results

Clinicopathological Data

Totals of 275, 90, and 59 patients started chemotherapy within 4 weeks (group 1), within 4–6 weeks (group 2), and after

6 weeks (group 3), respectively. No significant difference in any of age, sex, T stage, N stage, or histological differentiation was observed among the groups. Group 3 patients underwent more FL than FOLFOX chemotherapy compared to the other groups ($p=0.014$) (Table 1).

Patients who had completed chemotherapy were divided into two groups; those who completed within 200 days (group 1a; $n=194$) and those who completed in >200 days (group 2a; $n=159$). No significant difference was observed in terms of age, sex, T stage, or histological differentiation between the two groups. Significantly more lymph node metastasis ($p<0.0001$) and significantly more FOLFOX than FL chemotherapy ($p<0.0001$) were observed in group 2a than group 1a (Table 1). Prolonged chemotherapy (>200 days) was mainly attributable to neutropenia (100 patients) or hospital factors (38 patients) (Table 2).

Analysis of DFS and Prognostic Factors

The prognostic factors for DFS upon univariate analysis were T stage ($p=0.0187$) and N stage ($p<0.0001$). The prognostic factors for DFS upon multivariate analysis were also T stage ($p=0.0232$) and N stage ($p<0.0001$) (Table 3).

The 5-year DFS rates were 74.97 % in group 1, 76.94 % in group 2, and 63.97 % in group 3 ($p>0.05$) (Fig. 1). The 5-year DFS rates were 75.49 % in the group that received adjuvant

chemotherapy within 6 weeks after surgery and 63.97 % in the group that received adjuvant chemotherapy >6 weeks after surgery. The 5-year DFS rates in the two groups differed with borderline significance ($p=0.0539$) (Fig. 1). The 5-year DFS rates were 77.21 % in group 1a and 81.82 % in group 2a ($p>0.05$) (Fig. 2).

Discussion

Most surgical oncologists tend to start adjuvant chemotherapy as soon as possible after resection, based on reports suggesting that surgery promotes the expression of oncogenic growth factors, such as transforming growth factor, which results in tumor growth [15, 16]. Furthermore, the risk of metastasis may be elevated because of the decrease in angiogenesis inhibitors triggered by tumor resection [17, 18].

No clear NCCN guidelines indicate when adjuvant chemotherapy should be initiated in patients with colon cancer. Nevertheless, several large-scale studies conducted to demonstrate the efficacy of adjuvant chemotherapy started treatment within 42 days [19–22]. Only 10 % of all patients with breast cancer in the SEER-Medicare database received chemotherapy 3 months after surgery, and their overall mortality hazard ratio (HR) was 1.5 (95 % confidence interval [CI], 1.2–1.8) [23]. Hershman et al. reported that 19 % of all patients with

Table 1 Clinicopathological characteristics of the patients in groups 1–3

Factor		Group 1	Group 2	Group 3	<i>p</i> value	Group 1a	Group 2a	<i>p</i> value
Age	≥65	67	32	13	0.0846	46	45	0.2921
	<65	208	58	46		148	114	
Sex	Male	159	49	38	0.4679	115	91	0.8443
	Female	116	41	21		79	68	
T stage	1	2	0	1	0.2111	2	1	0.1035
	2	12	6	3		15	4	
	3	247	78	49		169	142	
	4a	13	2	5		5	10	
	4b	1	4	1		3	2	
N stage	0	88	32	17	0.6381	87	30	<0.0001
	1a	51	20	11		24	44	
	1b	53	12	11		32	34	
	2a	45	11	8		25	25	
	2b	38	15	12		26	26	
Differentiation	Well	10	5	1	0.8151	9	4	0.3935
	Moderately	246	77	52		173	140	
	Poorly	11	4	4		6	10	
	Mucinous	7	4	2		6	4	
	Signet-ring cell	1	0	0		0	1	
Chemotherapy type	FL	123	46	38	0.0140	182	2	<0.0001
	Folfox4	152	44	21		12	157	

