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Depth of mesorectal extension has prognostic significance in patients with T3 rectal cancer

T3 병기의 직장암 환자에서 예후인자로서의 직장간막 침범깊이

2013 년 2 월

서울대학교 대학원

의학과 석사 과정

신 루 미

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신 루 미

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2012년 12월

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Depth of mesorectal extension has prognostic significance in patients with T3 rectal cancer

by

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

December, 2012

Approved by Thesis Committee:

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ABSTRACT

Introduction : More than half of all rectal cancers are T3 lesions, but they are classified as a single stage category. In the case of rectal cancer, some authors reported a prognostic influence of the mesorectal infiltration depth and have suggested that this parameter should be included in therapeutic decision-making. The aim of this study was to validate prognostic significance of mesorectal extension depth in T3 rectal cancer.

Methods: We studied 291 patients with T3 rectal cancer who underwent a curative intent surgery between January 2003 and December 2009 at Seoul National University Hospital. This study is a retrospective analysis of oncologic outcomes of patients with T3 rectal cancer grouped by mesorectal extension depth (T3a: <1mm, T3b: 1~5mm, T3c: 5~15mm, T3d: >15mm). Oncologic outcomes in terms of disease-free survival were analyzed.

Results: The 5-year disease free survival rate according to T3 subclassification was 86.5 % for T3a, 74.2 % for T3b, 58.3 % for T3c and 29.0 % for T3d, respectively. It was significantly higher in T3a, b tumors than that in T3c, d tumors (77.6% vs. 55.2%, $p<0.001$). On univariate and multivariate analysis, prognostic factors affecting recurrence were preoperative carcinoembryonic antigen (CEA) level ≥

5ng/ml (hazard ratio =2.617, 95% CI 1.620-4.226), lymph node metastasis (hazard ratio =3.347, 95% CI 1.834-6.566) and mesorectal extension depth >5mm (hazard ratio =1.661, 95% CI 1.013-2.725). In subgroup analysis, independent prognostic factors were preoperative CEA level and mesorectal extension depth >5mm for 200 ypT3 rectal cancer patients and preoperative CEA level and lymph node metastasis for 91 pT3 rectal cancer patients.

Conclusions: Depth of mesorectal extension >5mm is a significant prognostic factor in patients with T3 rectal cancer. Especially, depth of mesorectal extension may be more important than the nodal status in predicting the oncologic outcome for patients who had received preoperative chemoradiotherapy.

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Keywords: T3 substaging, rectal cancer, preoperative chemoradiotherapy, prognostic factor, recurrence, mesorectal extension depth

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LIST OF ABBREVIATIONS

APR : AbdominoPerineal Resection

CEA : CarcinEmbryonic Antigen

CRT : Chemoradiotherapy

CRM : Circumferential Resection Margin

DRM : Distal Resection Margin

MED : Mesorectal Extension Depth

SPS : Sphincter-preserving Surgery

TME : Total Mesorectal Excision

INTRODUCTION

Current TNM staging system has been regarded as a standard staging system for colorectal cancer ever since its introduction in 1987 by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) owing to its superb reflection of prognosis. The depth of infiltration of primary tumor (T classification) and nodal status (N classification) were known as important prognostic factors for local recurrence and distant metastasis after surgery in patient with colorectal cancer. In the case of rectal cancer, some authors reported a prognostic influence of the mesorectal infiltration depth and have suggested that this parameter should be included in therapeutic decision making. (1-7)

In 1993, the UICC proposed optional cut-off points for mesorectal extension in the context of pT3 and pT4 tumors.(8) Thereafter, several studies have described prognostic heterogeneity in patients with T3 rectal cancer with different prognostic cut-off points to subdivide the mesorectal extension depth (MED). Those studies used various prognostic cut-off points such as 2mm (2), 3mm (5, 9), 4mm (4, 6, 7, 10, 11), 5mm(12-14), and 6mm (1). On the Surveillance, Epidemiology, and End Results (SEER) database analysis, a clear difference in survival rates were found for patients with stage II rectal cancer (T4aN0, 55.7 %; T4bN0, 44.7 %) when the T4 tumors were subdivided into T4a and T4b according to the invasion or adhesion to adjacent organs or structures.(15) Subsequently, these expanded outcomes based on SEER rectal and colon cancer database analysis have been reflected in the 7th edition

TNM staging system and changed the process of substaging stages II and III. However, these subdivided T4 tumors account for only 14.3 % of the entire colorectal cancer and T3 tumors which account for more than 60% on SEER database were classified as a single stage disease. Furthermore, the reliability of several cut-off points for stratifying the mesorectum in T3 tumors remains controversial. The aim of present study was to investigate the prognostic significance of the MED in T3 rectal cancer.

