

Original Article

No Definite Benefit of 5-FU/LV Chemotherapy in Patient with Stage III Colorectal Cancer but Only One Lymph Node Metastasis

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Key Words

Stage III colorectal cancer

Purpose. Adjuvant chemotherapy can reduce mortality and recurrence of patients with stage III colorectal cancer (CRC). The purpose of this study is to evaluate efficacy of chemotherapy in patients with stage III colorectal cancer accompanied with solitary lymph node metastasis.

Method. A total of 405 patients with stage III colorectal cancer and only one lymph node metastasis, who underwent surgery in Tri-Service General Hospital and Taipei Veterans General Hospital from February 27th, 1990, to September 18th, 2006, were enrolled. The patients with the number of total examined lymph nodes less than 12 were excluded. The 5-year overall survival rate and 5-year disease free survival rate were analyzed.

Results. The number of patients with and without 5-FU/LV adjuvant chemotherapy was 186 and 219, respectively. Comparing the two groups, those younger patients tended to receive chemotherapy ($p = 0.04$). The 5-year overall survival rates in the stage III patients with only one lymph node metastasis, who received and didn't receive adjuvant chemotherapy, were 65% and 68%, respectively. The 5-year disease free survival rates of the two groups were 59.6% and 57.2% respectively. Both results did not reach statistical significance. ($p = 0.576$ and $p = 0.42$)

Conclusion. The result showed that 5-FU/LV adjuvant chemotherapy in stage III patients with solitary lymph node metastasis did not affect the 5-year overall survival and 5-year disease free survival. Therefore, applying 5-FU/LV chemotherapy for this group of patients with one lymph node metastasis is controversial.

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Colorectal cancer is the third leading cause of cancer death in Taiwan. Many factors have been identified of impacting survival of patients with colon cancer. In 1991, the National Institutes of Health (NIH; National Cancer Institute, United States) pub-

lished the first evidence-based guidelines for applying adjuvant therapy to patients with colorectal cancer.¹ Multiple randomized trials also showed reduction of death and disease recurrence in patients with stage III colon cancer treated by adjuvant chemotherapy.² The

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peer-review group determined that patients with stage III colon cancer can benefit from adjuvant fluorouracil (5-FU) – based chemotherapy.³⁻⁵ In patients with non-metastatic colorectal cancer, the status of lymph node metastasis is the strongest pathologic factor influencing their survival. The five-year survival of CRC patients is about 80%-85% in stage I and about 70%-75% in stage II. In contrast, only 45% of patients with stage III CRC accepting surgery alone survive; therefore, adjuvant chemotherapy is recommended for patients with colon cancer in stage III and stage II accompanied with high risk features. However, only half of such patients in advanced ages undergo adjuvant therapy after surgical resection.^{6,7} The optimal therapeutic strategies in this group of patients must balance risks and benefits of treatment. Adjuvant chemotherapy in stage III CRC patients with the solitary lymph node metastasis was controversial, especially in elderly patients. Due to prolonged life expectancy, patients in their 70s and even 80s require a better therapeutic plan for this potentially curable disease.⁸⁻¹² The purpose of this study is to clarify effects of adjuvant chemotherapy on stage III CRC patients with solitary lymph node metastasis.

Material and Methods

CRC patients with solitary lymph node metastasis receiving surgery and chemotherapy in Tri-Service General Hospital and Taipei Veterans General Hospital from February 27th, 1990 to September 18th, 2006 were enrolled. End of follow up was December 31, 2009. All clinical and pathological data were retrieved from computer files and charts. The patients who lost follow up, didn't finish the chemotherapy and with less than twelve lymph nodes examined were excluded.¹³ The average number of lymph nodes examined was 14. The chemotherapy included the fluorouracil (5-FU) – based regimen (5-Fluorouracil 1500 mg/M² plus leucovorin 75 mg/M², intravenously for 20 hours, on days 1-2, per 2 weeks for 12 courses) and the other similar ones in both hospitals. The patients received oral chemotherapy were excluded. The data were collected and analyzed.

