의학석사 학위논문

Survival Paradox Between Stage IIB/C (T4N0) and Stage IIIA (T1-2N1) Colon Cancer

IIB/C(T4N0)와 IIIA (T1-2N1) 병기 대장암의 역설적 생존율 분석

2014 년 02 월

서울대학교 대학원

의학과 외과학 전공

김민정

의학석사 학위논문

Survival Paradox Between Stage IIB/C (T4N0) and Stage IIIA (T1-2N1) Colon Cancer

IIB/C(T4N0)와 IIIA (T1-2N1) 병기 대장암의 역설적 생존율 분석

2014 년 02 월

서울대학교 대학원

의학과 외과학 전공

김민정

Master of Science in Medicine

Survival Paradox Between Stage IIB/C (T4N0) and Stage IIIA (T1-2N1) Colon Cancer

IIB/C(T4N0)와 IIIA (T1-2N1) 병기 대장암의 역설적 생존율 분석

February 2014

The Department of Surgery,
Seoul National University
College of Medicine
Min Jung Kim

IIB/C (T4N0)와 IIIA (T1-2N1)

병기대장암의 역설적 생존율 분석

지도 교수 정 승 용

이 논문을 의학석사 학위논문으로 제출함
2013년 10월

서울대학교 대학원

의학과 외과학 전공

김 민 정

김민정의 의학석사 학위논문을 인준함
2014년 1월

위 원 장 강 경 훈 (인)
부위원장 정 승 용 (인)
위 원 이 남 준 (인)

Survival Paradox Between Stage IIB/C (T4N0) and Stage IIIA (T1-2N1) Colon Cancer

by
Min Jung Kim, M.D.

(Directed by Seung-Yong Jeong, M.D., Ph.D.)

A thesis submitted to the Department of Surgeryin partial fulfillment of the requirements for the Master's Degree in Surgery at Seoul National University College of Medicine

January 2014

Approved by Thesis Committee:

Professor	**Chairman**
Professor	**Vice chairman**
Professor	

ABSTRACT

Introduction: The survival paradox between stage IIB/C (T4N0) and stage IIIA (T1–2N1) colon cancer still remains in the 7th edition of the American Joint Committee on Cancer staging system. This multicenter study aimed to compare the oncologic outcomes of T4N0 and T1–2N1 colon cancers and to investigate the presumptive prognostic factors that might influence the survival paradox.

Methods: Patients who underwent curative surgery for pT4N0 (n = 224) and pT1–2N1 (n = 135) primary colon cancer between January 1999 and December 2010 at 5 tertiary referral cancer centers were included for analysis. The clinicopathologic, treatment-related factors, and oncologic outcomes in terms of the 5-year overall survival (5-OS) and 5-year disease-free survival (5-DFS) were compared.

Results: The T4N0 group had significantly worse 5-OS and 5-DFS rates than the T1–2N1 (5-OS: 84.0% vs. 92.3%, p = 0.012; 5-DFS: 73.6% vs. 88.0%, p = 0.001). T4N0 cancers more frequently showed elevated preoperative carcinoembryonic antigen, lower grade of differentiation, large

tumor size, and higher proportions of perineural invasion, microsatellite instability, obstruction, and perforation than T1–2N1cancers. Peritoneal seeding and liver metastasis were the predominant recurrence pattern in the T4N0 and T1–2N1 groups, respectively (p = 0.042). The T4N0 group showed inferior survival to the T1–2N1 group in postoperative adjuvant chemotherapy (5–OS: 87.1% vs. 93.2%, p = 0.045; 5–DFS: 76.1% vs. 89.0%, p = 0.001).

Conclusions: T4N0 colon cancer had significantly worse oncologic outcomes than T1–2N1 cancer regardless of adjuvant chemotherapy. The survival paradox may result from the biologic aggressiveness of T4N0 colon carcinomas.

Keywords: T4N0, colon cancer, survival paradox, adjuvant chemotherapy

Student number: 2012–21675

CONTENTS

LIST OF TABLES AND FIGURES

Tables

Figures

LIST OF ABBREVIATIONS

5-DFS	5-year Disease-free Survival
5-OS	5-year Overall Survival
AJCC	American Joint Committee on Cancer
ASA	American Society of Anesthesiologists
BMI	Body Mass Index
CEA	Carcinoembryonic Antigen
CI	Confidence Interval
DFS	Disease-free Survival
FL	5-Fluorouracil plus Leucovorin
FOLFOX	5-Fluorouracil plus Leucovorin plus Oxaliplatin
JSCCR	Japanese Society of Cancer of the Colon and Rectum
LN	Lymph Node
MSI	Microsatellite Instability
MSI-H	High-frequency Microsatellite Instability
MSI-L	Low-frequency Microsatellite Instability
MSKCC	Memorial Sloan-Kettering Cancer Center
MSS	Microsatellite Stable
No.	Number
OS	Overall Survival
RSC	Signet-ring Cell Carcinoma
SD	Standard Deviation
SEER	Surveillance, Epidemiology, and End Results
UFT/LV	Uracil/Tegafur plus Leucovorin
XELOX	Capecitabine plus Oxaliplatin
XELRIRI	Capecitabine plus Irinotecan

INTRODUCTION

The stratification of the colon cancer staging system has been progressively increased to predict better the oncologic outcomes and to provide the most effective adjuvant therapy (1-4). Until its 5th edition, the American Joint Committee on Cancer (AJCC) staging system, the most popular classification in use, divided the stages of colon carcinoma into 4 different categories according to both the degree of bowel wall penetration by the primary tumor and the presence of nodal metastasis. From the 5th to 6th editions, stages II and III were subdivided into a total of 5 stages (stages IIa, IIb, IIIa, IIIb, and IIIc) based on the classification of the primary tumor as T3 or T4 and the number of nodal metastases. However, in a study based on the Surveillance, Epidemiology, and End Results (SEER) database, an evaluation of the survival rates associated with colon cancer stages defined according to the 6th edition revealed better survival for stage IIIa (T1-2N1) than stage IIb (T4N0) colon cancer (1). As of the 7th edition of the AJCC staging system, this survival paradox remains unresolved, and its resolution could offer better treatment outcomes for patients

with T4N0 tumors.