Table 2 Factors associated with completing chemotherapy in more than 200 days

Hospital factor	38
Pancytopenia	5
Peripheral neuropathy	7
Neutropenia and peripheral neuropathy	5
Neutropenia	100
Bronchiolitis	1
Colostomy repair	1
DM retinopathy	1
Hematuria	1

colon cancer in the SEER-Medicare database underwent adjuvant chemotherapy 2 months after surgery, and their cancer-specific mortality rates were higher than patients who started chemotherapy within 1 month. (2–3 month HR, 1.41; 95 % CI 1.15–1.74; > 3 month HR, 1.62; 95 % CI 1.31–1.99) [9]. Numerous studies have reported that patients who start adjuvant chemotherapy 6–8 weeks after surgery have better

survival rates than those who do not [24–26]. We analyzed the 5-year DFS rates of patients who started chemotherapy within 4 weeks (group 1, 80.26 %), within 4–6 weeks (group 2, 83.03 %), and >6 weeks (group 3, 70.08 %) after resection, but found no differences ($p=0.2096$). However, the 5-year group 3 DFS rate tended to be lower than those of groups 1 or 2, so we divided the groups into two subgroups of within 6 weeks and >6 weeks after surgery. The results showed that patients who started adjuvant chemotherapy within 6 weeks tended to have a higher 5-year DFS rate than those who started it later. This result is similar to that of other studies [24–26], reporting that it is beneficial to start adjuvant chemotherapy within 6 weeks after surgery. However, as previous studies and our study show, initiating chemotherapy too early does not guarantee a satisfactory 5-year DFS rate. Goldman et al. [27] reported that patients who undergo gastrointestinal surgery usually have poor oral intake abilities, which could affect the immune system, suggesting that initiating chemotherapy too early could result in numerous side effects. Moreover,

Table 3 Univariate and multivariate analyses of prognostic factors for the disease-free survival rate

Factor	Classification	Univariate			Multivariate		
		Hazard ratio	95 % confidence interval	P-value	Hazard ratio	95 % confidence interval	P-value
Sex	Female						
	Male	0.808	0.550	1.186			0.2760
Age	65						
	≥65	1.238	0.817	1.876			0.3132
Differentiation	Well						
	Moderately						0.3689
	Poorly						
	Signet-ring cell						
T stage	Mucinous cell						
	1	Ref			Ref		0.0232
	2	0.530	0.055	5.095	0.363	0.037	3.524
	3	0.950	0.132	6.817	0.732	0.101	5.309
	4a	2.521	0.319	19.902	1.895	0.235	15.270
	4b	2.690	0.280	25.874	1.911	0.194	18.811
N stage	0	Ref			Ref		.0001
	1a	1.204	0.612	2.369	1.573	0.788	3.140
	1b	1.722	0.926	3.203	2.121	1.125	4.000
	2a	1.812	0.956	3.435	1.961	1.014	3.795
	2b	4.447	2.577	7.674	5.055	2.911	8.778
Chemotherapy type	FL						0.8093
	FOLFOX4	1.048	0.715	1.537			
Initiation time	4 wks	Ref					0.1570
	6 wks	0.937	0.568	1.547			
	≥6 wks	1.582	0.958	2.612			
Initiation time	6 wks	Ref					0.0563
	≥6 wks	1.607	0.987	2.617			
Length	200 days	Ref			Ref		0.0037
	≥200 days	0.634	0.417	0.965	0.530	0.345	0.814

Fig. 1 5-year DFS of patients by chemotherapy initiation time

chemotherapy initiated immediately after surgery (in an animal study) increased the incidence of anastomotic leakage [28].

