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Significance of lymph node metastasis in the survival of stage IV colorectal cancer by hematogenous metastasis

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Purpose: Although lymph node (LN) metastasis is an important prognostic marker of colorectal cancer (CRC), the effect of LN metastasis on the survival of stage IV CRC is debated yet.
Methods: LN status and survivals as well as clinicopathological features of synchronous stage IV CRC patients, operated for 8 years, were analyzed. Patients with hematogenous metastases were included only but those with peritoneal seeding or preoperative adjuvant therapy were not included.
Results: Total 850 patients were enrolled and 77 (9.1%) were without LN metastases (N0M1). N0M1 patients were older and have favorable pathological features including lower CEA than patients with LN metastasis (N + M1). The pathologically poor features accumulated with N stage progression within N + M1. N0M1 had better 5-year overall survival (OS) and disease free survival than N + M1. And 5-year OS's within N + M1 group were stratified and different according to N stage progression, although the effect of N stage progression is different according to curative resection or not. When compared with stage III, 5-year OS of N0M1 with curative resection was comparable to that of anyTN2aM0 and was better than anyTN2bM1.
Conclusion: LN metastasis is a significant prognostic factor in stage IV by hematogenous metastasis, too. N stage progression accumulates pathologically poor prognostic factors. However, the effect on survival of each N stage progression differs depending on curative resection or not of the hematogenous metastases.
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Key Words: Colorectal neoplsms, Neoplasm metastasis, TNM classification

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer worldwide. About 500,000 die of CRC all over the world in a year and are about half of the annual incidence [1]. Although early detection by screening and advances in therapeutic strategies decreased mortality of CRC [2-4], the survival of stage IV patients is poor yet. Hematogenous metastasis, the major cause of death, is detected in 20%–50% of the patients at diagnosis [5-7], and survival of stage IV patients has been regarded poor but details of their survival are not well understood. By the way, efforts to divide the survival of stage IV patients have emerged due to the recent improvement in survival by the advances in surgical and medical treatment. The 7th edition of American

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Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) staging system separated stage IV to IVa and IVb (M1a and M1b) [8]. This reforming reflects the need for stratification of the survival of stage IV.

Lymph node (LN) metastasis is the most important prognostic factor in CRC without hematogenous metastasis or peritoneal seeding. However, it is not clear whether the LN metastasis is also a prognostic factor in stage IV patients. There are debate on that issue [9] because some studies reported that LN metastasis was a prognostic factor in stage IV [3,10-14], while others did not [7,15-18]. It is not clear either if the effect of LN metastasis differs according to the resection of metastases. The debate is because there are few studies on that issue and few papers showed the survival functions discriminated by the LN status.

Improved safety of aggressive surgery and development of new chemotherapeutics may extend the survival of stage IV patients [19,20]. However, in order to elevate the cure rate of stage IV, identification of potentially curable patients through the stratification of survivals, by more understanding of the survival factors, is mandatory. Therefore, this study was to identify the effect of LN metastasis on the survival of stage IV CRCs.

METHODS

This study was performed by retrospective review of stage IV colorectal adenocarcinoma patients, operated from January 2003 to December 2010, from the prospectively collected Seoul Colorectal Group database. This study was reviewed and approved by the Institutional Review Board of the Seoul National University Hospital (H-1312001536). During that period, stage IV patients were 1,285 of the total 12,625 CRC patients operated for the primary resection. Patients with peritoneal seeding (n = 349) or preoperative chemotherapy (n = 86) were excluded. Therefore, the number of patients with stage IV by hematogenous metastasis, enrolled in this study, was 850 (Fig. 1). Patients of stage IV by recurrences were not included in this study. Clinicopathological characteristics and survivals were compared according to the degree of LN metastases.

Primary tumor was resected in every patient and there were no patients in whom LN metastasis could not be evaluated due to non-resection of the primary tumor, such as colostomy procedure only. Simultaneous metastasectomy was decided by each operator. It was defined as curative resection when all the metastatic lesions were resected simultaneously and as palliative resection when metastatic lesions were not resected. Metachronous metastasectomy was performed in 15 of the patients with palliative resection and these patients were not included in the survival function analyses. In 37 patients (4.4%), ten or less LN's were harvested and twelve of them underwent curative resection. Metastases were detected in all the LN's harvested in 10 patients (1.2%) and 2 of them underwent the metastasectomy. However, these two patients were classified as