The preferential administration of adjuvant chemotherapy for stage IIIa patients and the inherently aggressive biology of T4N0 tumors have been offered as possible explanations for the survival paradox between the two cancer stages (1, 5). In current clinical practice, T4N0 colon cancer patients are recommended for receiving adjuvant chemotherapy, since patients with T4 tumors have been classified as a high-risk group among those with stage II colon cancers along with inadequate lymph node (LN) harvesting, poor differentiation, obstruction/perforation, and lymphovascular invasion (6-9). However, an ongoing debate is whether the inadequate use of adjuvant chemotherapy can fully explain the poor oncologic outcome of T4N0 colon cancer (5, 10). Further, only a limited number of studies have evaluated the oncologic outcomes and prognostic factors in these patient groups because of an insufficient number of cases in a single center and a lack of fully detailed records in a nation-wide administrative cancer database.

We therefore analyzed and compared oncologic outcomes in T4N0 and T1-2N1 colon cancer patients in 5 qualified

tertiary referral cancer centers over 12 years, and investigated the presumptive prognostic factors that might result in the survival paradox between the two patient groups.

MATERIALS AND METHODS

1. Data sources

Clinical, pathologic, surgical, and oncologic outcome data were retrieved from the prospectively collected cancer databases of 5 tertiary referral cancer centers in Korea between January 1999 and December 2010. During the study period, a total of 14,062 surgeries for colorectal cancers (colon: 8,500 cases, rectum: 5,562 cases) were performed (range: 383~5,313 per center).

2. Patient selection

We analyzed the data of patients with pathologically confirmed T4N0 or T1-2N1 colon cancer after curative colectomy. Tumors located in the cecum, ascending, hepatic flexure, transverse, splenic flexure, descending, and sigmoid colon were included in the analysis. Patients with rectosigmoid colon cancer, rectal cancer, anal cancer, appendiceal cancer, a histology other than adenocarcinoma, and surgery-related mortality (death during admission for the colorectal surgery or within 30 days after discharge) were excluded. Patients who received neoadjuvant chemotherapy and surgeries with

microscopic or macroscopic positive resection margins (R1 or R2 surgery) were also excluded.

3. Variables

The demographics, perioperative outcomes, pathologic results, the use of adjuvant chemotherapy, overall survival (OS), disease-free survival (DFS), and recurrence patterns were analyzed. The demographic information included the age, sex, body mass index (BMI), comorbidity, and American Society of Anesthesiologists (ASA) class. The preoperative variables related to the primary cancer were the preoperative carcinoembryonic antigen (CEA) level, tumor location, and the presence of tumor-related obstruction and perforation. The tumor location was divided into the right (cecum, ascending, hepatic flexure, and transverse) and left (splenic flexure, descending, and sigmoid) colon. The perioperative data analyzed were the intraoperative transfusion, operation time, length of hospital stay, and operation-related morbidities.

4. Pathologic analysis

The colon cancers were staged according to the 6th and 7th edition AJCC staging system. The tumor differentiation, number of harvested LNs, and tumor invasion were documented.

Tumor size was recorded according to the largest diameter of the tumor.

Microsatellite instability (MSI) testing of the tumors was performed in 3 centers. A microsatellite stable (MSS) tumor was defined as no change in the panel of five microsatellite markers (BAT25, BAT26, D5S346, D2S123, and D17S250) recommended by the National Cancer Institute (11). Low-frequency MSI (MSI-L) refers to changes in only one of the five markers; high-frequency MSI (MSI-H), to changes in two or more of the five microsatellite markers.

5. Survival analysis and determination of recurrence

OS was defined as the time from surgery to death from any cause; DFS, as the time from surgery to the first event of either relapse of colon cancer or death. For assessing the effect of chemotherapy on oncologic outcomes, the survival of patients with T4N0 and T1-2N1 colon carcinoma were analyzed in a subgroup of patients according to whether patients received adjuvant chemotherapy. An analysis of the survival data according to different chemotherapy regimens was also performed. The chemotherapy regimen was divided into two categories: the FU-basedchemotherapy group

[capecitabine alone, 5-fluorouracil plus leucovorin (FL), uracil/tegafur plus leucovorin (UFT/LV), or capecitabine plus irinotecan (XELRIRI)], and the oxaliplatin-combined group [FL plus oxaliplatin (FOLFOX),or capecitabine plus oxaliplatin (XELOX)].

The recurrence patterns were dichotomized into local and distant recurrences. Local recurrence was defined as clinical, radiologic, and/or pathologic evidence of locoregional relapse of the colon cancer, such as recurrence at an anastomosis site or a previously treated tumor bed. Clinical, radiologic, and/or pathologic evidence of tumor spread to distant organs, including the liver, lung, or distant LNs, was referred to as distant recurrence. The site of recurrence was recorded according to the location of the first identified organ/location involved by the recurrent tumor during the follow-up period. If multiple organs were detected as recurrent at the same time, all metastasized sites were documented.

A subgroup analysis was performed to compare the oncologic outcomes between T4aN0 (tumor perforated the visceral peritoneum) and T4bN0 (tumor directly invaded other organs or structures) colon cancer. In this study, all T4bN0

tumors were resected with negative resection margins, as confirmed by pathologists.