MATERIALS AND METHODS

1. Patients and Surgical Treatments

The study was performed in accordance with the guidelines of our Institutional Review Board, which deemed that informed consent was not required. We retrospectively studied 291 patients with T3 rectal cancer who underwent a curative intent surgery between January 2003 and December 2009 at Seoul National University Hospital. All patients had primary rectal adenocarcinoma without any evidence of distant metastasis, and located within 15cm from the anal verge. A standardized total mesorectal excision (TME) technique including high ligations of the inferior mesenteric vessels was used in all patients. For patients who underwent preoperative chemoradiotherapy (CRT), surgical resection was scheduled between 6 to 8 weeks after completion of CRT.

2. Preoperative CRT and Adjuvant Therapy

Radiotherapy was delivered to whole pelvis at a dose of 45 Gy in 25 fractions, followed by a boost of 5.4 Gy to the primary tumor in 3 fractions over 5.5 weeks. One of the following preoperative chemotherapeutic regimens was delivered concurrently with radiotherapy: (1) 5-fluorouracil (FU) (2 cycles of bolus intravenous 5-FU 500 mg/m^2/d for 3 days in the first and the fifth weeks of radiotherapy); (2) capecitabine (oral administration of capecitabine 1,650 mg/m^2 twice daily during radiotherapy with weekend breaks). Postoperative adjuvant chemotherapy was started in patients with

stage II and III disease within 3-4 weeks after surgery. The regimen is one of followings: (1) FL [six cycles of 5- FU 375mg/m^2/day and leucovorin 20mg/m^2/day on D1-5 every week]; (2) FOLFOX [intravenous oxaliplatin (85mg/m^2/day) and leucovorin (400mg/m^2/day) on the first day, bolus intravenous 5-FU (400mg/m^2/d) on the first day, then continuous infusion of 1,200mg/m^2/d for 2 days] ; (3) capecitabine (oral administration of capecitabine 2,000-2,500 mg/m^2/day in two divided doses, D1-14 with 7 day rest, repeat every 3 weeks). Postoperative CRT protocol was identical to that of preoperative CRT.

3. Measurement of Mesorectal Extension Depth

T3 tumors were stratified according to the T3 subclassification proposed by Hermaneck et al (Table 1).(8) It was subdivided on the basis of the histological measurement of the maximum depth of invasion beyond the outer border of the muscular layer. Two specialized GI pathologists analyzed the depth of tumor invasion by dividing the tumor at the deepest invasion spot grossly into four sections in the form of cross. For the depth inspection, they put at least four sections; and for the inspection of the entire tumor, they put two additional sections making at least six sections. Hematoxylin-and-eosin stained sections are presented in Figure 1.

T3 classification		
pT3a	Minimal	Tumor invades through the muscularis propria into the subserosa into nonperitonealized pericolic or perirectal tissues not >1 mm beyond the outer border of muscularis propria
pT3b	Slight	Tumor invades through the muscularis propria into the subserosa into nonperitonealized pericolic or perirectal tissues >1 mm but not >5 mm beyond the outer border of muscularis propria
pT3c	Moderate	Tumor invades through the muscularis propria into the subserosa into nonperitonealized pericolic or perirectal tissues >5 mm but not >15 mm beyond the outer border of muscularis propria
pT3d	Extensive	Tumor invades through the muscularis propria into the subserosa into nonperitonealized pericolic or perirectal tissues >15 mm beyond the outer border of muscularis propria

Table 1. T3 subclassification by Hermaneck et al.

When the outer border of the muscular layer was completely identifiable (sometimes identifiable as fragments of muscle), the distance from the outer

border of the muscular layer to the deepest part of the invasion was measured. If the outer border was not clear, we checked the outer border at both ends of tumor where it was clear and drew a tentative line considering it as the outer border of muscle layer. For a separate mesorectal tumor nodule to be recognized as tumor deposit, it had to be large enough to be recognized as a lymph node and freely movable and not continuously connected to the main mass. If it was very small and closely located to the main mass, it was considered as tumor invasion rather than tumor deposit.