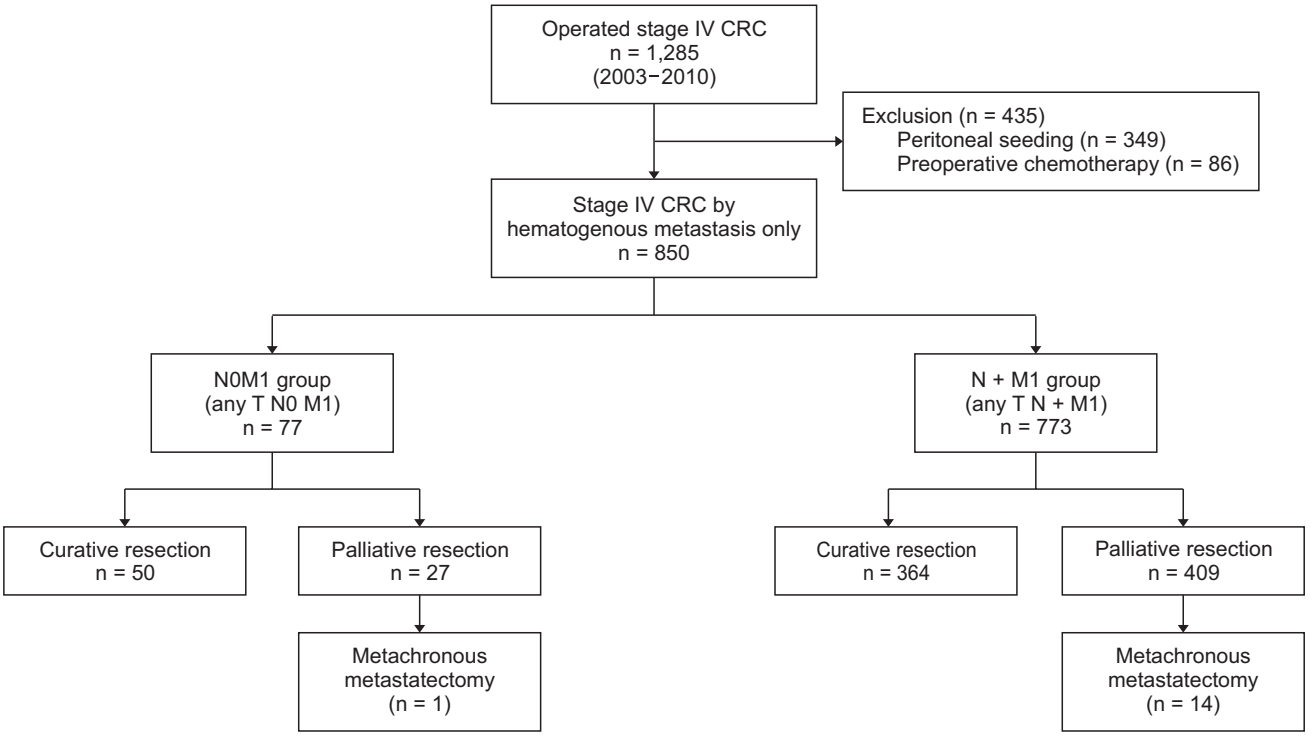

Fig. 1. Number of patients enrolled in each group and exclusion criteria. CRC, colorectal cancer.

Table 1. Comparison of the clinical characteristics between N0M1 and N + M1 and among subgroups of N + M1

Variable	N0M1 (n = 77)	N + M1 (n = 773)	P-value[a]	N1M1 (n = 203)	N2aM1 (n = 227)	N2bM1 (n = 343)	P-value[b]
Sex			0.053				0.869
Male	38 (49.4)	469 (60.7)		120 (59.1)	139 (61.2)	210 (61.2)	
Female	39 (50.6)	304 (39.3)		83 (40.9)	88 (38.8)	133 (38.8)	
Age (yr)	64.0 ± 10.6	59.5 ± 11.4	0.001	60.0 ± 10.8	59.5 ± 11.7	59.2 ± 11.6	0.734
BMI (kg/m^2)	23.0 ± 3.6	23.0 ± 3.8	0.998	23.0 ± 3.8	23.1 ± 4.1	22.9 ± 3.6	0.796
ASA PS classification							
I	24 (31.2)	298 (38.6)	0.485	81 (39.9)	98 (43.2)	119 (34.7)	0.328
II	46 (59.7)	423 (54.7)		109 (53.7)	115 (50.7)	199 (58.0)	
III	7 (9.1)	49 (6.3)		13 (6.4)	14 (6.2)	22 (6.4)	
IV	0 (0.0)	3 (0.4)		0 (0.0)	0 (0.0)	3 (0.9)	
Tumor location			0.020				0.174
Right colon	23 (29.9)	171 (22.1)		51 (25.1)	46 (20.3)	74 (21.2)	
Left colon	36 (46.8)	297 (38.4)		78 (38.4)	99 (43.6)	120 (35.0)	
Rectum	18 (23.3)	305 (39.5)		74 (36.5)	82 (36.1)	149 (43.4)	
Tumor size (cm)	5.58 ± 2.5	5.65 ± 2.2	0.778	5.33 ± 1.9	5.50 ± 2.1	5.95 ± 2.4	0.003[e]
Tumor multiplicity[c]			0.508				0.314
1	72 (93.5)	732 (94.7)		191 (94.1)	213 (93.8)	328 (95.6)	
2	5 (6.5)	30 (3.9)		11 (5.4)	10 (4.4)	9 (2.6)	
3	0 (0)	10 (1.3)		1 (0.5)	3 (1.3)	6 (1.7)	
4	0 (0)	1 (0.1)		0 (0)	1 (0.4)	0 (0)	
Site of synchronous metastasis			0.307				0.458
Liver	59 (76.6)	583 (65.9)		161 (79.3)	166 (73.1)	256 (74.6)	
Extrahepatic	13 (16.9)	101 (18.7)		24 (11.8)	29 (12.8)	48 (14.0)	
Lung	7	62		18	17	27	
Bone	2	16		3	4	9	
Ovary[d]	2	10		0	5	5	
Brain	1	7		1	2	4	
Adrenal	1	5		1	1	3	
Pancreas	0	1		1	0	0	
Liver+extrahepatic	5 (6.5)	89 (9.2)		18 (8.9)	32 (14.1)	39 (11.4)	
Curative resection	50 (64.9)	364 (47.1)	0.003	127 (62.6)	109 (48.0)	128 (37.3)	<0.001[f]
Preoperative CEA	74.8 ± 282.9	207.4 ± 794.8	0.003	163.6 ± 591.7	188.3 ± 701.9	245.4 ± 941.8	0.471
<5 ng/mL	29 (37.7)	215 (27.8)	0.026	58 (28.6)	63 (27.8)	94 (27.4)	0.919
≥5 ng/mL	42 (54.5)	545 (70.5)		140 (69.0)	159 (70.0)	246 (71.7)	
Not available	6 (7.8)	13 (1.7)		5 (2.5)	5 (2.2)	3 (0.9)	