6. Statistical analysis

Demographic data are expressed as the mean or median, with the standard deviation or range, as appropriate. For comparing variables between the two staging groups, the Chi-square or Fisher's exact test were used for categorical variables, while the student' s t-test was used for continuous variables. The OS and DFS were analyzed by the Kaplan-Meier method. Group comparisons were performed by Log-rank tests. A Cox proportional hazards model was used to adjust the comparisons for each variable, while covariate-adjusted hazard ratios (with 95% confidence intervals [CIs]) and corresponding Wald P values produced by the Cox models were used to describe the associations. Significant variables in the univariate analysis were included in a multivariate forward stepwise regression analysis to determine the independent predictors of survival. P values of <0.05 were considered statistically significant. All data were analyzed by SPSS software, version 19 (SPSS, Chicago, IL). This study was reviewed and approved by institutional review boards of 5 centers.

RESULTS

Demographic and clinical characteristics

Between January 1999 and December 2010, a total of 359 patients underwent curative colectomy for T4N0 (n = 224) and T1–2N1 (n = 135) colon cancers at the 5 Korean tertiary referral cancer centers that participated in the study. The demographics and clinical characteristics are listed in Table 1. Sex, age, ASA class, and comorbidity were not significantly different between the T4N0 and T1–2N1 patients. Patients with T4N0 colon cancer had significantly lower BMI, a higher rate of elevated preoperative CEA levels, and cancer-related obstruction/perforation than patients with T1–2N1 colon cancer.

Patients with T4N0 colon carcinomas were more likely to receive intraoperative blood transfusions when compared to the T1–2N1 group. Further, the mean operation time and mean length of hospital stay was significantly longer in the T4N0 group than in the T1–2N1 group. However, the overall perioperative morbidity was not significantly different between the two groups. The majority of patients received adjuvant chemotherapy, with the rates of chemotherapy administration not significantly different between the two groups.

Pathologic data

The pathologic data are shown in Table 2. T4N0 carcinomas showed a higher incidence of poor, mucinous/signet ring-cell differentiation, and perineural invasion than T1-2N1 tumors. A higher number of examined nodes and a lower rate of inadequate LN harvesting occurred in the T4N0 group when compared to the T1-2N1 group. The T4N0 tumors had a greater mean tumor size than the T1-2N1 ones. MSI data was obtained in 137 patients of T4N0 group and 81 patients of T1-2N1 group. T4N0 colon cancer had more frequent MS than T1-2N1 colon cancer (MSI-L: 7.1% vs. 5.9%, MSI-H: 9.8% vs. 0%, $p < 0.0001$).

Oncologic outcomes

The mean follow up time was 71.8 and 69.7 months in the T4N0 and T1-2N1 groups, respectively. Kaplan-Meier survival analysis revealed worse 5-year OS (5-OS) and 5-year DFS (5-DFS) in the T4N0 group than in the T1-2N1 group (5-OS: 84.0% vs. 92.3%, $p = 0.012$; 5-DFS: 73.6% vs. 88.0%, $p = 0.001$; Fig. 1, A and B).

T4N0 patients had a higher rate of local recurrence and distant organ metastasis than the T1-2N1 patients (local

recurrence rate: 6.7% vs. 0.7%, p = 0.008; distant metastasis rate: 14.7% vs. 4.4%, p = 0.002). Sites of distant metastasis were distant LNs, liver, lung, and peritoneum (Table 3). The peritoneum was the predominant distant metastasis sites in the T4N0, whereas liver in T1–2N1 groups.

Among the 224 T4N0 patients, 85 (37.9%) had T4bN0 carcinomas. The oncologic outcomes of the T4bN0 patients were not inferior to the T4aN0 patients (5-OS: 83.3% vs. 85.1%, p = 0.473; 5-DFS: 71.7% vs. 76.2%, p = 0.832, respectively).

Survival analysis according to adjuvant chemotherapy

In the subgroup analysis of patients undergoing adjuvant chemotherapy, the T4N0 group showed a significantly worse 5-year survival than the T1–2N1 group despite chemotherapy (5-OS: 87.1% vs. 93.2%, p = 0.045; 5-DFS: 76.1% vs. 89.0%, p = 0.001; Fig. 2, A and B). In the nonchemotherapy group, the 5-OS and 5-DFS in the T4N0 patients were likewise inferior compared to those in the T1–2N1 patients, although the difference did not achieve statistical significance (5-OS: 63.5% vs. 83.9%, p = 0.121; 5-DFS: 56.7% vs. 80.8%, p = 0.155; Fig. 3, A and B). We also analyzed the oncologic outcomes

according to chemotherapy regimen. The 5-OS of the T4N0 patients was not significantly different between the FU-based and oxaliplatin-combined groups (88.4% vs. 84.2%, p = 0.496).

To examine the survival benefit attributable to each prognostic factor, we performed a Cox proportional hazards regression analysis. In the univariate analysis, the age, ASA class, comorbidity, number of LNs examined, perineural invasion, and adjuvant chemotherapy were significant predictors of OS (Table 4). Multivariate analysis demonstrated that young age, ASA class I/II, and administration of chemotherapy were independent prognostic factors for improved OS. In the analysis of DFS, the age, BMI, ASA class, comorbidity, preoperative CEA, chemotherapy, tumor differentiation, number of LNs examined, tumor size, lymphatic invasion, venous invasion, and perineural invasion were significant predictors (Table 5). Among these factors, old age, high BMI, poor tumor differentiation, less than 12 LNs examined, and venous invasion were found to be associated with decreased DFS.