Differences of their ages were analyzed by t test.

The general parameters, such as age, sex, CEA level etc., were compared with χ^2 test. *p* values for the survival curves were determined from the Kaplan-Meier survival curves and compared by using the log-rank test. Chi-square test was used for univariate analysis of the prognostic value of these variables. All variables that showed *p* < 0.05 were entered into the multivariate model. A *p* value less than 0.05 was considered statistically significant. Statistical analysis were performed using SPSS software (SPSS Inc., Chicago, IL).

Results

The characteristics of stage III CRC patients with solitary lymph node metastasis either receiving or lacking adjuvant chemotherapy are shown in Table 1. The mean age was 64.9 years old and the patients were further categorized into younger and older groups by taking the mean age as the cutoff value. Most patients without chemotherapy were in the older group (54%, *p* = 0.04) and with well to moderate grade (49%, *p* = 0.03). The patient numbers of both groups were not statistically different in the other factors.

In Fig. 1, the T stage of the TNM system is a statistically significant factor affecting the overall survival rate (*p* = 0.004), indicating a poor outcome in both groups with an advanced tumor.

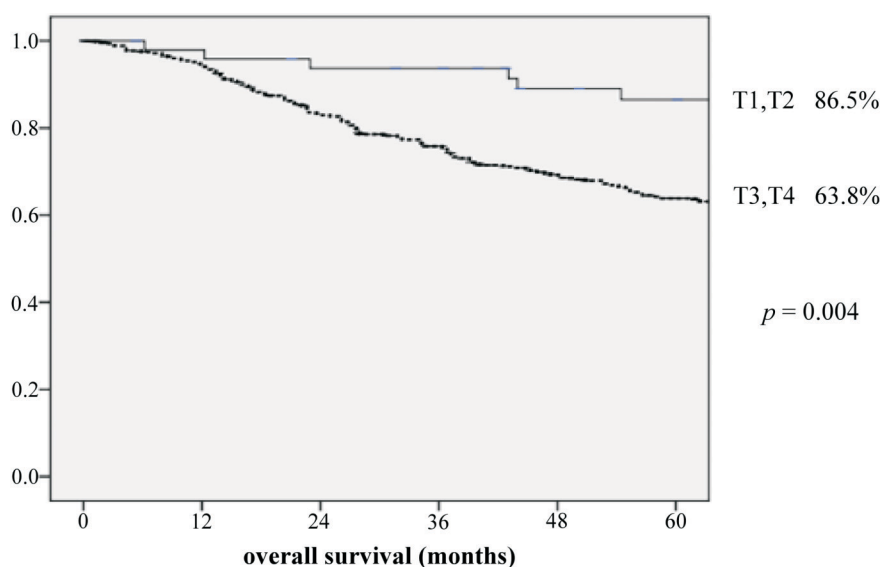
The 5-year overall survival rate and 5-year disease free survival rate were not significantly different (*p* = 0.576 and *p* = 0.42) between two groups (Figs. 2 and 3).

Discussion

The National Institutes of Health launched evidence-based assessment of the adjuvant therapy for colon and rectal cancer in 1990. Adjuvant chemotherapy with FU and levamisole was recommended for patients with stage III colon cancer because the evidences showed reduction of disease relapse and mortality by 30% to 40% at 5 years. The status of lymph node metastasis is important to determine the stage of colonic cancer and a critical indicator of prognosis to

Table 1. The patients' demographic and clinicopathologic distribution of 405 stage III CRC with only one lymph node metastasis

	Chemotherapy (-)	(%)	Chemotherapy (+)	(%)	<i>p</i> value
Age					
Mean ± SD	65.96 ± 10		63.65 ± 11		0.04
	219	54%	186	46%	
Gender					
Male	151	37%	131	32%	0.76
Female	70	17%	53	14%	
Location					
Right colon	80	20%	57	14%	0.86
Left colon	64	16%	83	21%	
Rectum	75	19%	46	10%	
T stage					
T1+2	29	7%	20	5%	0.21
T3+4	190	47%	166	41%	
Grade					
Well to moderate	201	49%	159	39%	0.03
Poor to undifferentiated	21	5%	24	7%	
CEA level					
CEA ≤ 5	134	33%	126	31%	0.19
CEA > 5	85	21%	60	15%	