Values are presented as number (%) or mean ± standard deviation.
BMI, body mass index; ASA PS, American Society of Anesthesiologists physical status.
[a]Statistical significance between N0M1 and N+M1. [b]Statistical significance among N1M1, N2aM1 and N2bM1. [c]Synchronous tumors only; Metachronous tumors were not counted. [d]In these patients, there were no evidences of peritoneal carcinomatosis except ovary metastasis. [e]Tumor size is larger in N2bM1 patients than in N1M1 (P_{adj} = 0.004) and in N2aM1 (P_{adj} = 0.048). [f]P_{adj} = 0.006 between N1M1 and N2aM1. P_{adj} = 0.033 between N2aM1 and N2bM1.

Table 2. Comparison of the pathological characteristics between N0M1 and N + M1 and among subgroups of N + M1

Variable	N0M1 (n = 77)	N + M1 (n = 773)	P-value[a]	N1M1 (n = 203)	N2aM1 (n = 227)	N2bM1 (n = 343)	P-value[b]
Differentiation			<0.001				<0.001
Adenocarcinoma W/D	13 (16.9)	34 (4.4)		15 (7.4)	9 (4.0)	10 (2.9)	
Adenocarcinoma M/D	61 (79.2)	653 (84.5)		182 (89.7)	201 (88.5)	270 (78.7)	
Adenocarcinoma P/D	2 (2.6)	70 (9.1)		5 (2.5)	14 (6.2)	51 (14.9)	
Mucinous carcinoma	1 (1.3)	14 (1.8)		1 (0.5)	3 (1.3)	10 (2.9)	
Signet ring cell carcinoma	0 (0.0)	2 (0.2)		0 (0.0)	0 (0.0)	2 (0.6)	
T stage			0.015				0.004
1	1 (1.3)	2 (0.2)		1 (0.5)	1 (0.4)	0 (0.0)	
2	3 (3.9)	7 (0.9)		5 (2.5)	2 (0.9)	0 (0.0)	
3	55 (71.4)	503 (65.1)		140 (69.0)	152 (67.0)	211 (61.5)	
4	18 (23.4)	261 (33.8)		57 (28.1)	72 (31.7)	132 (38.5)	
Lymph node							
Harvest	26.9 ± 13.0	27.5 ± 14.7	0.746	27.6 ± 16.0	23.9 ± 12.6	29.9 ± 14.7	<0.001[c]
With metastasis	0	7.8 ± 6.5		2.0 ± 0.8	4.9 ± 0.8	13.2 ± 6.4	
Angiolymphatic invasion			<0.001				<0.001
Yes	38 (49.4)	625 (80.9)		142 (70.0)	170 (74.9)	313 (91.3)	
No	39 (50.6)	148 (19.1)		61 (30.0)	57 (25.1)	30 (8.7)	
Venous invasion			<0.001				<0.001[d]
Yes	23 (29.9)	450 (58.2)		105 (51.7)	111 (48.9)	234 (68.2)	
No	54 (70.1)	323 (41.8)		98 (48.3)	116 (51.1)	109 (31.8)	
Perineural invasion			<0.001				<0.001
Yes	22 (28.6)	480 (62.1)		106 (52.2)	131 (57.7)	243 (70.8)	
No	55 (71.4)	293 (37.9)		97 (47.8)	96 (42.3)	100 (29.2)	
Microsatellite instability			0.228				0.097
Stable	38 (49.4)	422 (54.6)		96 (47.3)	138 (60.8)	188 (54.8)	
Low instability	3 (3.9)	34 (4.4)		9 (4.4)	10 (4.4)	15 (4.4)	
High instability	3 (3.9)	9 (1.2)		1 (0.5)	2 (0.9)	6 (1.7)	
Unknown	33 (42.8)	308 (39.8)		97 (47.8)	77 (33.9)	134 (39.1)	

Values are presented as number (%) or mean ± standard deviation.
W/D, well differentiated; M/D, moderately differentiated; P/D, poorly differentiated.
[a]Statistical significance between N0M1 and N + M1. [b]Statistical significance among N1M1, N2aM1 and N2bM1. [c]Less lymph nodes were harvested in N2a group than in N1 (P_{adj} = 0.024) and N2b (P_{adj} < 0.001). [d]N2bM1 patients had more venous invasions than N1M1 (P_{adj} < 0.001) and N2aM1 (P_{adj} < 0.001).

palliative resection. Postoperative chemotherapy was performed in 738, not performed in 96 (11.3%) and unknown in 16 patients (1.9%). Median follow-up duration was 34.3 months (range, 1–119 months). Operative mortalities (within 30 postoperative days) were 7 cases.

The patients were grouped as patients without LN metastasis (N0M1 group) and with LN metastasis (N + M1 group) by according to N stage progression. And overall survival (OS) was evaluated in all enrolled patients and compared in patients with curative resection and in patients with palliative resection, respectively. Additionally, OS of stage III patients during the study period (n = 5,452) was surveyed to compare with the survival of N0M1 group.

TNM stage is based on the criteria of AJCC/UICC staging system 7th edition [8]. However, subclassification of stage III patients (IIIA–IIIC) was based on the 6th edition because T stage was not identified as T4a or T4b of those pathologies in this study.