Table 1. Demographic and clinical characteristics of the patients

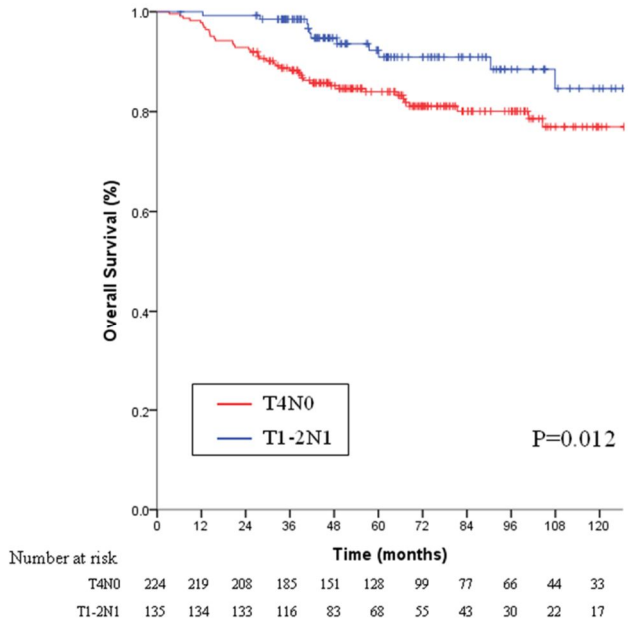
Variable	T4N0 stage	T1−2N1 stage	P
No. of patients	224	135	
Male (%)	124 (55.4%)	100 (74.1%)	0.359
Mean age (± SD), years	61.6 (±12.7)	62.3 (±10.8)	0.543
BMI (± SD), kg/m^2	22.5 (±3.1)	24.4 (±3.2)	<0.0001
ASA class			0.185
I	88 (39.3%)	58 (43.0%)	
II	115 (51.3%)	73 (54.1%)	
III	13 (5.8%)	2 (1.5%)	
IV	1 (0.4%)	0	
Comorbidity	93 (41.5%)	62 (45.9%)	0.414
Preoperative CEA, ng/mL			<0.0001
≤ 5	134 (59.8%)	127 (94.1%)	
> 5	77 (34.4%)	6 (4.4%)	
Tumor location			0.01
Right colon	88 (39.3%)	35 (25.9%)	
Left colon	136 (60.7%)	100 (74.1%)	
Obstruction	117 (52.2%)	3 (2.2%)	<0.0001
Perforation	13 (5.8%)	0	0.002
Blood transfusion (%)	34 (15.2%)	6 (4.4%)	0.002

Mean operation time (range), min	196.3 (35−575)	165.4 (50−542)	0.001
Mean length of hospital stay (range), days	12.8 (5−100)	10.2 (5−56)	0.002
Overall morbidity (%)	35 (15.6%)	13 (9.6%)	0.106
Adjuvant chemotherapy	190 (86.0%)	119 (89.5%)	0.338

Table 2. Pathologic data

Variable	T4N0 stage	T1−2N1 stage	P
Tumor differentiation			0.007
Well/Moderate	185 (82.6%)	126 (93.3%)	
Poor	13 (5.8%)	3 (2.2%)	
Mucinous/SRC	25 (11.2%)	6 (4.4%)	
Examined lymph nodes			
Total no. examined	27 (0−108)	17 (2−154)	< 0.0001
<12 examined	18 (8.0%)	36 (26.7%)	< 0.0001
Mean tumor size	7.0	2.5	< 0.0001
(range), cm	(1.2−220.2)	(0.6−63.0)	
Tumor invasion			
Lymphatic invasion	97 (45.1%)	67 (51.5%)	0.247
Venous invasion	42 (19.5%)	30 (23.1%)	0.129
Perineural invasion	69 (32.1%)	22 (16.9%)	0.002

(A)



(B)

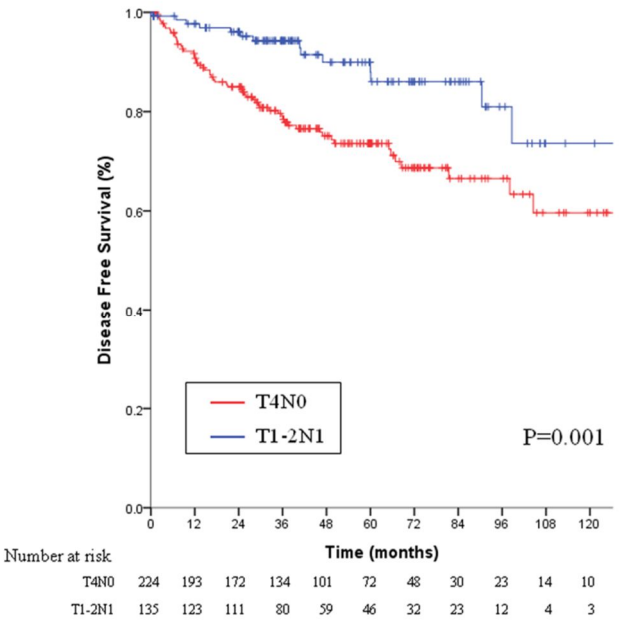


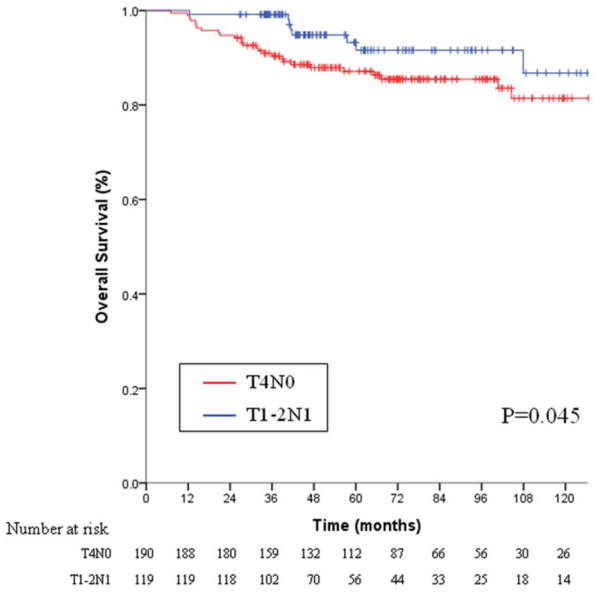
Figure 1.Kaplan-Meier curves for T4N0 and T1-2N1 colon cancer patients.