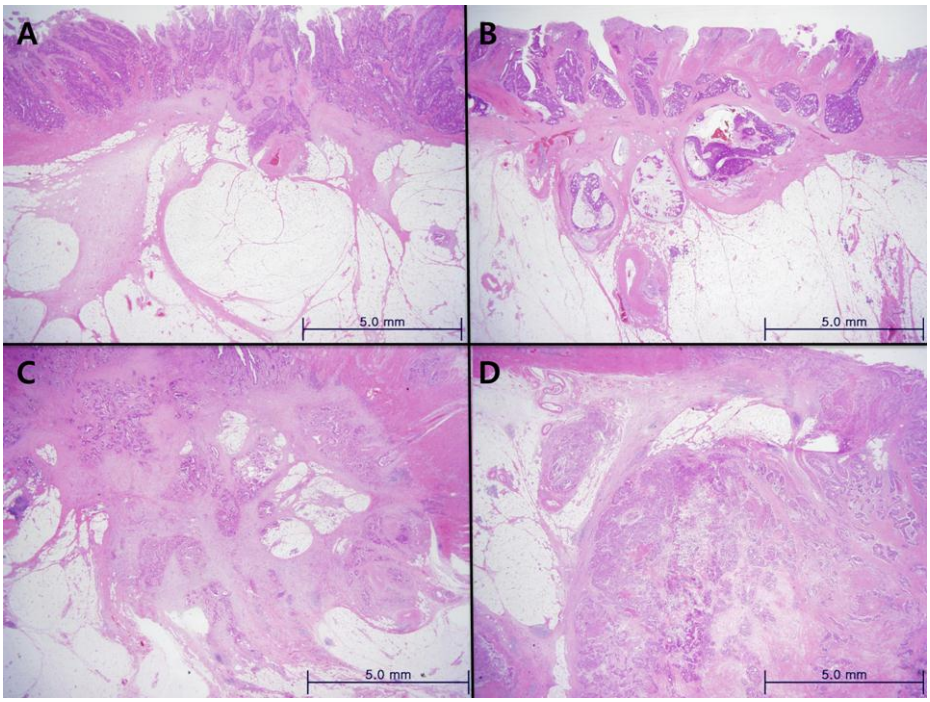


Figure 1. Microscopic subclassification of T3 rectal cancer according to the mesorectal extension depth (MED) beyond the outer border of muscularis propria is demonstrated.

(A) T3a, MED ≤1 mm. (B) T3b, 1 mm < MED ≤5mm. (C)T3c, 5 mm <

MED ≤15 mm. (D) T3d, MED >15 mm.

4. Statistical Analysis

The Kaplan-Meier method was used for the univariate analysis of the prognostic value of sex, age category, subdivided T3 category, lymph node involvement, tumor differentiation, angiolymphatic invasion, circumferential resection margin and preoperative CRT. The Cox regression analysis was used to analyze the independent prognostic factors for recurrence-free survival. Statistical analyses were performed using SPSS version 19 (IBM inc., Somers, NY).

RESULTS

1. Clinicopathologic characteristics of patient

The clinicopathological characteristics of 291 patients [214 males (73.5%), mean age = 60.4 ± 11.5 (range, 23~86) years] are shown in Table 2. Mean follow-up period of these patients was 43.8 ± 22.9 (range, 4.1-98.3) months.

Features	**Number of patients (n=291)**
Age, y	60.4 ±11.5
Follow up period, m	43.8 ±22.9
Sex	
Male	214 (73.5)
Female	77 (26.5)
Differentiation	
G1+G2	274 (94.2)
G3+G4	17 (5.8)
CEA level (ng/ml)	9.3 ±31.4
Mean number of harvested lymph nodes	16.8 ±10.3
T3 subclassification	
T3a	48 (16.5)
T3b	128 (44.0)
T3c	100 (34.4)
T3d	15 (5.2)
N stage	
N-	121 (41.6)

N+	170 (58.4)
Preoperative CRT[a]	
No	200 (68.7)
Yes	91 (31.3)
Adjuvant chemotherapy	
No	39 (12.4)
Yes	255 (87.6)
Operation	
Anterior resection	7 (2.4)
Low anterior resection	255 (87.6)
Abdominoperineal resection	18 (6.2)
Hartmann procedure	10 (3.4)

Table 2. Clinicopathological characteristics of 291 patients with T3 rectal cancer