Statistical analyses were performed by using the IBM SPSS Statistics ver. 20.0 (IBM Co., Armonk, NY, USA) and R ver. 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org). Pearson chi-square or Fisher exact test were used for categorial variables and Student t-test or 1-way analysis of variance were used for continuous variables. For multiple comparisons, Bonferroni correction was applied. Kaplan-Meier method was used for estimating the cumulative survival rates and log-rank test was used for the comparison between the groups. Additionally, Cox proportional hazard model was used for the univariable and multivariable analysis for the contributors in survival. P-value less than 0.05 was considered significant.

RESULTS

Clinicopathological features between patients with and without LN metastases

The number of patients without LN metastasis (N0M1) was 77 and comprised 9.1% of the total, operated stage IV patients by hematogenous metastases. In clinical features, N + M1 patients were younger and preferred rectal cancers to right (P_{adj} = 0.030) or left (P_{adj} = 0.044) colon cancer (Table 1). However, pathological features of N + M1 were distinct from N0M1, having gradual change to high grade differentiation and advanced T stages (P < 0.05, Linear-by-linear test). Angiolymphatic invasion (ALI), perineural invasion, and venous invasion were less in N0M1 (Table 2). There were five patients (6.5%) in N0M1 and 301 (38.9%) in N + M1 who have all the 3 invasions.

N0M1 patients have lower recurrence and better survival.

Follow-up was not possible in 13 patients with curative

Table 3. Recurrence rates and first recurrence sites in patients with curative resection

Variable	N0M1 (n = 50)	N + M1 (n = 364)	P-value[a]	N1M1 (n = 127)	N2aM1 (n = 109)	N2bM1 (n = 128)	P-value[b]
Recurrence[c]			0.002				0.002[e]
Yes	26 (52.0)	265 (72.8)		82 (64.6)	79 (72.5)	104 (81.3)	
No	22 (44.0)	88 (24.2)		42 (33.1)	28 (25.7)	18 (14.1)	
Unavailable	2 (4.0)	11 (3.0)		3 (2.4)	2 (1.8)	6 (4.7)	
Recurrence site			0.280[d]				0.360[d]
Liver	13 (50.0)	131 (49.4)		45 (54.9)	39 (49.4)	47 (45.2)	
Lung	10 (38.5)	65 (24.5)		21 (25.6)	23 (29.1)	21 (20.2)	
Distant lymph node	1 (3.8)	33 (12.5)		5 (6.1)	8 (10.1)	20 (19.2)	
Pelvic local recurrence	0 (0.0)	8 (3.0)		2 (2.4)	1 (1.3)	5 (4.8)	
Anastomosis site	1 (3.8)	6 (2.3)		2 (2.4)	1 (1.3)	3 (2.9)	
Brain	0 (0.0)	4 (1.5)		3 (3.7)	0	1 (1.0)	
Bone	0 (0.0)	4 (1.5)		1 (1.2)	2 (2.5)	1 (1.0)	
Adrenal gland	0 (0.0)	4 (1.5)		1 (1.2)	1 (1.3)	2 (1.9)	
Peritoneal seeding	0 (0.0)	10 (3.8)		2 (2.4)	4 (5.1)	4 (3.8)	
Bladder	1 (3.8)	0 (0)		0 (0)	0 (0)	0 (0)	

Values are presented as number (%).
[a]Statistical significance between N0M1 and N + M1. [b]Statistical significance among N1M1, N2aM1 and N2bM1. [c]Chi-square test was done with exclusion of patients with unavailable recurrence data. [d]Fisher exact test. [e]N2bM1 patients had more recurrence than N1M1 (P_{adj} < 0.001).

resection (two in N0M1 and 11 in N + M1). The recurrence rate was significantly higher in N + M1 group (52.0% *vs.* 72.8%, P = 0.002). However, there were no differences in the site of first recurrence (Table 3).

The 5-year OS rate was higher in N0M1 than N + M1 in 835 patients, excluding 15 metachronous metastasectomy patients. The survival of N0M1 was better in both curative and palliative resection group. The 5-year disease free survival (DFS) in patients with curative resection was also better in N0M1 (Fig. 2). Chemotherapy regimens were not different fundamentally between N0M1 and N + M1 or among N stages (Table 4).

Prognositic factors and survivals are stratified according to the N stage progression.

We compared the N + M1 patients according to the N stage progression (N1–N2b). Of the clinical factors showing differences between N0M1 and N + M1, only the curative resection rate was different, but the others such as age were not, with N stage progression within N + M1. By the way, tumor size tended to increase contrary to comparison between N0M1 and N + M1 (Table 1). That is, there were no common clinical factors showing differences in both comparisons between N0M1 and N + M1 and among N stages within N + M1. However, the poor pathological features accumulated according to the N stage progression, except for VI, as they were more prevalent in N + M1 than N0M1 (Table 2). And N stage progression increased recurrence rate (P < 0.001, Linear-by-linear test), although no differences in sites of first recurrence (Table 3).

The survival curves were stratified and significantly different between each 2 groups (P < 0.05). The survival curves were also stratified when the patients were separated by curative resection or not. However, 5-year OS's were different neither between N1M1 and N2aM1 in curative resection group nor