(A) Overall survival. (B) Disease-free survival.

Table 3. Locations of distant metastasis in T4N0 vs. T1−2N1 colon cancer

Variable	T4N0 stage	T1−2N1 stage	P
Distant LNs	4 (9.3%)	2 (28.6%)	0.042
Liver	13 (30.2%)	4 (57.1%)	
Lung	12 (27.9%)	2 (28.6%)	
Peritoneum	12 (27.9%)	0	

(A)



(B)

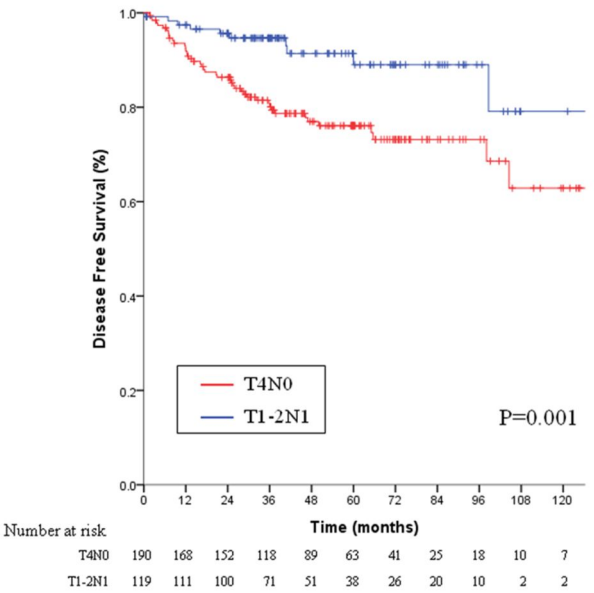
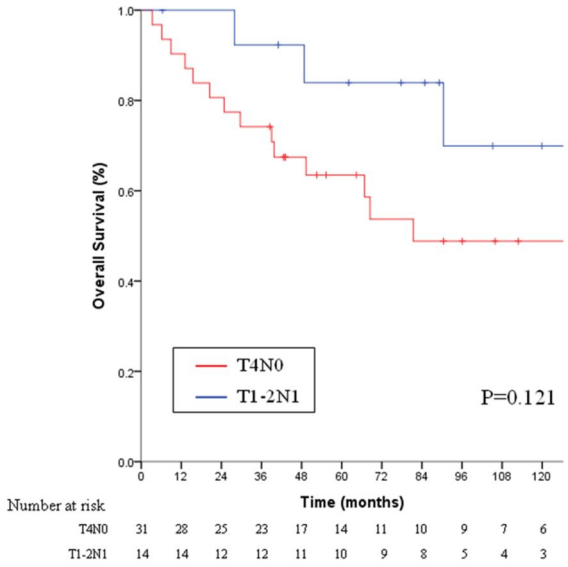


Figure 2.Kaplan-Meier curves for T4N0 and T1-2N1 colon cancer patients with adjuvant chemotherapy

(A) Overall survival. (B) Disease-free survival.

(A)



(B)

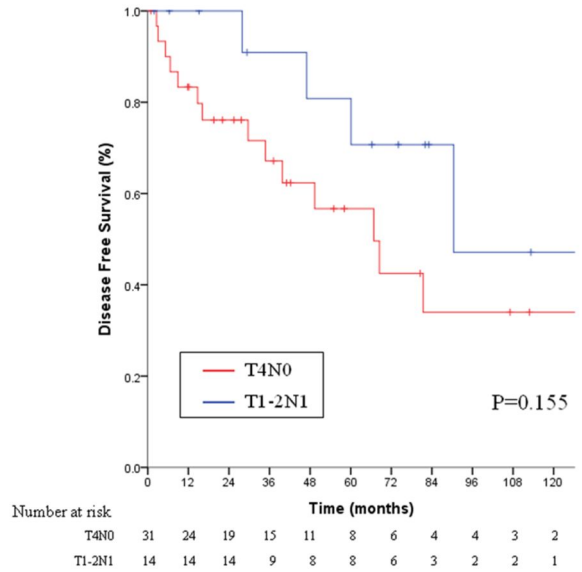


Figure 3.Kaplan-Meier curves for T4N0 and T1-2N1 colon cancer patients without adjuvant chemotherapy

(A) Overall survival. (B) Disease-free survival.

Table 4. Univariate and multivariate analysis for overall survival in T4N0 colon cancer

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P
Sex						
Men	1.0					
Women	1.151	0.628–2.111	0.649			
Age, year						
≤ 65	1.0			1.0		
> 65	4.073	2.114–7.850	< 0.0001	2.357	1.125–4.939	0.023
BMI, kg/m^2						
≤ 25	1.0					
> 25	1.048	0.486–2.273	0.907			
ASA class						
I & II	1.0			1.0		
III & IV	4.841	2.308–10.157	<0.0001	2.542	1.126–5.736	0.025
Comorbidity						
No	1.0					
Yes	2.024	1.087–3.769	0.026			

Preoperative CEA, ng/mL			
≤ 5	1.0		
> 5	1.891	0.990–3.612	0.054
Tumor location			
Right	1.0		
Left	1.274	0.679–2.387	0.451
Obstruction			
No	1.0		
Yes	1.297	0.688–2.443	0.421
Perforation			
No	1.0		
Yes	1.461	0.450–4.747	0.528
Overall morbidity			
No	1.0		
Yes	0.723	0.284–1.843	0.497
Tumor differentiation			
Well/ Moderate	1.0		
Poor	2.210	0.783–6.242	0.134
Mucinous/ SRC	0.549	0.169–1.785	0.319