2. The prognostic factors affecting the recurrence in patient with T3 rectal cancer

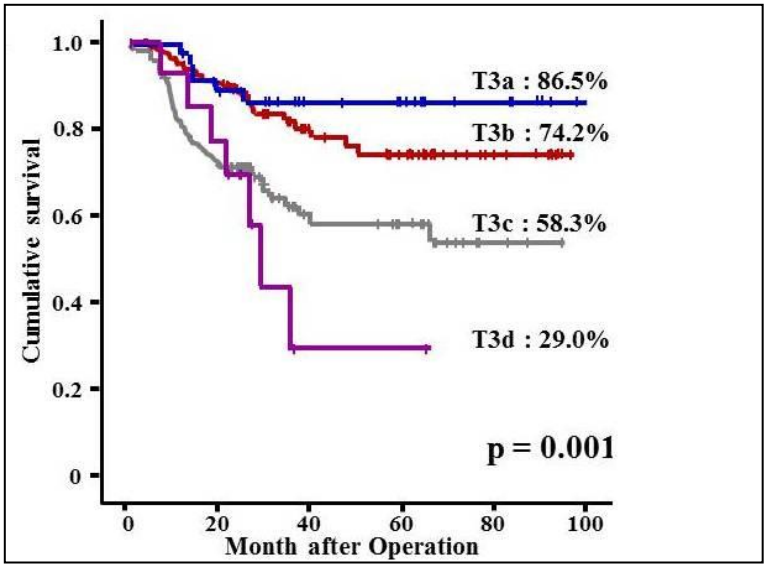
Postoperative recurrence occurred in 74 patients (25.4%), including 12 patients (9.9%) in stage IIA, 35 patients (32.1%) in stage IIIB and 27 patients (44.3%) in stage IIIC. Eight patients (2.7 %) had local recurrence only, 54 patients (18.6 %) had distant metastasis only, and 12 patients (4.1 %) had both local recurrence and distant metastases.

Disease-free survival rates according to MED were 86.5 % in T3a, 74.2 % in T3b, 58.3 % in T3c, and 29.0 % in T3d (Fig. 2A), respectively. The difference was not statistically significant between T3a and T3b, and also between T3c

and T3d. However, when re-categorized as T3ab (MED 5mm) and T3cd (MED > 5mm), the 5-year disease-free survival rate of patients with T3ab rectal cancer was significantly higher than that of patients with T3cd (77.6% vs. 55.2%, respectively, $p<0.001$) (Fig. 2B). On univariate analysis, factors affecting the recurrence were preoperative CEA level ≥5ng/ml, the status of lymph node metastasis and MED >5mm (Table 3).

Multivariate analysis showed that the lymph node metastasis (H.R.: 3.347, 95 % CI: 1.834-6.566, $p<0.001$), preoperative CEA level ≥5ng/ml (H.R. 3.347, 95 % C.I. 1.620-4.226, $p<0.001$) and MED >5mm (H.R. 1.661, 95% C.I. 1.013-2.725, $p=0.044$) were independent factors for recurrence.

(A)



(B)

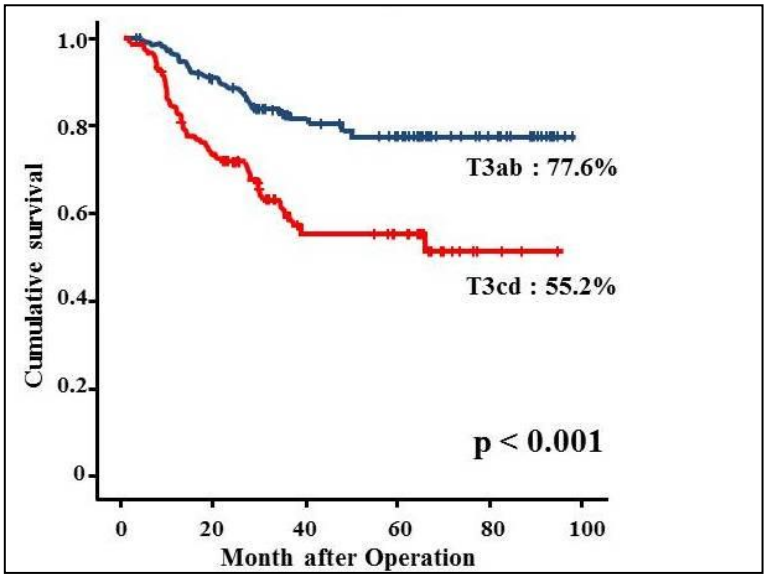


Figure 2. Disease-free survival rates according to subdivision of mesorectal extension depth (MED)

(A) There was no significant difference in 5-year disease-free survival rate between T3a/T3b ($p = 0.35$) and T3c/T3d ($p = 0.37$). (B) Disease-free survival rates in the patients with reclassifying with the use of a MED cutoff point of 5 mm are shown.