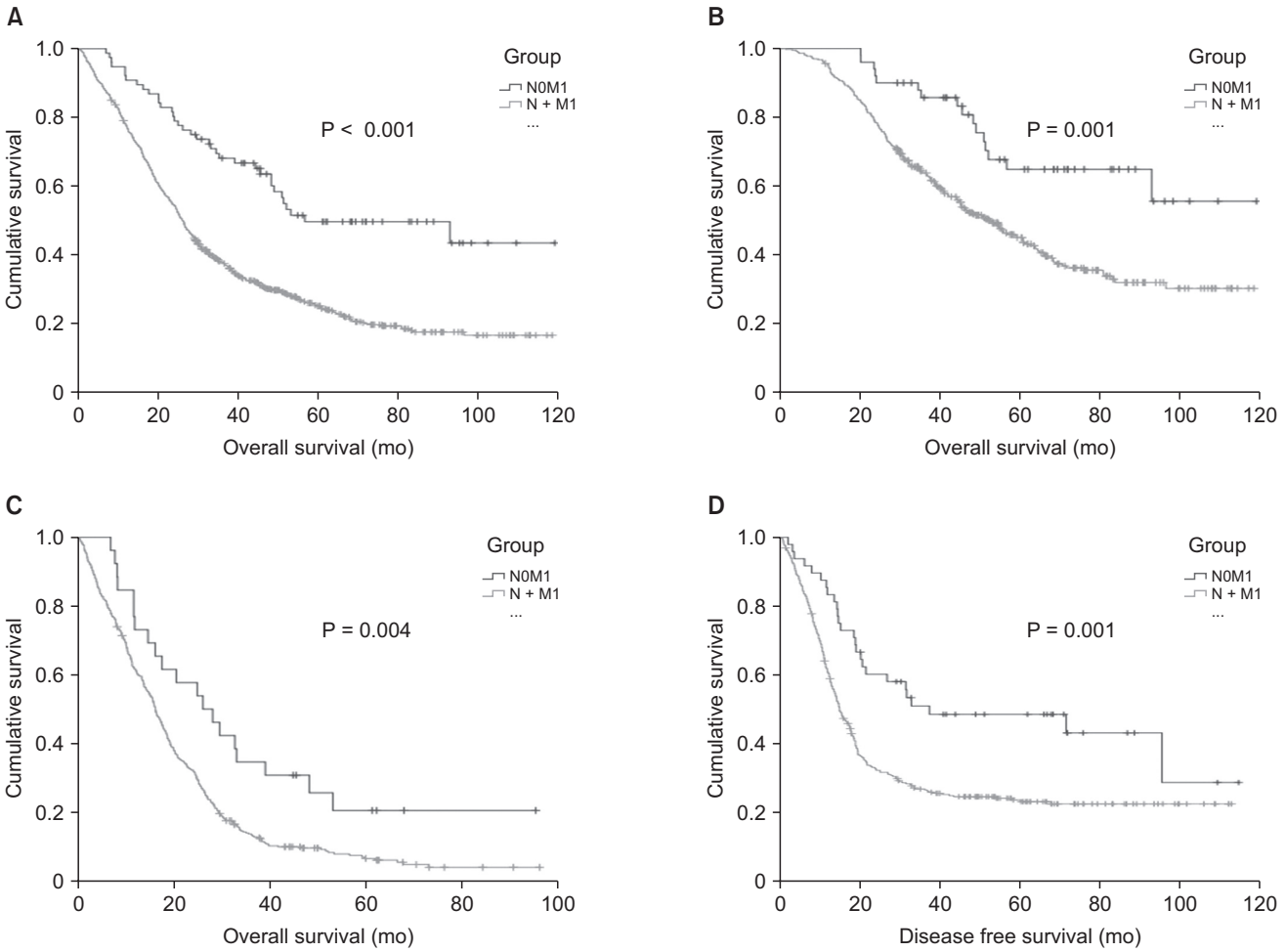

Fig. 2. Kaplan-Meier survival curves of N0M1 and N + M1. (A) Overall survivals (OSs) of N0M1 (5-year OS: 49.7% ± 6.2%, n = 76) and N + M1 (25.1% ± 1.7%, n = 759) (P < 0.001, Log-rank test). (B) OSs of N0M1 (5-year OS: 64.9% ± 7.5%) and N + M1 (45.1% ± 2.8%) with curative resection (P = 0.001) (C) OSs of N0M1 (5-year OS: 20.5% ± 8.5%) and N + M1 (*vs.* 6.4% ± 1.4%) with palliative resection (P = 0.004) (D) Disease free survivals (DFSs) of N0M1 (5-year DFS: 47.4% ± 7.5%) and N + M1 (23.1 ± 2.3) with curative resection (P = 0.001).

Table 4. Postoperative chemotherapy regimens[a]

Variable	N0M1 (n = 77)		N1M1 (n = 203)		N2aM1 (n = 227)		N2bM1 (n = 343)	
	Curative (n = 50)	Palliative (n = 27)	Curative (n = 127)	Palliative (n = 76)	Curative (n = 109)	Palliative (n = 118)	Curative (n = 128)	Palliative (n = 215)
Not available	1 (2.0)	1 (3.7)	1 (0.8)	0 (0)	2 (1.8)	2 (1.7)	3 (2.3)	6 (2.8)
No chemotherapy	3 (6.0)	2 (7.4)	5 (3.9)	9 (11.8)	4 (3.7)	21 (17.8)	5 (3.9)	47 (21.9)
Chemotherapy regimen								
FOLFOX	14 (28.0)	11 (40.7)	56 (44.1)	22 (28.9)	40 (36.7)	39 (33.1)	52 (40.6)	53 (24.7)
FOLFIRI	7 (14.0)	5 (18.5)	13 (10.2)	16 (21.1)	15 (13.8)	25 (21.2)	25 (19.5)	39 (18.1)
XELOX	12 (24.0)	3 (11.1)	28 (22.0)	8 (10.5)	27 (24.8)	11 (9.3)	22 (17.2)	31 (14.4)
Xeloda	5 (10.0)	4 (14.8)	10 (7.9)	12 (15.8)	8 (7.3)	10 (8.5)	9 (7.0)	18 (8.4)
FOLFOX + target agent	2 (4.0)	0 (0)	8 (6.3)	3 (3.9)	7 (6.4)	4 (3.4)	4 (3.1)	7 (3.3)
FOLFIRI + target agent	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (1.7)	0 (0)	6 (2.8)
XELOX + target agent	2 (4.0)	0 (0)	4 (3.1)	3 (3.9)	4 (3.7)	2 (1.7)	2 (1.6)	3 (1.4)
XELIRI	2 (4.0)	0 (0)	1 (0.8)	3 (3.9)	1 (0.9)	1 (0.8)	2 (1.6)	5 (2.3)
Leucovorin + fluorouracil	2 (4.0)	1 (3.7)	1 (0.8)	0 (0)	1 (0.9)	1 (0.8)	4 (3.1)	0 (0)