Moertel et al. reported that 12 months of adjuvant chemotherapy with 5-FU plus levamisole yielded excellent outcomes [29]. Thereafter, the Intergroup trial 0089 (INT-0089) and the Groupe Cooperateur Multidisciplinaire en Oncologie trial found no difference in efficacy among 6, 9, and 12 months of 5-FU/LV [13, 14]. The ideal duration for adjuvant chemotherapy in patients with colon cancer is 6 months, which is 12 cycles of FOLFOX and 6 of FL. Patients with colon cancer receiving adjuvant chemotherapy may experience numerous hematological, gastrointestinal, and dermatological side effects. Chemotherapy cycles are often delayed by patient or

hospital factors or side effects, rendering patients' anxious. No studies have been conducted on chemotherapy length; thus, we analyzed data from patients who completed chemotherapy within or >200 days after surgical resection and found no difference in the 5-year DFS rate (76.69 vs. 83.24 %, $p=0.1337$) between the two groups. These results could suggest that a longer adjuvant chemotherapy length might have no effect on prognosis.

There are a few limitations to our study. First, this was a retrospective study based on clinical records; thus, some unrecorded factors may have affected survival rates, and the reasons for prolonged chemotherapy duration may be inadequately clear on records. Second, this was a nonrandomized non-prospective study, for ethical reasons.

In conclusion, starting adjuvant chemotherapy within 6 weeks after surgical excision in patients with colon cancer could lead to a better oncological outcome, even considering postoperative complications and general physical condition. Moreover, a longer adjuvant chemotherapy length might have no effect on prognosis. Therefore, adjuvant chemotherapy should be safely offered after considering the patient's general physical condition and hematological factors, even if the chemotherapy length is prolonged.

Conflict of Interest No potential conflict of interest relevant to this article was reported.

References

1. Jung KW, Park SH, Won YJ et al (2012) Prediction of cancer incidence and mortality in Korea, 2012. *Cancer Res Treat* 44(1): 25–31