Variable	Univariate analysis				Multivariate analysis		
	No. of patients	**Rate of recurrence**	**5-year disease-free survival (%)**	**P value**	**Hazard ratio**	**95% CI of H.R.**	**P value**
Sex				0.454			
Male	214	26.7	67.9				
Female	77	24.0	70.8				
Age				0.224			
<65	117	28.6	66.0				
≥65	114	21.8	72.9				
Histologic grade				0.110			
G1+G2	274	25.0	70.1				
G3+G4	17	41.2	43.4				
Venous invasion				0.149			
Positive	84	29.3	54.3				
Negative	207	24.6	71.6				
Angiolymphatic				0.062			

invasion							
Positive	138	29.4	62.6				
Negative	153	22.8	73.6				
Perineural invasion				0.072			
Positive	103	24.5	59.1				
Negative	188	28.7	72.0				
DRM[a]				0.583			
≤1cm	88	23.3	69.0				
>1cm	203	27.1	68.5				
CRM[b]				0.134			
≤1mm	45	38.6	63.8				
>1mm	171	24.7	68.4				
Preoperative CEA				<0.001	2.617	1.620 - 4.226	<0.001
<5ng/ml	202	18.7	77.0				
≥5ng/ml	72	46.5	47.6				
Adjuvant chemotherapy				0.165			
Yes	252	27.0	66.9				

No	39	18.9	80.7				
Preoperative CRT				0.165			
Yes	91	18.7	75.0				
No	200	29.4	66.2				
Lymph node metastasis				<0.001	3.347	1.834 - 6.566	<0.001
Negative	121	10.3	88.2				
Positive	170	36.9	54.8				
Mesorectal Extension Depth				<0.001	1.661	1.013 - 2.725	0.04
T3ab (≤5mm)	176	17.4	77.6				
T3cd (>5mm)	115	38.9	55.2				
Operation procedure				0.24			
SPS[c]	272	24.3	69.9				
APR[d]	18	38.9	57.6				

Table 3. Risk factors for postoperative recurrence in patients with T3 rectal cancer using univariate and multivariate analysis.

3. The prognostic factors for recurrence in patients treated with or without preoperative CRT

Univariate and multivariate regression analyses showed that the lymph node metastasis was the most powerful independent risk factor followed by the preoperative CEA level for postoperative recurrence in patients with T3 rectal cancer without preoperative CRT (Table 4). In these patients, although MED was statistically significant on the univariate analysis, it was not on the multivariate analysis.

	Variable	Hazard Ratio	95% CI of HR	*P* value
pT3 rectal cancer	CEA level(≥5ng/ml)	2.479	1.432-4.293	0.001
	Lymph node metastasis	6.067	2.375-15.501	<0.001
	Mesorectal Extension Depth (T3ab/T3cd)	1.379	0.789-2.412	0.26
ypT3 rectal cancer	CEA level(≥5ng/ml)	3.095	1.112-8.611	0.03
	Mesorectal Extension Depth (T3ab/T3cd)	2.950	1.082-8.043	0.04

Table 4. Summary of significant factors of all multivariate analyses performed.

Preoperative CRT was delivered to 91 patients. Univariate and multivariate regression analyses showed that MED (H.R. 2.950, 95 % C.I. 1.085-8.043, p=0.04) and preoperative CEA level (H.R. 3.095, 95 % C.I. 1.112-8.611, p=0.03) were the independent risk factors in these patients. In this subgroup, nodal metastasis did not affect recurrence (Table 5). In addition, analysis of ypT3 rectal cancer patients according to MED and lymph node status showed lower 5-year survival rate of T3cdN- group than that of T3abN+ group (56.3% vs. 79.3%, p=0.27) (Table 6, fig. 3)

