Original Article

Prognosis of Stage IIIA Colorectal Cancer Patients with or without Postoperative Adjuvant Chemotherapy

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Key Words
Adjurant therapy;
Colon & rectum adenocarcinoma

Introduction. The new definition of stage IIIA colorectal cancer (CRC) was introduced in the Seventh Edition of the American Joint Committee on Cancer (AJCC 7th). Because the outcomes of patients with stage IIIA CRC are not worse than those of patients with stage II disease, we evaluated whether chemotherapy would also benefit this group of patients.
Patients and Methods. Patients who received curative surgery and were diagnosed with stage IIIA CRC between 1995 and 2006 were enrolled and analyzed.
Results. Total 149 patients diagnosed stage IIIA colorectal cancer were enrolled. In these patients, 31 were T1 stage with only one found recurrence. Whether adjuvant therapy performed or not, there was no significant meaning for their prognosis. For T2 patients, higher recurrence rate was noted with N1b patients. Though no statistical meaning achieved, for those without chemotherapy, mucinous type, insufficient lymph node exam, higher recurrent rate were noted. The new AJCC 7th made difference in T1N2a group. Though only 5 patients collected in this study, none was found tumor recurrence, and the result was compatible with the new staging system.
Conclusion. Adjuvant therapy is recommended for stage IIIA CRC patients with T2 disease. However, adjuvant chemotherapy may not be beneficial for stage IIIA CRC patients with T1 disease.
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Colorectal cancer (CRC) is one of the leading causes of cancer death in developed countries. Surgical resection remains the standard curative treatment. For stage III disease defined by the American Joint Committee on Cancer seventh edition (AJCC 7th), the National Comprehensive Cancer Network (NCCN) guidelines recommend adjuvant chemotherapy to reduce the recurrence rate and achieve long-term survival.[1]

There is no consensus on the treatment of stage III CRC, especially for older patients and for those with a poor performance status.[2-5] The AJCC 7th was first published in 2010 and replaced Dukes' staging system, previously used for pathologic staging. There are no reports regarding the efficacy of chemotherapy on stage IIIA CRC. The protocol for adjuvant chemotherapy in our hospital was established and adjusted according to the findings of recent studies. Patients

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were given adjuvant chemotherapy if they tolerated it according to the treatment guidelines. However, for older patients and for those with the risk of toxic side effect (judged by the attending physician in our hospital), doctors advised clinical observation.

With the current trend, more precise treatment is required at the individual level. Although the prognosis of patients with stage IIIA CRC is better than that of patients with other stage III CRC, whether all stage IIIA patients require adjuvant therapy is still unclear. The aim of this study was to evaluate whether adjuvant chemotherapy would benefit pathologically diagnosed stage IIIA CRC patients. For this purpose, we analyzed the effects of adjuvant therapy on each subgroup of stage IIIA CRC patients — T1N1aM0, T1N1bM0, T1N2aM0, T2N1aM0 and T2N1bM0.

Patients and Methods

We retrospectively reviewed the database of the Colorectal Cancer Registry of the colorectal surgery section of Chang Gung Memorial Hospital. All patients with colorectal cancers who underwent colorectal resection at a single institution between February 1995 and December 2005 were recruited.

Patients with pathologically confirmed primary colorectal stage IIIA adenocarcinoma according to the AJCC 7th edition were retrospectively enrolled. All patients were treated with curative surgery had a follow-up duration of more than 5 years. Complete history was recorded and physical examination, complete blood count, carcinoembryonic antigen (CEA) level determination, and computed tomography (CT) to determine the presence of possible distant metastasis were performed prior to treatment. During follow-up, digital examination, chest radiography, CEA level determination, CT, positron emission tomography (PET), abdominal ultrasonography, and colonoscopy were performed to evaluate metastatic or recurrent disease. Informed consent was obtained from all patients. Clinical information on age, gender, preoperative CEA level, administration of adjuvant therapy, tumor pathological type, pathological grade, number of examined lymph nodes, and T and N stages — possible risk factors for tumor recurrence after curative surgery — were recorded.[6-10] The post operation adjuvant chemotherapy were 5-Fu based regimens. Patients with other non-metastatic malignancies or patients who had received neoadjuvant chemotherapy or radiotherapy were excluded from the study.