**Fig. 1.** Multivariate analyses for overall survival.

guide the requirement of adjuvant chemotherapy. But elderly patients with stage III colorectal cancer receiving treatment are often related to lower overall survival, especially in those with dementia or the other underlying diseases. This study aimed to explore the effect of chemotherapy on overall survival in stage III CRC patients with solitary lymph node metastasis.

Although chemotherapy was a standard therapy for the stage III CRC patients, quite a few patients do not follow the standard guidelines because of advanced age and comorbidity. In fact, T1-2N1 have similar prognosis to T2N0/T3N0.¹⁴ Therefore, it is important to understand the effect of chemotherapy on overall survival (or disease-free survival) in the clinical prac-

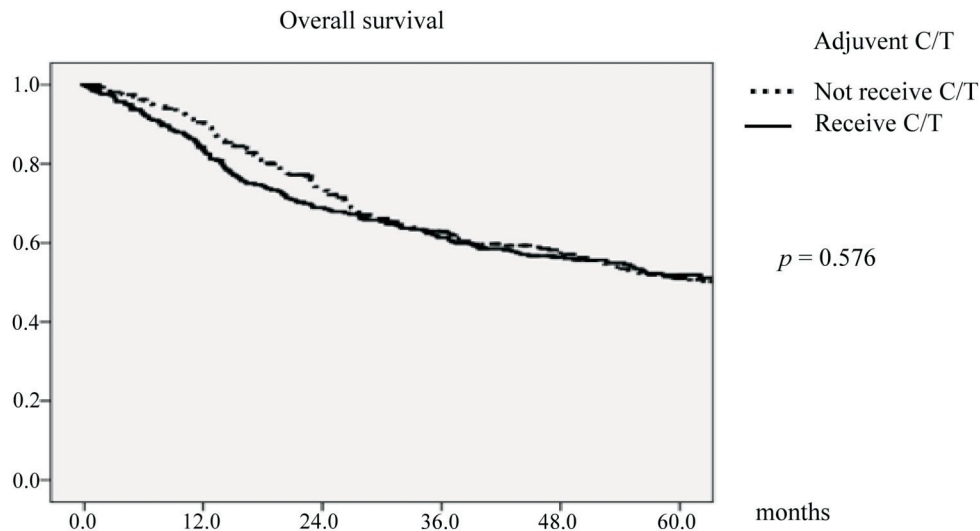


Fig. 2. Univariate analyses for overall survival.