No. of LNs examined						
≥ 12	1.0					
< 12	2.633	1.166–5.948	0.020			
Tumor size, cm						
≤ 5	1.0					
> 5	0.600	0.323–1.112	0.105			
Lymphatic invasion						
No	1.0					
Yes	1.549	0.823–2.914	0.175			
Venous invasion						
No	1.0					
Yes	1.376	0.652–2.906	0.403			
Perineural invasion						
No	1.0			1.0		
Yes	1.914	1.015–3.610	0.045	1.976	1.034–3.775	0.039
MSI status						
MSS	1.0					
MSI-L	0.560	0.131–2.391	0.434			
MSI-H	0.662	0.197–2.222	0.505			

Adjuvant chemotherapy						
No	1.0			1.0		
Yes	0.296	0.156–0.564	<0.0001	0.359	0.175–0.734	0.005

Table 5. Univariate and multivariate analysis for disease free survival in T4N0 colon cancer

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P
Sex						
Men	1.0					
Women	1.084	0.645–1.823	0.760			
Age, year						
≤ 65	1.0			1.0		
> 65	2.877	1.698–4.873	<0.0001	2.971	1.616–5.462	<0.0001
BMI, kg/m^2						
≤ 25	1.0			1.0		
> 25	1.841	1.026–3.303	0.041	2.697	1.411–5.155	0.003
ASA class						
I & II	1.0					
III & IV	3.135	1.539–6.386	0.002			
Comorbidity						
No	1.0					
Yes	2.021	1.199–3.409	0.008			

Preoperative CEA, ng/mL						
≤ 5	1.0					
> 5	1.934	1.132–3.304	0.016			
Tumor location						
Right colon	1.0					
Left colon	1.592	0.906–2.798	0.106			
Obstruction						
No	1.0					
Yes	1.523	0.884–2.624	0.130			
Perforation						
No	1.0					
Yes	1.442	0.521–3.996	0.481			
Overall morbidity						
No	1.0					
Yes	1.085	0.549–2.145	0.814			
Tumor differentiation						
Well/ Moderate	1.0			1.0		
Poor	3.008	1.191–7.594	0.020	3.618	1.233–10.615	0.019
Mucinous /SRC	0.360	0.112–1.156	0.086	0.581	0.172–1.962	0.382

No. of LNs examined						
≥ 12	1.0			1.0		
< 12	2.794	1.368–5.707	0.005	2.342	1.113–4.928	0.025
Tumor size, cm						
≤ 5	1.0					
> 5	0.581	0.343–0.983	0.043			
Lymphatic invasion						
No	1.0					
Yes	1.987	1.156–3.416	0.013			
Venous invasion						
No	1.0			1.0		
Yes	2.156	1.213–3.831	0.009	2.066	1.116–3.827	0.021
Perineural invasion						
No	1.0					
Yes	2.046	1.200–3.488	0.009			
MSI status						
MSS	1.0					
MSI-L	0.393	0.093–1.654	0.203			
MSI-H	0.720	0.252–2.060	0.541			

Adjuvant chemotherapy			
No	1.0		
Yes	0.491	0.266–0.904	0.022

DISCUSSION

Several nation-wide database-based studies have reported worse oncologic outcomes in patients with T4N0 colon cancers compared to those with early stage III colon cancers (1, 3, 5, 8). Further, the 3 SEER database analyses have identified an inferior 5-year stage-specific survival of 72.2%, 71.5%, and 70.0% for T4N0 patients as compared to 83.4%, 87.7%, and 84.0% for T1-2N1 patients, respectively (1, 3, 12). Analysis conducted by the Japanese Society of Cancer of the Colon and Rectum (JSCCR) also showed similar results to our study (86.3% vs. 95.1%, respectively) (12). However, these prior studies based on a nation-wide database had no detailed clinicopathologic records of the patients, such as the number of harvested LNs, lymphovascular invasion, tumor differentiation, and obstruction/perforation. Moreover, these studies did not control for treatment strategies, including adjuvant chemotherapy among institutions, and included patients that had been treated several decades ago.

O' Connell et al. have suggested that the following four reasons can explain the poor oncologic outcomes of T4N0 carcinomas: 1) preferential administrations of chemotherapy for

stage III patients, 2) understaging of T4N1 tumors as T4N0, 3) greater likelihood of a curative en bloc resection for stage III, and 4) biologically more aggressive tumors in T4N0 carcinoma (1, 5). The SEER and JSCCR registries did not contain data about the receipt of chemotherapy, and thus the effect of chemotherapy could not be assessed in these analyses. According to the Memorial Sloan-Kettering Cancer Center (MSKCC) Tumor Registry Database analysis in 2005, only 44% of T4N0 colon cancer patients received adjuvant chemotherapy compared to 83% in T1-2N1 (5). In addition, T4N0 patients in the chemotherapy group showed lower survival than those in the nonchemotherapy group, which appears to have resulted from selection bias. A recent study on the oncologic outcome of T4N0 also reported the proportion of patients receiving postoperative chemotherapy as 12.7% (10). In our study, 86% of the T4N0 colon cancer patients received adjuvant chemotherapy, which was similar to the 89.5% of the T1-2N1 groups. The current clinical guidelines for colon cancer recommending adjuvant chemotherapy for T4N0 tumors were strongly followed in the present study because time period of our study was more recent than previous ones (13). Despite

the similar rate of adjuvant chemotherapy, both the OS and DFS between T4N0 and T1–2N1 still showed the paradoxical survival curves observed in previous studies. To increase the homogeneity of the treatment modality, we performed a subgroup analysis according to the receipt of adjuvant chemotherapy and a chemotherapy regimen. The reversed survival still remained in the subgroup of patients with chemotherapy, and no survival difference was observed according to the chemotherapy regimen.