Fig. 2 5-year DFS of patients by chemotherapy length time

2. Obrand DI, Gordon PH (1997) Incidence and patterns of recurrence following curative resection for colorectal carcinoma. *Dis Colon Rectum* 40:15–24
3. O'Connell JB, Maggard MA, Ko CY (2004) Colon cancer survival rates with the new American Joint Committee on Cancer sixth edition staging. *J Natl Cancer Inst* 96:1420–1425
4. Moertel CG, Fleming TR, Macdonald JS et al (1995) Fluorouracil plus levamisole as effective adjuvant therapy after resection of stage III colon carcinoma: a final report. *Ann Intern Med* 122:321–326
5. O'Connell MJ, Laurie JA, Kahn M et al (1998) Prospectively randomized trial of postoperative adjuvant chemotherapy in patients with high-risk colon cancer. *J Clin Oncol* 16:295–300
6. Benson AB III, Schrag D, Somerfield MR et al (2004) American Society of Clinical Oncology recommendations on adjuvant chemotherapy for stage II colon cancer. *J Clin Oncol* 22(16):3408–3419
7. Figueredo A, Charette ML, Maroun J et al (2004) Adjuvant therapy for stage II colon cancer: a systematic review from the Cancer Care Ontario Program in evidence-based care's gastrointestinal cancer disease site group. *J Clin Oncol* 22(16):3395–3407
8. Chau I, Cunningham D (2006) Adjuvant therapy in colon cancer—what, when and how? *Ann Oncol* 17:1347–1359
9. Hershman D, Hall MJ, Wang X et al (2006) Timing of adjuvant chemotherapy initiation after surgery for stage III colon cancer. *Cancer* 107:2581–2588
10. Berglund A (2008) Is it deleterious to delay the start of adjuvant chemotherapy in colon cancer stage III? *Ann Oncol* 19:400–402
11. Lima IS, Yasui Y, Scarfe A et al (2011) Association between receipt and timing of adjuvant chemotherapy and survival for patients with stage III colon cancer in Alberta, Canada. *Cancer* 117:3833–3840
12. Biagi JJ, Raphael MJ, Mackillop WJ et al (2011) Association between time to initiation of adjuvant chemotherapy and survival in colorectal cancer: a systematic review and meta-analysis. *JAMA* 305:2335–2342
13. Haller DG, Catalano PJ, Macdonald JS et al (2005) Phase III study of fluorouracil, leucovorin, and levamisole in high-risk stage II and III colon cancer: final report of Intergroup 0089. *J Clin Oncol* 23:8671–8678
14. André T, Quinaux E, Louvet C et al (2007) Phase III study comparing a semimonthly with a monthly regimen of fluorouracil and leucovorin as adjuvant treatment for stage II and III colon cancer patients: final results of GERCOR C96.1. *J Clin Oncol* 25(24):3732–3738
15. Ono I, Gunji H, Suda K, Iwatsuki K, Kaneko F (1994) Evaluation of cytokines in donor site wound fluids. *Scand J Plast Reconstr Surg Hand Surg* 28:269–273
16. Eggermont AM, Steller EP, Sugarbaker PH (1987) Laparotomy enhances intraperitoneal tumor growth and abrogates the antitumor effects of interleukin-2 and lymphokine-activated killer cells. *Surgery* 102:71–78
17. Folkman J (1990) What is the evidence that tumors are angiogenesis dependent? *J Natl Cancer Inst* 82:4–6
18. Gunduz N, Fisher B, Saffer EA (1979) Effect of surgical removal on the growth and kinetics of residual tumor. *Cancer Res* 39:3861–3865
19. Wolmark N, Rockette H, Wickerham DL et al (1990) Adjuvant therapy of Dukes' A, B, and C adenocarcinoma of the colon with portal-vein fluorouracil hepatic infusion: preliminary results of National Surgical Adjuvant Breast and Bowel Project protocol C-02. *J Clin Oncol* 8:1466–1475
20. Wolmark N, Rockette H, Fisher B et al (1993) The benefit of leucovorin-modulated fluorouracil as postoperative adjuvant therapy for primary colon cancer: results from National Surgical Adjuvant Breast and Bowel Project protocol C-03. *J Clin Oncol* 11:1879–1887
21. Wolmark N, Bryant J, Smith R et al (1998) Adjuvant 5-fluorouracil and leucovorin with or without interferon alfa-2a in colon carcinoma: National Surgical Adjuvant Breast and Bowel Project protocol C-05. *J Natl Cancer Inst* 90:1810–1816
22. Poplin EA, Benedetti JK, Estes NC et al (2005) Phase III Southwest Oncology Group 9415/Intergroup 0153 randomized trial of fluorouracil, leucovorin, and levamisole versus fluorouracil continuous infusion and levamisole for adjuvant treatment of stage III and high-risk stage II colon cancer. *J Clin Oncol* 23:1819–1825
23. Hershman DL, Wang X, McBride R, Jacobson JS, Grann VR, Neugut AI (2006) Delay in initiating adjuvant radiotherapy following breast conservation surgery and its impact on survival. *Int J Radiat Oncol Biol Phys* 65:1353–1360
24. Kang KM, Hong KS, Noh GT et al (2013) Optimal time of initiating adjuvant chemotherapy after curative surgery in colorectal cancer patients. *Ann Coloproctol* 29(4):150–154
25. Czapkowski PM, Gill S, Kennecke HF, Gordon VL, Turner D (2011) Adjuvant chemotherapy for stage III colon cancer: does timing matter? *Dis Colon Rectum* 54:1082–1089
26. Chau I, Norman AR, Cunningham D, Tait D, Ross PJ, Iveson T et al (2005) A randomised comparison between 6 months of bolus fluorouracil/leucovorin and 12 weeks of protracted venous infusion fluorouracil as adjuvant treatment in colorectal cancer. *Ann Oncol* 16:549–557
27. Goldman LI, Lowe S, al-Saleem T (1969) Effect of fluorouracil on intestinal anastomoses in the rat. *Arch Surg* 98:303
28. Morris T (1979) Retardation of healing of large-bowel anastomoses by 5-fluorouracil. *Aust N Z J Surg* 49:743–745
29. Moertel CG, Fleming TR, Macdonald JS et al (1990) Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. *N Engl J Med* 322(6):352–358