Variable	Univariate analysis				Multivariate analysis		
	n	Rate of recurrence	5-year disease-free survival(%)	P value	Hazard ratio	95% CI of H.R.	P value
Sex				0.062			
Male	71	22.5	68.3				
Female	20	5.0	94.4				
Age (year)				0.055			
<65	61	24.6	68.0				
≥65	30	6.7	90.5				
Histologic grade				0.501			
G1+G2	89	19.1	74.4				
G3+G4	2	0.0	100				
Venous invasion				0.150			
Positive	28	28.6	60.9				
Negative	63	14.3	67.7				
Angiolymphatic invasion				0.331			
Positive	33	24.2	61.9				
Negative	58	15.5	70.7				

Perineural invasion				0.243			
Positive	34	23.5	58.4				
Negative	57	15.8	69.1				
DRM[b]				0.886			
≤1cm	25	20.0	66.4				
>1cm	66	18.2	78.1				
CRM[c]				0.517			
≤1mm	15	26.7	72.7				
>1mm	48	16.7	74.6				
Preoperative CEA				0.008	3.095	1.112-8.611	0.03
<5ng/ml	60	10.0	85.4				
≥5ng/ml	29	37.5	59.4				
Adjuvant Chemotherapy				0.135			
Yes	81	21.0	72.2				
No	10	0.0	100				
Lymph node metastasis				0.206			
Negative	49	14.3	79.7				
Positive	42	23.8	69.1				

Mesorectal Extension				0.004			
					2.950	1.082-8.043	0.04
Depth							
T3ab (≤5mm)	62	11.3	84.5				
T3cd (>5mm)	29	34.5	54.9				
Operation procedure				0.15			
SPS[d]	83	16.9	76.1				
APR[e]	8	37.5	60.0				
Tumor regression grade				0.94			
0 (Complete)	0	0	—				
1 (moderate)	53	18.9	75.1				
2 (minimal)	29	20.7	73.9				
3 (poor)	1	0	100				

Table 5. Univariate and multivaiate analysis for risk factors of postoperative recurrence in patients who had received preoperative CRTa (n=91)

		ypT3 rectal cancer (n=91)		
		No. of patients	5yr DFS (%)	*p* value
LN-	T3ab	37	88.1	0.02
	T3cd	12	56.3	
LN+	T3ab	25	79.3	0.08
	T3cd	17	52.4	

Table 6. Disease-free survival according to MED and lymph node status.

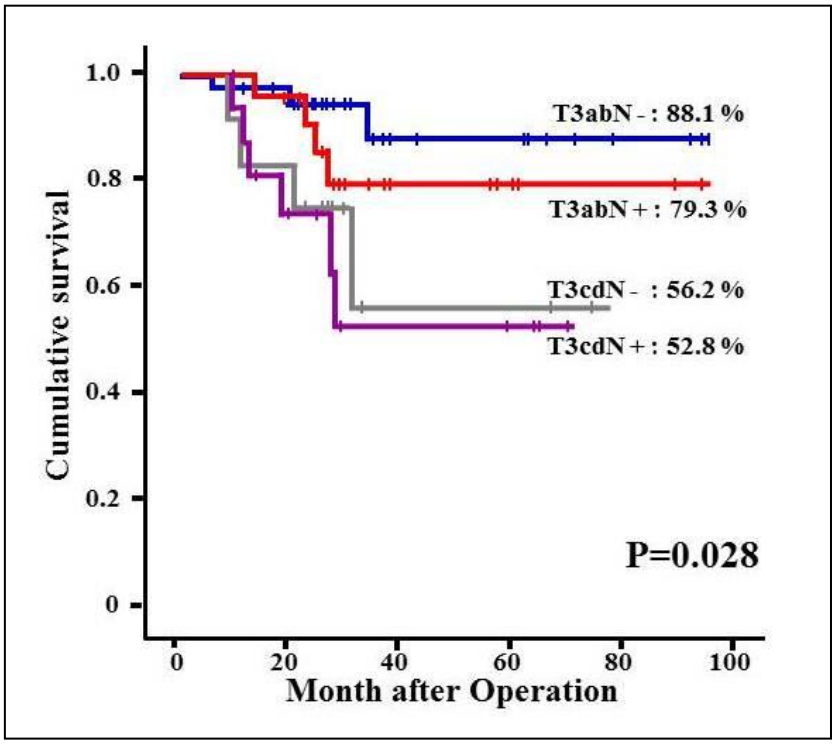


Figure 3. Disease-free survival rates according to MED and nodal status are shown. In each of ypT3ab and ypT3cd rectal cancer group, there were no significant differences in the 5-year disease free survival rate according to the nodal status (p = 0.35, p = 0.71). Despite the lymph node metastasis, the survival rate of ypT3abN+ patients was higher than that of T3cdN− patients (79.3% vs 56.2%, p = 0.27).