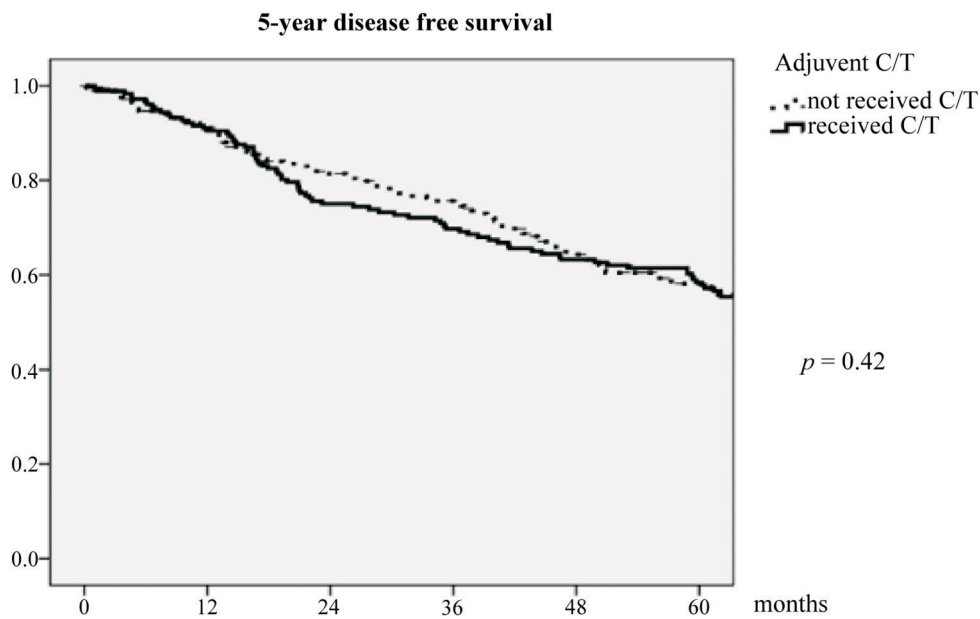


Fig. 3. Univariate analyses for disease-free survival.

tice instead of the statistically significant analysis. Most recommended regimens of adjuvant chemotherapy, such as systemic FU plus levamisole or folinic acid, are not only associated with measurable side effects, but also with subjective symptoms, such as fatigue, anorexia, loss of taste and medical dependence, which affect quality of life, especially in patients with advanced age. Elderly patients in our study were less willing to receive chemotherapy due to fear of side effects.

Some limitations were noted in this study. This is

a retrospective study instead of a prospective randomized study; the duration of follow up is still too short to completely analyze the recurrence rate and long-term survival; the chemotherapy in this study was only intravenous fluorouracil (5-FU) – based regimen, but not oxaliplatin based ones that are more effective. Besides, the patients received oral fluoropyrimidine were not included, the choice of the elder patients to receive oral adjuvant chemotherapy might have no difference with the younger patients. Further investigation is needed to determine whether patients'

preference, their functional status, physicians' attitude, or other barriers affect therapeutic decisions.^{15,16} Now colon cancer is common and adjuvant chemotherapy is an efficacious intervention. Application of adjuvant chemotherapy is an indicator of high-quality cancer care. To assess whether treatment is appropriately applied, further studies exploring physicians' and patients' knowledge and attitudes toward treatment are essential.

Conclusion

The result showed that 5FU/LV chemotherapy in stage III CRC patients with solitary lymph node metastasis did not impact the 5-year overall survival and 5-year disease free survival. Therefore, 5-FU/LV chemotherapy is still controversial for this group of patients with one lymph node metastasis. Further trials to investigate the advantages of chemotherapy in these patients with advanced age are recommended.

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原 著

5-FU/LV 化學治療對於第三期大腸直腸癌 只有一顆淋巴轉移病人並沒有明顯益處

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目的 術後輔助性化學治療可以減低第三期大腸直腸癌病人的死亡率及復發率，我們分析第三期大腸直腸癌病人中只有一顆淋巴轉移的結果。

方法 總共收案 405 個第三期大腸直腸癌只有一顆淋巴轉移的病人，於 1990 年 2 月 27 日至 2006 年 9 月 18 日在三軍總醫院及台北榮民總醫院接受手術，我們分析五年存活率及五年無疾病存活率。

結果 回溯性觀察第三期大腸直腸癌只有一顆淋巴轉移的病人中有接受化療及沒有接受化療的數目分別為 186 和 219 位，比較兩組病人，較年輕的病人傾向接受化療 ($p = 0.04$)，五年存活率在有接受化療及沒有接受化療的兩組中分別是 65% 及 68%，五年無疾病存活率分別是 59.6% 和 57.2%，兩組都沒有達到統計學上意義 ($p = 0.576$ 及 $p = 0.42$)。

結論 結果顯示 5-FU/LV 輔助性化學治療並沒有影響第三期大腸直腸癌只有一顆淋巴轉移的病人的五年存活率及三年復發率，因此化療對於這一個族群病人的影響還是值得討論。

關鍵詞 第三期大腸直腸癌。