Data were analyzed using SPSS software (version 20, IBM). Comparisons between groups were made using Fisher's exact test. Survival was calculated using univariate analysis according to the Kaplan-Meier method. Survival difference was compared using the log rank test. To assess all the independent variables, a p value of < 0.05 in the univariate analyses was used for the final Cox proportional hazards model used in the multivariate analysis. Statistical significance was set at $p < 0.05$.

Results

The total patients diagnosed stage III colorectal cancer underwent curative colorectal tumor surgery in our hospital between 1995 and 2006 were 2750 (1310 colon cancer and 1440 rectal cancer). A total 169 (6.1%) patients with stage IIIA CRC were enrolled in the study. Twenty patients were excluded because of other malignancies or because they received preoperative chemotherapy or radiotherapy. Medical records for the remaining 149 patients were retrospectively analyzed. The mean followed up duration for these patients were 6.8 years. Among them, 46 were diagnosed as having colon cancer and the remaining 103 were diagnosed as having rectal cancer. The mean age was 60.9 ± 14.5 years for patients with colon cancer and 60.3 ± 12.7 years for those with rectal cancer. The general characteristics of the patients are summarized in Table 1. There were no significant differences between colon cancer group and rectal cancer group except higher rate of moderate differentiated adenocarcinoma was found in rectal cancer group. The mean exam lymph nodes were 15.6.

T stage was a risk factor for recurrence (Table 2). Patients diagnosed as having T2 CRC (T2N1 disease) showed a higher recurrence rate than those diagnosed as having T1 CRC (T1N1 and T1N2a disease) (1 of 31 vs. 22 of 118, $p = 0.047$). With regard to adjuvant therapy,

Table 1. Patients' general characteristics

	Location		*p* value
	Colon	Rectum	
Patient number	46	103	
Age/year/mean ± S.D.	60.9 ± 14.5	60.3 ± 12.7	
Gender (M/F)	18/28	50/53	0.287
Age (> 65/≦ 65)	19/27	37/66	0.312
Adjuvant therapy (yes/no)	29/17	72/31	0.318
Pre-op CEA level (ng/ml) (≧ 5/< 5)	8/38	16/87	0.776
Histologic type (adenocarcinoma/mucinous carcinoma)	42/4	101/2	0.053
Histologic grade (well/moderate/poor differetiated)	17/28/1	20/75/8	0.040
Exam lymph nodes (≧ 12/< 12)	35/11	62/41	0.189
T stage (T1/T2)	12/34	19/84	0.382
N stage (N1/N2)	45/1	99/4	1.000
Recurrence (yes/no)	7/39	15/87	1.000

Table 2. The risk factors with the recurrence rate for both colon and rectal cancer. Total patient number = 149, recurrent number = 22 (14.8%)

Factors		Recurrent number (%)	total	*p*-value
Examined lymph node	< 12	7 (13.4)	52	0.802
Age	> 65	8 (14.3)	56	
Histologic type	Mucinous adenocarcinoma	1 (16.7)	6	1.000
	adenocarcinoma	21 (14.7)	143	
Histologic grade	Well-differentiated	5 (13.5)	37	0.85
	Moderate-differentiated	16 (15.5)	103	
	Pooly-differentiated	1 (11.1)	9	
Adjuvant therapy	No	8 (16.7)	48	0.911
	Chemotherapy	12 (13.0)	92	
	Radiotherapy	1 (25)	4	
	CCRT	1 (20)	5	
CEA (ng/ml)	≥ 5	7 (29.1)	24	0.061
T stage	T1	1 (3.2)	31	0.047
	T2	21 (17.8)	118	
N stage	N1	22 (15.3)	144	1.000
	N2	0 (0)	5	
Location	Colon	6 (13.0)	46	0.746
	Rectum	16 (15.5)	103	

patients without adjuvant therapy showed a higher recurrence rate than those who received adjuvant therapy (8 of 48, 16.7% vs. 13 of 101, 12.8%), although the difference did not reach statistical significance ($p = 0.911$).

The only found tumor recurrence with T1 stage was first diagnosed in 2000 and received radical resection of the rectal tumor including inferior mesenteric artery high ligation and paraaortic lymph node dissection. No adjuvant therapy was given after operation. Liver metastasis was found 4 years after operation and one segmental hepatectomy was done for solitary metastatic lesion. Further chemotherapy with Irinotecan, and 5-Fu (FOLFIRI) were done for 12 courses. The patient was still under clinical follow up after oncology department.