DISCUSSION

Accurate staging system to categorize patients into relatively homogeneous groups according to their prognosis is crucial because these enable clinicians to provide a tailored adjuvant therapy or surveillance to patients. The current TNM staging system was refined based on several studies identifying prognostic factors for survival and local or distant recurrence. The local extent of the primary tumor, lymph node metastases (pT and pN category according to the TNM staging system of the UICC/AJCC), angiolymphatic invasion, perineural invasion, and preoperative CEA level were found to have prognostic impact based on multiple trials. In addition, the prognostic significance of the mesorectal extension depth in rectal cancer was advocated in several articles (1-5, 11) .

Cawthorn et al (4) demonstrated that the patients with mesorectal extension of more than 4mm had lower overall survival rate (< 4 mm; 55% vs. ≥ 4 mm; 25%, $P < 0.001$), but their study had some limitations in that they included the patients with rectal cancer without mesorectal invasion (stage I) and those who had undergone palliative surgery. For the cut-off value of 3mm as independent prognostic factor, the results were inconsistent among authors (5, 9).

Fore mentioned studies were conducted in a single institute, but Merkel et al. (12) analyzed the Erlangen Registry for Colo-Rectal Carcinomas (ERCRC) and the Study Group for Colo-Rectal Carcinoma (SGCRC) data. They demonstrated that the 5-year disease-free survival rate was significantly higher in tumors with MED ≤5 mm, compared with tumors with MED >5 mm (85.4% vs. 54.1% respectively, $p<0.001$) in the ERCRC data, but this result could not be reproduced in the SGCRC data. Miyoshi et al. (1) determined the optimal cut-off point of 6mm using statistical analysis and advocated that the 5-year recurrence-free survival rate in the patients with MED < 6mm was higher (69 % vs. 55 %, $p<0.05$). They measured actual values and established the cutoff point in the first data set and validated the prognostic impact of the MED of 6mm in the second data set.

Recently, Shirouzu (7) and Akagi et al (10) analyzed the database from the Study Group of the Japanese Society for Cancer of the Colon and Rectum (JSCCR) to determine the optimal cut-off

depth of mesorectal invasion for predicting the clinical oncologic outcome in patients with T3 rectal cancer. They also determined the optimal cut-off point statistically but the value was different from that of Miyoshi et al (1). They also advocated that the independent prognostic factors for recurrence-free survival in patients with stage T3 rectal cancer were lymph node metastasis (H.R.: 2.70, 95 % CI: 2.070-3.525), depth of mesorectal extension, histologic grade (H.R.: 1.41, 95 % CI: 1.084-1.833), and lymphatic invasion (H.R.: 1.44, 95 % CI: 1.135-1.838). However, in these studies, none of the patients received preoperative radiotherapy or neoadjuvant chemotherapy before operative management and more than half of the patients had undergone prophylactic lateral pelvic lymph node dissection. These clinical set of patients are currently unusual in countries other than Japan.

In the present study, we confirmed that MED was one of the independent prognostic factors in patients with T3 rectal cancer, together with nodal status and CEA level which are already well-known prognostic factors for colorectal cancer. This study included 91 patients who received preoperative CRT. On subgroup analysis of these patients, MED consistently had a significant impact on postoperative recurrence rate along with CEA level which had been suggested as a useful prognostic factor in patients treated with preoperative CRT by several previous studies. (1, 13, 14, 16) For T3 patients as a whole or T3 patients without preoperative CRT, lymph node metastasis was clearly the most important prognostic factor. However, interestingly, nodal status was not a significant prognostic factor for ypT3 rectal cancer. It is well known that radiotherapy or CRT has an involutional effect on lymphatic tissues and this was reflected as decreased number of retrieved lymph nodes in patients treated with preoperative CRT. (17) It can be hypothesized that this involutional effect and nodal down staging by preoperative CRT might obtund the prognostic impact of lymph node metastasis. So far, most of studies on the prognostic impact of the mesorectal extension depth in the T3 rectal cancer included patients who did not receive preoperative CRT except for the study by Picon et al. (5) However, they argued that the microscopic perirectal fat invasion with cut-off of 3mm could not predict the oncologic outcome, but the analysis was not done in subgroup of ypT3 rectal cancer. This study

is meaningful in that the current study identified the prognostic significance of MED not only in all T3 rectal cancer but also in ypT3 rectal cancer.