Values are presented as number (%).
[a]Chi-square test for chemotherapy or not between N0M1 and N + M1 did not reveal significant difference (P = 0.147). However, chi square test for chemotherapy or not among N stages (N0–N2b) showed significant difference (P = 0.01) and *post hoc* test revealed less patients underwent chemotherapy in N2bM1 (282/343 = 82.2%) than N1M1 (188/203 = 92.6%) (P_{adj} = 0.024). However, when the patients were separated to the curative resection or palliative resection, there were no statistical differences in comparisons of chemotherapy or not between N0M1 and N + M1 or among N stages (N0–N2b), each. Fisher exact test for chemotherapy regimens between N0 and N+ or among N stages (N0–N2b) revealed no statistically significant differences (P > 0.05). When the patients were separated to curative or palliative resection, there were not statistical differences either.

between N2aM1 and N2bM1 in palliative resection group (Fig. 3).

To identify the factors affecting the survivals, we applied multivariable cox proportional hazard model with all the clinicopathological factors as well as N stage and chemotherapy. In curative resection group, tumor location, N stage and chemotherapy were significant factors in multivariable analysis. In palliative resection group, American Society of Anesthesiologists physical status classification, tumor size, multiplicity, site of metastasis, CEA, differentiation, N stage and chemotherapy were the significant factors in multivariable analysis. Therefore, N stage and chemotherapy were the consistently significant factors in both curative and palliative groups (Table 5).

Effect on survival decrease by hematogenous metastasis is comparable to N2a node metastases

We compared the survivals of N0M1 and stage III patients to assess the effects on survival by the LN metastasis and hematogenous metastasis, each, because the survival of N0M1 is so excellent. Only the N0M1 with curative resection were compared to stage III because surgical resections in stage III are basically curative intent. The 5-year OS of N0M1 group was similar to that of stage IIIb (by AJCC/UICC 6th edition). If the stage III patients were classified according to N stage only, the 5-year OS of anyTN0M1 patients was not different from those of anyTN1M0 or anyTN2aM0 but significantly higher than that of anyTN2bM0 (Fig. 4).

DISCUSSION

The 5-year OS of the study patients (27.7% ± 1.7%) was better than that of surveillance, epidemiology, and end results (SEER) data [21,22]. However, 5-year OS of patients with curative resection, 47.5% ± 2.7%, was very similar to those of de Jong et al. [11] and Nitsche et al. [14]. And 5-year DFS of patients with curative resection, 26.0% ± 2.3%, was comparable to that of D'Angelica et al. [12]. The superior survival of our patients to SEER data is probably because we included only patients with primary tumor resection and excluded patients with peritoneal seeding. Survivals of patients with primary tumor resection were reported better than those without resection [23-25] and survival of patients with periotoneal seeding was inferior to that of hematogenous metastasis [10]. We excluded peritoneal seeding because there is not an objective standard for quantitative assessment of periotoneal seeding yet. We included neither metachronous stage IV nor metachronous metastasectomy in order to compare survival functions. Also, preoperative chemotherapy patients were excluded to reflect the stage at the time of diagnosis [26]. Many previous reports said that LN metastais was a prognostic factor in stage IV