We further evaluated whether cancer recurrence was associated with other risk factors (Table 3). In the T1 group, no significant risk factor was noted, probably because of only 1 recurrent case. In the T2 group, N1b was a risk factor for tumor recurrence ($p = 0.014$). This result was in accordance with the trend seen for the general tumor staging system — a higher

recurrence rate in patients with higher stage disease. Besides, higher recurrence rate were noted with less lymph node exam (less than 12), mucinous type, and poorly differentiated grade. Although no statistical meaning shown with current studies, these may be risk factors for tumor recurrence in T2 groups. Further investigation with larger patient numbers is necessary to confirm the hypothesis.

Table 3. T2 stage with tumor recurrence

Factors		Recurrent (%)	total	*p*-value
Exam lymph nodes	< 12	8 (20.5)	39	0.609
Histologic type	mucinous	1 (20)	5	0.903
Histologic grade	well	5 (17.9)	28	0.911
	moderate	14 (16.9)	83	
	poor	2 (28.6)	7	
Adjuvant therapy	Performed	13 (16.0)	81	0.645
	None	8 (21.6)	37	
pre-op CEA (ng/ml)	≧ 5	6 (27.2)	22	0.166
Location	colon	6 (17.6)	34	0.967
	rectum	15 (17.9)	84	
N stage	N1a	9 (11.5)	78	0.014
	N1b	12 (30)	40	

Further survey for colon and rectum separately was shown in Tables 4 and 5. For colon cancer, the total number was 46 and no factors reached statistical meaning but the T1 stage showed less tumor recurrence rate. For rectal cancer patients, high pre-operative CEA level was found to be a possible risk and T stage also showed the trend to be a prognostic factor for rectal cancer patients.

To evaluate the benefit of adjuvant therapy and determine whether it prolonged the time from surgery to first recurrence, we used tumor recurrence as an endpoint (Fig. 1). Although the adjuvant therapy

Table 4. The risk factors with the recurrence rate for colon cancer. Total patient number = 46, recurrent number = 6 (13.0%)

Factors		Recurrent number (%)	Total	*p*-value
Examined lymph node	LN < 12	2 (18.2)	11	1.000
Adjuvant therapy	Performed	1 (5.9)	17	0.746
	None	5 (17.2)	29	
CEA (ng/ml)	≥ 5	1 (12.5)	8	1.000
T stage	T1	0	12	0.215
	T2	6 (15)	34	
N stage	N1	6 (13.3)	45	
	N2	0	1	
Histology grade	Well-differentiated	2 (11.7)	17	0.784
	Moderate-differentiated	4 (14.3)	28	
	Poorly-differentiated	0	1	
Histology type	Mucinousadenocarcinoma	1 (25)	4	1.000
	Adenocarcinoma	5 (12.0)	42	

Table 5. The risk factors with the recurrence rate for rectal cancer. Total patient number = 103, recurrent number = 16 (15.5%)

Factors		Recurrent number (%)	Total	*p*-value
Examined lymph node	LN < 12	5 (15.5)	41	0.629
Adjuvant therapy	Performed	9 (12.5)	72	0.482
	None	7 (22.5)	31	
CEA (ng/ml)	≥ 5	6 (37.5)	16	0.024
T stage	T1	1 (5.2)	19	0.309
	T2	15 (17.8)	84	
N stage	N1	16 (15.5)	103	
Histology grade	Well-differentiated	3 (15)	20	0.964
	Moderate-differentiated	12 (16)	75	
	Poorly-differentiated	1 (12.5)	8	
Histology type	Mucinous adenocarcinoma	0 (0)	2	1.000
	Adenocarcinoma	16 (15.8)	101	

group showed longer disease-free survival than the group that did not receive any therapy, the difference was not significant. In addition, we analyzed the 5-year disease-related survival to evaluate if adjuvant therapy resulted in prolongation of survival. The overall survival rate was significantly different between patients with and without adjuvant therapy (p = 0.002) (Fig. 2). Thus, although adjuvant therapy did not prolong the time to recurrence in stage IIIA patients, it improved their overall survival.