The number of retrieved LNs is associated with the accuracy of nodal and overall tumor staging and with the oncologic outcomes in colon cancer (14–16). An insufficient number of LNs examined may lead to the misdiagnosis of T4N1 as T4N0 tumors. Studies involving SEER, JSCCR, and the MSKCC Tumor Registry Database provided no information about the number of harvested nodes; thus, the possibility of stage migration from T4N1 to T4N0 could not be precluded. Meanwhile, the stage migration of T4N1 to T4N0 was able to be minimized in our study because 92% of the surgeries for the T4N0 tumors harvested more than 12 LNs. Additionally, the mean number of examined LNs for the T4N0 tumors was 27,

which was even higher than that of T1–2N1. When we analyzed in subgroup of patients with more than 12 examined LNs, the DFS of T4N0 was also inferior compared to that of T1–2N1 patients (75.8% vs. 88.8%, p = 0.016).

To minimize the influence of incomplete surgical resection on survival, we included only R0 resections of the cancer. Recently, Rottoli et al. analyzed 106 T4N0 and 95 T1–2N1 colon cancer patients who underwent R0 resection and had more than 12 LNs collected. This group demonstrated that T4N0 cancer still had a higher recurrence rate and cancer-specific mortality than T1–2N1 tumors (10), which is in concordance with our results. As well, our study found that T4N0 tumors had a higher MSI and different recurrence pattern than T1–2N1 tumors. Collectively, these results imply that T4N0 tumors may have different tumor biology than other tumors.

The AJCC staging system for colon cancer contains information about the tumor status at the time of surgery; however, the tumor biology itself is not considered. Each tumor involves diverse biologic pathways, and the current staging system has no information on how the tumor will behave as the

time sequence progresses, including the rate of tumor growth, response to therapy, and pattern of recurrence. In view of our study results, tumors that show faster bowel wall infiltration but slower regional LN metastasis, like the T4N0 tumor, seem to have different characters from those with slower bowel penetration and earlier lymphatic invasion, such as the T1–2N1 tumor. Because the AJCC staging system lacks information with respect to these biologic factors, the earlier stage does not always mean a better oncologic outcome or less recurrence.

The strength of our investigation is that an adequate number of patients were evaluated over a 12–year period in 5 centers. Because the prevalence of T4N0 colon cancer is reported as only 5~14% among colon cancer patients (1, 3, 12), the majority of studies on stage II colon cancer in a single center included only a small number of T4N0 stage cancers. An additional merit of our study is that we also performed a survival analysis on the T4N0 cancers using detailed clinical and pathologic information.

The present study also had several limitations. First, because the analysis was retrospective in nature, the possibility of selection bias among subgroups is present. Second, there

was lack of information on the molecular or genetic markers of cancer. The disease course of T4N0 carcinoma seems to be influenced by an inherent biologic aggressiveness not explained by previously known clinical risk factors. With gene expression profiling assays such as ColoPrint® (Agendia NV, Amsterdam, Netherland) or OncotypeDX ® (Genomic Health, California, USA), several recent studies have shown that the recurrence of colon cancer is correlated with the tumor gene profile (17, 18). For stage II colon cancer, two assays have been validated and have succeeded in stratifying colon cancer patients according to the risk of recurrence. Genomic profiles and tumor biology as a result of gene expression may have an answer for the poor oncologic outcome and the high recurrence rate of T4N0 colon cancer.

In conclusion, T4N0 colon cancers showed worse oncologic outcomes than T1-2 colon cancers regardless of adjuvant chemotherapy. This paradox may result from the biological aggressiveness of T4N0 carcinomas.

REFERENCES

1. O'Connell JB, Maggard MA, Ko CY. Colon cancer survival rates with the new American Joint Committee on Cancer sixth edition staging. Journal of the National Cancer Institute. 2004;96(19):1420-5. Epub 2004/10/07.

2. Quirke P, Williams GT, Ectors N, Ensari A, Piard F, Nagtegaal I. The future of the TNM staging system in colorectal cancer: time for a debate? The lancet oncology. 2007;8(7):651-7. Epub 2007/07/07.

3. Gunderson LL, Jessup JM, Sargent DJ, Greene FL, Stewart AK. Revised TN categorization for colon cancer based on national survival outcomes data. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2010;28(2):264-71. Epub 2009/12/02.

4. Lorenzon L, Pilozzi E, La Torre M, Ziparo V, Ferri M. Impact and prognostic implications of colon cancers stage II sub-classification through the years. International journal of colorectal disease. 2012;27(10):1311-8. Epub 2012/05/09.

5. Jeong SY, Chessin DB, Schrag D, Riedel E, Wong WD, Guillem JG. Re: Colon cancer survival rates with the new American Joint Committee on Cancer sixth edition staging.

Journal of the National Cancer Institute. 2005;97(22):1705-6; author reply 6-7. Epub 2005/11/17.

6. Morris M, Platell C, de Boer B, McCaul K, Iacopetta B. Population-based study of prognostic factors in stage II colonic cancer. The British journal of surgery. 2006;93(7):866-71. Epub 2006/04/20.

7. Merkel S, Wein A, Gunther K, Papadopoulos T, Hohenberger W, Hermanek P. High-risk groups of patients with Stage II colon carcinoma. Cancer. 2001;92(6):1435-43. Epub 2001/12/18.