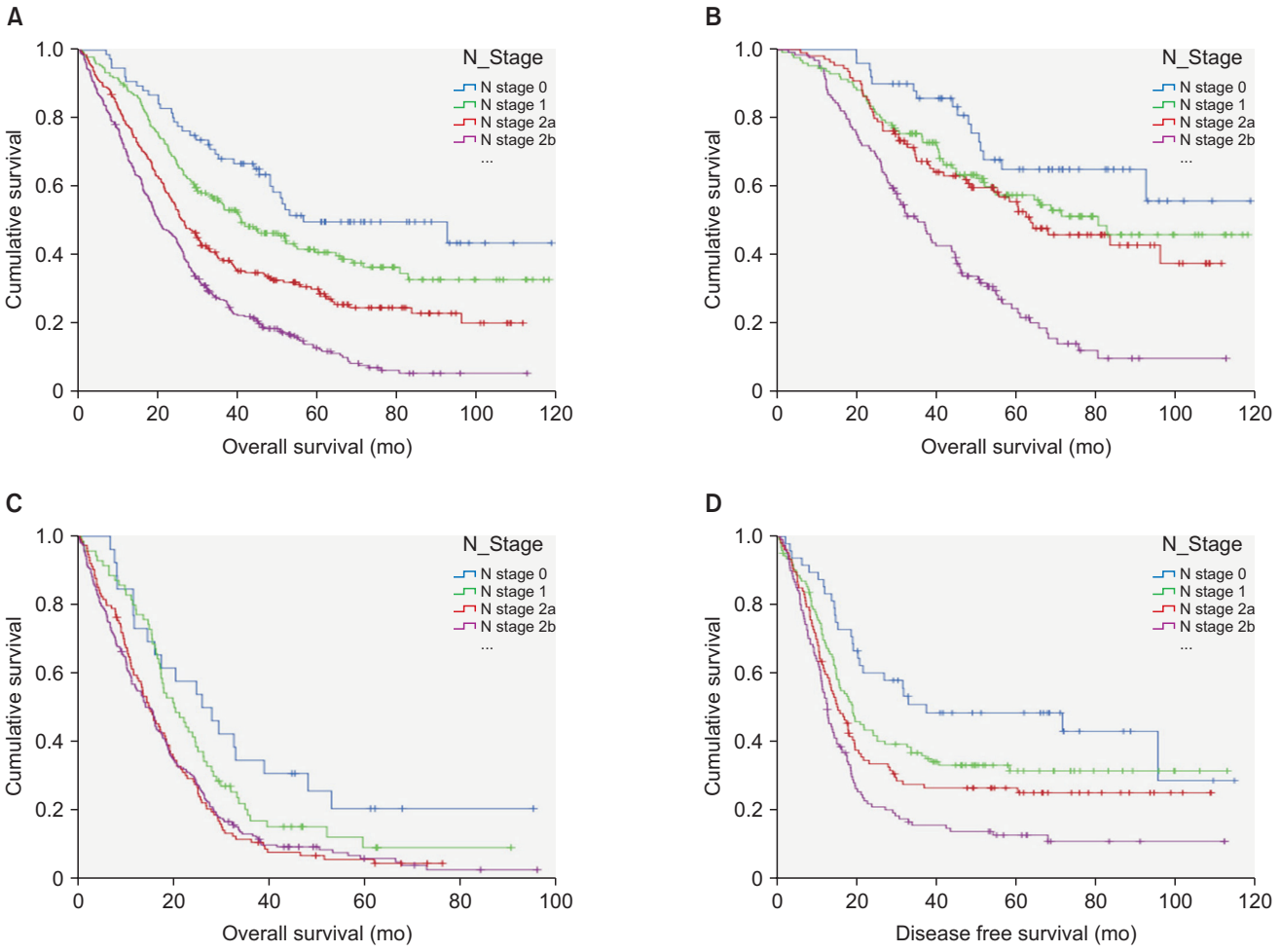

Fig. 3. Kaplan-Meier survival curves according to N stages. (A) Overall survivals (OSs) of all (n = 835) patients. The 5-year OS's of N0M1, N1M1, N2aM1, and N2bM1 were 49.7% ± 6.2%, 40.7% ± 3.8%, 29.9% ± 3.2%, and 12.8% ± 2.0% each (P = 0.037 for N0M1 *vs.* N1M1; P = 0.001 for N1M1 *vs.* N2aM1; P < 0.001 for N2aM1 *vs.* N2bM1, Log-rank test). (B) OSs of patients with curative resection. The 5-year OS's of N0M1, N1M1, N2aM1 and N2bM1 were 64.9% ± 7.5%, 57.4% ± 4.8%, 55.4% ± 5.1% and 22.7% ± 4.2% each (P = 0.084 for N0M1 *vs.* N1M1; P = 0.501 for N1M1 *vs.* N2aM1; P < 0.001 for N2aM1 *vs.* N2bM1; P = 0.030 for N0M1 *vs.* N2aM1). (C) OSs of patients with palliative resection. The 5-year OS's of N0M1, N1M1, N2aM1, and N2bM1 were 20.5% ± 8.5%, 9.1% ± 4.3%, 5.6% ± 2.3%, and 5.9% ± 1.9% each (P = 0.152 for N0M1 *vs.* N1M1; P = 0.014 for N1M1 *vs.* N2aM1; P = 0.987 for N2aM1 *vs.* N2bM1). (D) Disease free survivals (DFSs) of patients with curative resection. The 5-year DFS's of N0M1, N1M1, N2aM1, and N2bM1 were 47.4% ± 7.5%, 31.6% ± 4.4%, 26.2% ± 4.3%, and 12.9% ± 3.2% each (P = 0.081 for N0M1 *vs.* N1M1; P = 0.140 for N1M1 *vs.* N2aM1; P = 0.026 for N2aM1 *vs.* N2bM1; P = 0.005 for N0M1 *vs.* N2aM1).

patients. However, most of them could not show the survival functions because they included both synchronous and metachronous stage IV and because they did not put curative and palliative resection apart.

After Dukes demonstrated that invasion depth of colonic wall and LN metastases were important prognostic factors [27] and after Pierre Denoix suggested TNM staging system [28], AJCC have announced TNM stage classifications since 1977. However, for a long time, stage IV has been regarded merely as a stage of poor prognosis and of which prognostic factors were not drawn attention. Advances of imaging diagnosis made liver and lung metastases detectable preoperatively only in recent decades. And although anatomical liver resection was described as early as 1950s [29], it is lately that liver resection was positioned as a standard therapy for the liver metastasis [12]. Therefore, attentions and interests have not been paid for patients in whom exact assessment and proper treatment were not possible. However, advancement in preoperative imaging and improved survivals by the liver resection as well as new chemotherapeutics made stratification of the survivals necessary to differentiate better group from poorer group. Detailed analysis of survivals in stage IV can delineate subgroup with excellent survival and help improving the survival of overall stage IV patients ultimately.