Analysis of T stage showed that T1 patients had better disease-free survival (p = 0.044). The overall survival in the T1 and T2 groups was not statistically different but longer in the T1 group than in the T2 group (p = 0.123) (Fig. 3). In the T2 group, overall survival and disease-free status were compared between N1a and N1b groups (Fig. 4). Patients with

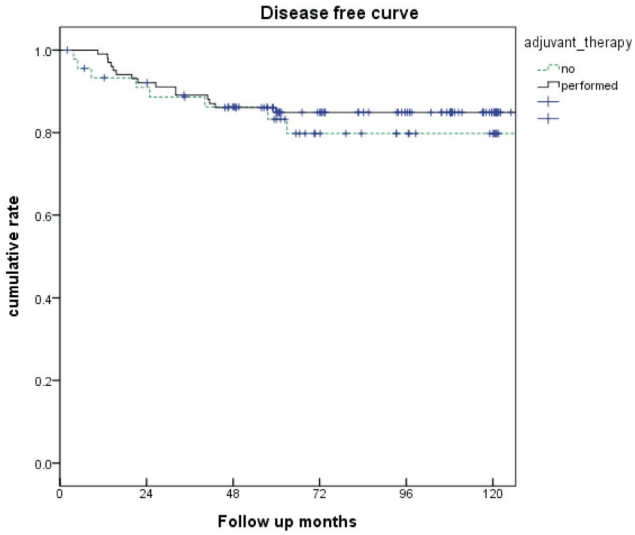

Fig. 1. The disease free duration to first diagnosed tumor recurrence. There was no significant effective for adjuvant therapy used on these patients. There is no evidence to support adjuvant therapy prevent tumor recurrence.

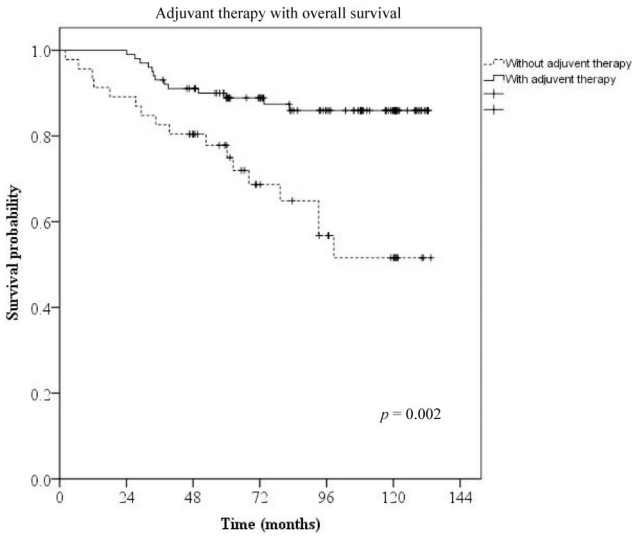

Fig. 2. The 5 year overall survival data showed significant difference with adjuvant therapy. Although adjuvant therapy may not be meaningful to tumor recurrence, it improved the overall survival.