However, there are two limitations in this study. One is that the specimens were examined in routine methods rather than by whole mount section by the pathologists. This may compromise the accuracy of invasion depth assessment to certain extent as using whole mount section would have provided the most accurate depth of invasion. Another limitation is that this study lacks identification of TME quality. Plane of surgery has emerged as a significant prognostic factor affecting oncologic outcomes in rectal cancer surgery and the importance of pathologic report about quality of TME has been highlighted recently. However, most of the patients in our study did not have information on the plane of surgery achieved. Leonard et al. (18) dictated that the quality of TME shows heterogeneity between surgeons, and the ability of surgeon to stay in the mesorectal plane is important in determining the quality of TME. In fact, all the operations included in our study were performed by three extremely highly experienced surgeons who have performed over thousands of colorectal cancer surgeries. The mesorectal quality of our practice was also demonstrated in our randomized prospective trial (COREAN trial (19)) which compared laparoscopic and open TME after preoperative chemoradiotherapy. Some of the cases in the present study were also enrolled in the COREAN trial. In that trial, the macroscopic TME quality was evaluated. For open surgery (n=170), the percentage of complete, nearly complete and incomplete was 74.7 %, 13.5 %, and 6.5 %, respectively. For laparoscopic surgery (n=170) the percentage was 72.4 %, 19.4%, and 4.7 %, respectively. These results were comparable or somewhat superior to other previous studies (20-22).

In conclusion, the depth of mesorectal extension >5mm is a significant prognostic factor in patients with T3 rectal cancer. Especially in patients who received preoperative CRT, the depth of mesorectal extension may be more important than the nodal status in predicting the oncologic outcome. If these findings can be reproduced or validated in the subsequent studies with larger number of cases, T3 substaging according to MED should be incorporated into the rectal cancer staging system.

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국문 초록

서론: 반 수 이상의 직장암 환자가 단일화된 T3 병기로 진단이 되고 있다. 직장암의 경우, 직장간막의 침범깊이에 따라 예후가 달라지며, 이러한 예후인자가 치료방법을 결정하는 데 고려되어야 한다는 주장이 제기되고 있다. 이에 이 연구는 T3 직장암 환자에서 예후인자로서 직장간막 침범깊이의 중요성을 알아보았다.

방법: 서울대병원에서 2003 년 1 월부터 2009 년 12 월까지 근치적 목적으로 수술받은 T3 병기의 직장암 환자 291 명을 대상으로 하였다. T3 직장암 환자를 직장간막 침범깊이(mesorectal extension depth, MED)에 따라 분류된 네 아집단의 무병생존율을 후향적으로 분석하였다. (T3a: <1mm, T3b: 1~5mm, T3c: 5~15mm, T3d: >15mm)

결과: 세분화된 T3 병기 직장암 아집단의 5 년 무병생존률은 각각 T3a, 86.5%; T3b, 74.2%; T3c, 58.3%; T3d, 29.0%이었다. T3a, b 병기 직장암 환자의 생존율은 77.6%로 T3c, d 병기 환자들의 생존율인 55.2%보다 통계적으로 유의하게 높았다. ($p<0.001$) 단변량 분석 및 다변량 분석에서 종양의 재발에 영향을 주는 예후인자로는 암태아성항원(CEA) 수치 ≥ 5ng/ml (hazard ratio =2.617, 95% CI 1.620-4.226, 전이된 림프절의 수 (hazard ratio =3.347, 95% CI 1.834-6.566), 직장간막의 침범 깊이 >5mm (hazard ratio =1.661, 95% CI 1.013-2.725)이다. 수술 전 항암방사선치료를 받은 200 명의 ypT3 직장암 환자들에서의 예후인자는 수술전 암태아성항원 수치와 직장간막의 침범 깊이이다. 반면에 91 명의 pT3 직장암 환자의 예후인자는 수술전 암태아성항원 수치와 전이된 림프절의 수이다.

결론: 5mm 이상의 직장간막의 침범깊이는 T3 직장암 환자에 있어 중요한 예후인자이다. 특히, 이 직장간막의 침범깊이는 수술전 항암방사선치료를 받은 환자들의 예후를 예측하는데 있어서 림프절 전이보다 더 중요한 인자이다.

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주요어: T3 병기, 직장암, 수술전 항암방사선 치료, 예후 인자, 재발, 직장간막의 침범깊이

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