8. McKenzie S, Nelson R, Mailey B, Lee W, Chung V, Shibata S, et al. Adjuvant chemotherapy improves survival in patients with American Joint Committee on Cancer stage II colon cancer. Cancer. 2011;117(24):5493-9. Epub 2011/06/22.

9. Engstrom PF, Arnoletti JP, Benson AB, 3rd, Chen YJ, Choti MA, Cooper HS, et al. NCCN Clinical Practice Guidelines in Oncology: colon cancer. Journal of the National Comprehensive Cancer Network : JNCCN. 2009;7(8):778-831. Epub 2009/09/17.

10. Rottoli M, Stocchi L, Dietz DW. T4N0 colon cancer has oncologic outcomes comparable to stage III in a specialized

center. Annals of surgical oncology. 2012;19(8):2500-5. Epub 2012/03/08.

11. Boland CR, Thibodeau SN, Hamilton SR, Sidransky D, Eshleman JR, Burt RW, et al. A National Cancer Institute Workshop on Microsatellite Instability for cancer detection and familial predisposition: development of international criteria for the determination of microsatellite instability in colorectal cancer. Cancer research. 1998;58(22):5248-57. Epub 1998/11/21.

12. Hashiguchi Y, Hase K, Kotake K, Ueno H, Shinto E, Mochizuki H, et al. Evaluation of the seventh edition of the tumour, node, metastasis (TNM) classification for colon cancer in two nationwide registries of the United States and Japan. Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland. 2012;14(9):1065-74. Epub 2011/12/20.

13. Benson AB, 3rd, Schrag D, Somerfield MR, Cohen AM, Figueredo AT, Flynn PJ, et al. American Society of Clinical Oncology recommendations on adjuvant chemotherapy for stage II colon cancer. Journal of clinical oncology : official journal of

the American Society of Clinical Oncology. 2004;22(16):3408-19. Epub 2004/06/17.

14. Law CH, Wright FC, Rapanos T, Alzahrani M, Hanna SS, Khalifa M, et al. Impact of lymph node retrieval and pathological ultra-staging on the prognosis of stage II colon cancer. Journal of surgical oncology. 2003;84(3):120-6. Epub 2003/11/05.

15. Joseph NE, Sigurdson ER, Hanlon AL, Wang H, Mayer RJ, MacDonald JS, et al. Accuracy of determining nodal negativity in colorectal cancer on the basis of the number of nodes retrieved on resection. Annals of surgical oncology. 2003;10(3):213-8. Epub 2003/04/08.

16. Wong JH, Severino R, Honnebier MB, Tom P, Namiki TS. Number of nodes examined and staging accuracy in colorectal carcinoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 1999;17(9):2896-900. Epub 1999/11/24.

17. Maak M, Simon I, Nitsche U, Roepman P, Snel M, Glas AM, et al. Independent Validation of a Prognostic Genomic Signature (ColoPrint) for Patients With Stage II Colon Cancer. Annals of surgery. 2013;257(6):1053-8. Epub 2013/01/09.

18. Webber EM, Lin JS, Evelyn PW. Oncotype DX tumor gene expression profiling in stage II colon cancer. Application: prognostic, risk prediction. PLoS currents. 2010;2. Epub 2010/09/30.

국문 초록

서론:대장암의 병기가 AJCC 7 판까지 개정되면서 종양의 침윤 정도와 림프절 전이 개수에 따라 2 기는 IIa, IIb 로 3 기는 IIIa, IIIb, IIIc 로 세분화되었다. 그러나 IIB/C 인 T4N0 대장암이 IIIA 인 T1-2N1 대장암에 비해 낮은 역설적인 생존율은 여전히 남아있으며 그 원인에 대해서는 명확히 밝혀진 바가 없다. 따라서 본 연구에서는 다기관 후향적 분석을 통해 T4N0 와 T1-2N1 병기 대장암의 생존율을 비교하고, T4N0 의 낮은 생존율에 영향을 미칠 수 있는 인자들을 알아보고자 한다.

방법:1999 년 1 월부터 2010 년 12 월까지 5 개의 기관에서 대장의 원발암으로 수술을 시행받은 환자를 대상으로 자료를 수집하였으며, 이 중 수술 후 병리학적 병기가 T4N0 인 224 명, T1-2N1 인 135 명의 환자를 대상으로 분석을 시행하였다. 두 군의 임상적 자료 및 병리학적 자료, 항암치료와 관련된 인자들, 그리고 5 년 전체 생존율 및 5 년 무병 생존율을 분석 비교하였다.

결과:T4N0 군은 T1-2N1 군에 비해 낮은 5 년 전체 생존율과 5 년 무병 생존율을 보였고, 이는 통계적으로 유의하였다 (5 년 전체 생존율: 84.0% vs. 92.3%, p = 0.012; 5 년 무병 생준율: 73.6% vs. 88.0%, p = 0.001). T4N0 대장암을 높은 수술 전 태아성 암 항원, 낮은 분화도, 큰 종양 크기를 보였고, 신경 침윤, 현미부수체 불안정

성, 장폐색, 그리고 장천공의 빈도가 T1-2N1 군에 비해 더 높게 나타났다. 수술 후 항암치료를 받은 군에서도 T4N0 대장암 환자의 생존율이 T1-2N1 대장암 환자에 비해 통계적으로 유의하게 낮았다(5 년 전체 생존율: 87.1% vs. 93.2%, p = 0.045; 5 년 무병 생존율: 76.1% vs. 89.0%, p = 0.001).

결론:T4N0 대장암은 T1-2N1 대장암에 비해 술 후 항암치료에 관계없이 유의하게 낮은 전체 생존율 및 무병 생존율을 보였다. 이 역설적인 생존율은 T4N0 대장암의 생물학적 특성에 기인한 것으로 보인다.

주요어 : 대장암, T4N0, 생존율, 항암치료

학 번 : 2012-21675