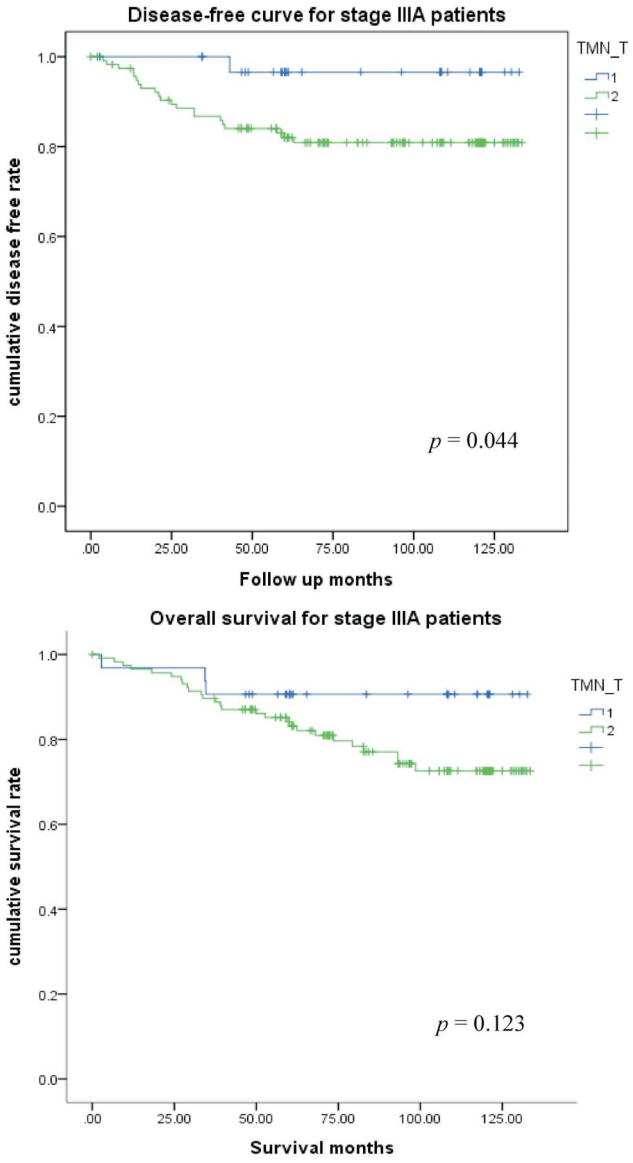

Fig. 3. The Disease free and overall survival status for stage IIIA patients. Comparison for T1 and T2 groups revealed better disease-free survival and overall survival in T1 group but non-significant difference seen in overall survival.

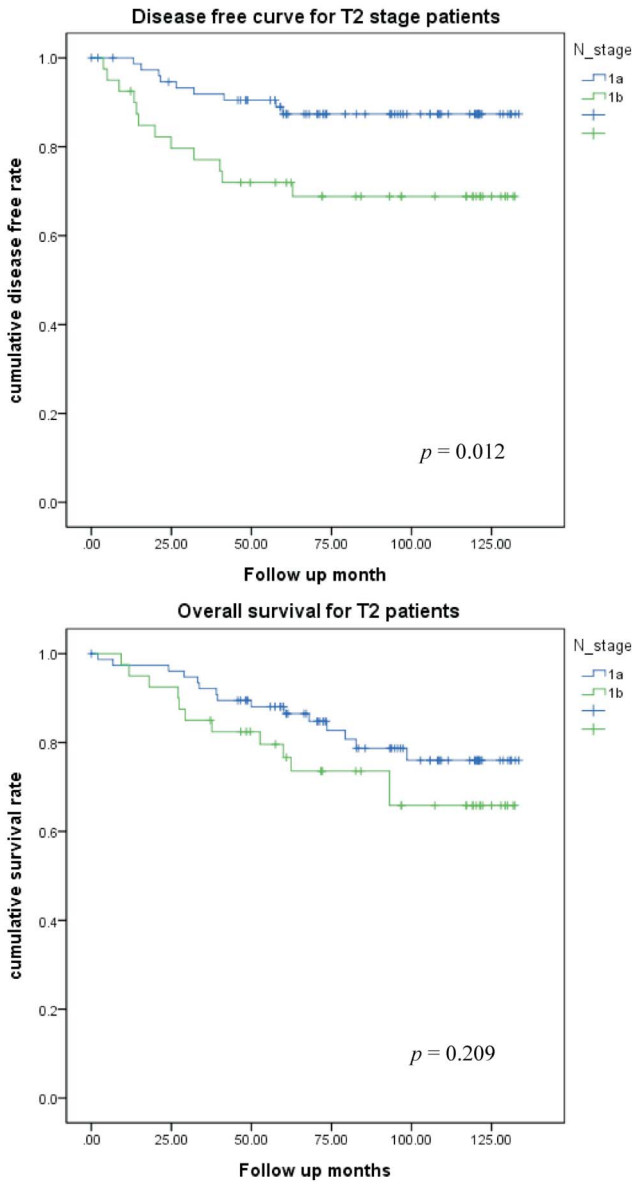

Fig. 4. Comparison of N1a and N1b group in T2 patients. With long term follow up, N1a patients showed better survival and disease free status than N1b patients but only disease free status reach significant difference.

N1a disease showed better disease-free and overall survival than those with N1b disease, but the difference was significant only for disease-free survival ($p = 0.012$ for disease-free survival and $p = 0.209$ for overall survival). To evaluate the benefit of adjuvant therapy for T2 patients, lower tumor recurrence rate was noted. The disease-free survival and overall survival were shown in Figs. 5 and 6. For T1 patients, adjuvant therapy showed non-significant change for both overall survival and disease free survival. For these T2 patients, adjuvant therapy showed non-statistical difference in disease-free status but better overall survival. The result is the same as the result of all stage IIIA patients.

Discussion

The treatment for stage IIIA CRC has not been reported in any specific study. While adjuvant therapy is recommended for patients with high-risk stage II CRC, this is not certain for patients with stage IIIA CRC, and our study showed results similar to those for stage II disease. Patients received adjuvant therapy as per the cancer treatment guidelines, but not all of them benefited from it.

Since 2000, the chemotherapy regimens used for CRC treatment have changed dramatically. The approval of irinotecan, oxaliplatin, and 2 humanized monoclonal antibodies that target vascular endothelial growth factor (bevacizumab) and epidermal growth factor receptor (cetuximab) has provided new alternatives for adjuvant and palliative chemotherapy. Several studies reported significant improvement in patients with stage III CRC treated with oxaliplatin or irinotecan compared to patients treated with 5-fluorocil-based therapies.[11-19] For more advanced treatment, individual patient treatment method would have to be developed on the basis of clinical data and examination results.

The outcomes of patients with stage IIIA disease are not worse than those of patients with stage IIB (T4aN0M0) or stage IIC (T4bN0M0) CRC.[20] In high-risk patients with stage II disease (characterized by perforation, obstruction, angiolymphatic invasion, perineural invasion, and poor differentiation), adjuvant chemotherapy is recommended because of the higher risk of tumor recurrence.

We evaluated the known risk factors for stage II disease that are used to determine the need for adjuvant chemotherapy and examined the use of chemotherapy in patients with stage IIIA disease to identify possible risk factors for recurrence. Patients with

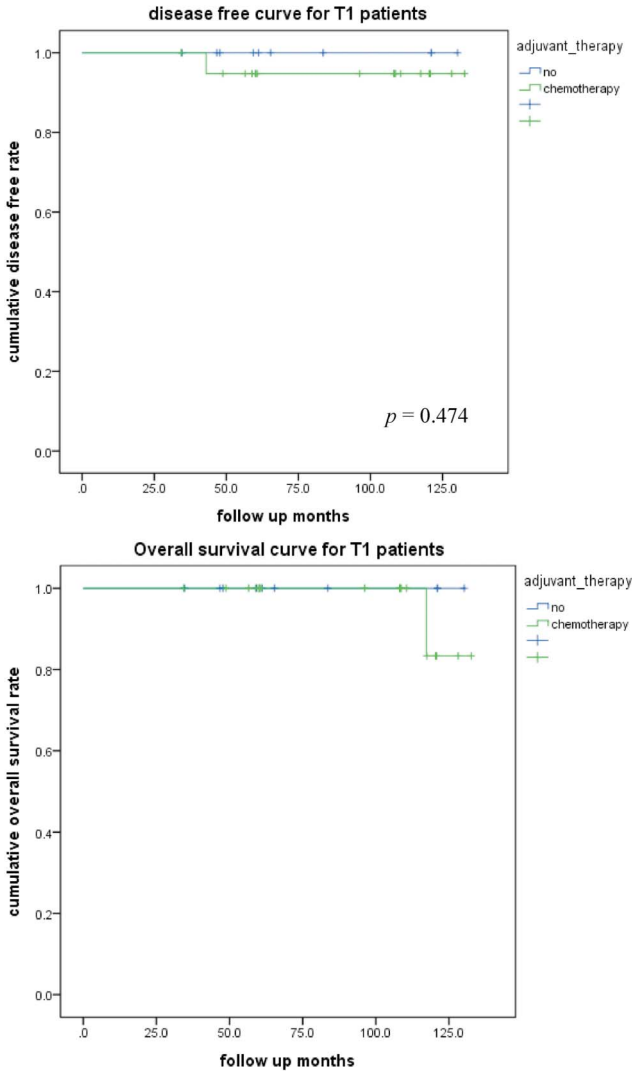

Fig. 5. The impact of adjuvant therapy on T1 patients in disease free and overall survival. No significant difference seen on both analysis with 5 year follow up.

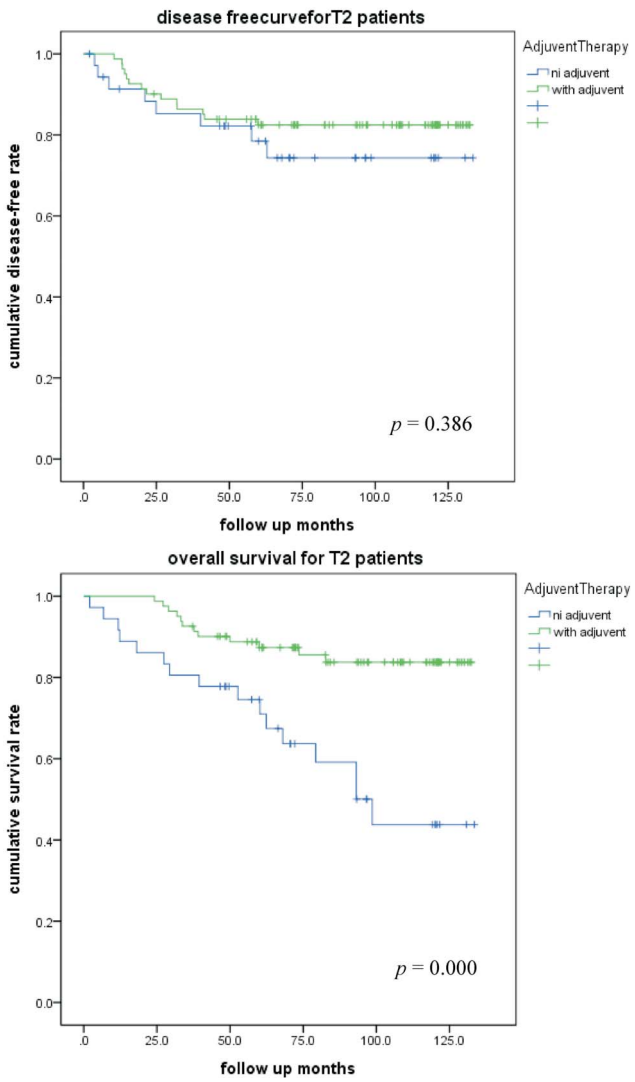

Fig. 6. The impact of adjuvant therapy on T2 patients in disease free and overall survival. No significant difference seen on disease-free but lower overall survival was seen for patients without adjuvant therapy.

pathologic T2 stage disease showed a higher risk for recurrence. However, it was still unclear whether adjuvant chemotherapy would benefit the small group of patients diagnosed with stage T1N2a. These patients are classified as having stage IIIC disease according to the sixth edition of the AJCC but as having stage IIIA disease according to the seventh edition. In our study, only 5 patients were diagnosed as having stage N2a disease and none of these patients developed recurrence. This finding is in agreement with the new staging system that is based on prognosis prediction. Review of the AJCC data showed that the 5-year disease-free survival for patients with stage IIIC disease was approximately 75%. Of these 5 patients, 2 received adjuvant therapy and the others did not. Further study is needed to determine whether a higher N stage is a possible risk factor. Thus, we suggest that patients diagnosed as having stage IIIA CRC receive adjuvant therapy, especially those with stage T2 disease, in order to increase overall survival. For patients with T1 disease, clinical observation may be a more suitable choice than adjuvant therapy for patients experiencing toxic side effects and for elderly patients.

The adjuvant therapy showed non-statistical dif-

ference in disease-free status but helpful in overall survival in all the stage IIIA group and stage T2 groups. The possible cause of these difference may be 2 reasons. One is that tumor recurrence with rapid progress may lead to earlier death. The other reason is related to patient's underlined condition. Usually, we advise these stage IIIA cancer patients to receive adjuvant therapy but not for some poor performance patients. Reviewed our data, 12/30 death were due to other cause. For these 12 patients, 8 of them had no adjuvant therapy.

Previous studies have shown that although the effectiveness of chemotherapy could be decreased in older patients, the side effects depend on dosage accumulation.[3] The benefit of adjuvant chemotherapy in older patients should be evaluated on considering their shorter life expectancy and the fact that its effectiveness decreases dramatically after the age of 75 years.[3,4] More aggressive treatment is recommended, especially for those considered as having a high risk of recurrence. Furthermore, additional studies are required to identify possible high-risk factors for recurrent disease, because older patients may benefit from adjuvant chemotherapy.

Among the risk factors analyzed in this study, only tumor invasion depth (T stage) was significantly predictive. However, our results differed from those of previous studies.[21-23] This could possibly be because of differences in patient ethnicity or age. For stage III CRC, increased recurrence rates were observed and adjuvant therapy was recommended. A statistic bias is possible because previous studies have shown an increased possibility of tumor recurrence. Further investigation of factors associated with a high recurrence rate is needed to define the population for whom aggressive chemotherapy is advisable.

One unexpected result seen in our study was the higher recurrence rate in patients with colon cancer treated with adjuvant chemotherapy than in those who did not receive adjuvant chemotherapy. This might be the result of a bias because of the small sample size. A larger cohort of patients is necessary to confirm our findings. Moreover, the small number of patients with stage IIIA CRC may have resulted in a statistical bias. With the use of current chemotherapeutic agents such as oxaliplatin, xeloda, or irinotecan, survival has improved. Further studies are required to validate the use of these new drugs.

One limitation of this study was that chemotherapy administration was not randomized. The criteria for administering adjuvant therapy were not defined. Further prospective studies on patients with stage IIIA T1 (T1N1 or T1N2a) CRC will be needed to examine whether the benefits of adjuvant therapy are similar to those for patients with other stage III CRC.

Currently, one study from Korea reviewed their 131 cases between 1995 to 2008 had shown no significant difference for adjuvant chemotherapy regiments performed on the stage IIIA colorectal cancer patients.[24] In their study, the 5-year overall survival and the 5-year disease-free survival were 97.2% and 94.5% in the FL/capecitabine patient group and 95.5% and 90.9% in the FOLFOX patient group, respectively, and no statistically significant differences were noted between the two groups. The survival data is similar to our result. There is no many data with regarding to the newly built stage IIIA classification colorectal cancer. Our result does not against the current treatment guideline that stage III colorectal patients to receive adjuvant chemotherapy. It is data from single institute in 10 years, and the chemotherapy regiments changed a lot in these 10 years. Larger studies for T1 group may offer a more clear result.

Conclusion

Adjuvant therapy may help improve overall survival in patients with stage IIIA CRC. For patients with stage T1N1 and T1N2 disease, clinical observation may represent a more suitable choice, given the lower recurrence rate, especially for those unable to tolerate the side effects of chemotherapy.

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原　著

第 IIIA 期之大腸直腸癌患者預後分析– 術後治療是否是有意義的？

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目的　在美國癌症協會第七版 (AJCC7) 的分期中，第 IIIA 期的患者預後比部分第 II 期的患者為佳。本研究回顧林口長庚紀念醫院過去治療結腸直腸第 IIIA 期患者之經驗，並討論化學治療對此類患者的意義。

方法　本研究回顧並收集林口長庚紀念醫院之結直腸癌及病理學資料庫於 1995 至 2006 年間，經診斷罹患結直腸癌之患者中，病理診斷結果為第 IIIA 期結直腸共 149 例。另回顧分析上述病患之個別醫療紀錄，並就其臨床病理及人口統計學特徵，病理分類、腫瘤位置、腫瘤期別、治療 (手術方式、化學治療或放射線治療) 成效、轉移情形，以及存活率等進行分析。

結果　T1 的患者共 31 名，其中僅一名在術後發現復發的現象，不論是否有做其他術後輔助性治療，對於預後並無顯著的意義；而在 T2 的患者中，依照淋巴結轉移的數目 (病理檢查 N1a 與 N1b)，N1b 的患者復發率較 N1a 為高。另外，即使尚未達到統計學上的顯著差異，未做化學治療的、較差的病理分類、淋巴結檢查數目充分，復發率仍有降低的現象。而在新版分期中歸類為 IIIA 期的 T1N2aM0 患者，僅有五名患者均未發生腫瘤復發的現象，與新版分期是相符合的。

結論　對第 IIIA 期中 T2 的患者，仍然建議要做術後的化學治療。T1 期的患者，或許可考慮化學治療的副作用與藥物使用的益處，來決定是否應建議患者接受術後輔助性治療。

關鍵詞　輔助性治療、結腸與直腸、腺癌。