Table 5. Clinicopathological factors contributing to overall survivals of patients with curative or palliative resection applied by Cox proportional hazard model with enter method

Variable	Curative resection group			Palliative resection group		
	Univariable	Multivariable[a]		Univariable	Multivariable[a]	
	P-value	P-value	HR (95% CI)	P-value	P-value	HR (95% CI)
Sex	0.966			0.692		
Age (yr)	0.162			0.002	0.321	
BMI (kg/m^2)	0.777			0.200		
ASA PS classification	0.316			0.001	0.023	
I						Reference
II						1.423 (1.112–1.820)
III						1.639 (1.054–2.549)
IV						1.769 (0.533–5.870)
Tumor location	0.086	0.019		0.012	0.177	
Right colon			1.520 (1.059–2.181)			
Left colon			0.902 (0.658–1.236)			
Rectum			Reference			
Tumor size	0.032	0.501		0.008	0.001	1.075 (1.031–1.121)
Tumor multiplicity	0.991			0.001	0.010	
1 Tumor						0.040 (0.004–0.362)
2 Tumors						0.027 (0.003–0.263)
3 Tumors						0.063 (0.006–0.638)
4 Tumors						Reference
Site of synchronous metastasis	0.654			0.020	0.012	
Liver						1.043 (0.787–1.383)
Lung						0.665 (0.445–0.994)
Bone						0.699 (0.372–1.312)
Brain						2.186 (0.900–5.310)
Ovary						0.339 (0.104–1.105)
Adrenal						0.279 (0.038–2.041)
Liver + extrahepatic						Reference
CEA	0.783			0.010	0.010	1.000 (1.000–1.000)[b]
Differentiation	0.869			0.001	0.015[c]	
W/D						0.481 (0.100–2.323)
M/D						0.458 (0.102–2.044)
P/D						0.448 (0.100–2.014)
Mucinous						1.598 (0.308–8.299)
Signet ring						Reference
T stage	0.006	0.145		0.001	0.170	
N stage	<0.001	<0.001		0.002	0.029[d]	
N0			0.279 (0.153–0.508)			0.765 (0.446–1.313)
N1			0.377 (0.263–0.540)			0.775 (0.561–1.072)
N2a			0.486 (0.345–0.685)			1.268 (0.967–1.662)
N2b			Reference			Reference

Table 5. Continued

Variable	Curative resection group				Palliative resection group			
	Univariable		Multivariable[a]		Univariable		Multivariable[a]	
	P-value	P-value	HR (95% CI)		P-value	P-value	HR (95% CI)	
Number of Harvested LN	0.835				0.338			
Angiolymphatic invasion	<0.001	0.754			0.005	0.135		
Venous Invasion	<0.001	0.172			0.002	0.223		
Perineural Invasion	<0.001	0.319			0.011	0.070		
Microsatellite instability	0.023	0.226			0.108			
Chemotherapy or not	0.004	<0.001			<0.001	<0.001		
No chemotherapy			3.221 (1.775–5.911)				3.708 (2.701–5.091)	
Chemotherapy			Reference				Reference	

HR, hazard ratio; CI, confidence interval; BMI, body mass index; ASA PS, American Society of Anesthesiologists physical status; W/D, well differentiated; M/D, moderately differentiated; P/D, poorly differentiated.
[a]Factors of P < 0.1 in the univariable analysis are included in the multivariable analyses. [b]If multivariable analysis was calculated with Log_{10}CEA, the hazard ratio is 1.237 (1.089–1.405). [c]Patients with adenocarcinoma well differentiated (0.301 [0.126–0.722]), moderately differentiated (0.287 [0.138–0.597]) and poorly differentiated (0.283 [0.128–0.623]) had low hazard ratio than patients with mucionus carcinoma. [d]Patients of N1M1 have low hazard ratio than patients of N2aM1 (0.629 [0.448–0.883]).

We could recognize by this study that N0M1 patients have better survival than N + M1 patients. N0M1 is a systemically spread disease but is a potentially curable disease. Better survival of N0M1 than N + M1 is due to neither more curative resection nor more active chemotherapy. DFS of patients with curative resection as well as OS of patients with palliative resection was better in N0M1 than in N + M1. Therefore, survival differences between the two groups are inherent in the LN metastases. That is also supported by that N+M1 patients had poorer pathological characteristics in differentiation, T stage, ALI, etc. Also, although quantitative comparison of metastatic burden is not possible, we observed that the number and size of metastatic liver tumor was lager in N + M1 than N0M1 (mean number of metastatic lesion: 2.41 *vs.* 1.56; mean maximal size of metastatic lesion: 2.87 *vs.* 2.27) of the patients in whom liver was the only site of metastasis and curative resection was performed. Poorer survival with N stage progression within N + M1 can be explained by the sequential accumulation of the pathologically poor characteristics. Thus, N stage is a prognostic factor in stage IV CRC patients by hematogenous metastasis, too. Therefore, resection of metastatic lesion is strongly recommended, if possible, when there is no evidence of advanced LN metastasis. Interestingly, meanwhile most pathological factors such as differentiation, T stage, ALI and PNI sequentially progressed from N0M1 to N2bM1, the clinical factors, for example age, did not. This implies that demographic features favoring hematogenous or LN metastases may be different. The meaning of this discrepancy between clinical and pathological features is worthwhile to be investigated in the future study.

Natural course of progression in CRCs are generally observed as; after the primary tumor develop, LN metastasis occurs initially and hematogenous metastasis develops finally. Are N0M1 patients accidental, then? However, sequential changes in the composition of pathological factors with the N stage progression (N0M1–N2bM1) mean N0M1 group is an inevitable one, not a chance, although the incidence is low. This fact rouses suspicions that LN metastasis and hematogenous metastasis are not sequential but only independent events. That is, hematogenous metastasis can occur earlier than LN metastasis, essentially. Because the LN metastasis is far more frequent than the hematogenous metastasis (5452: 77 ≃ 71: 1 in our series) we could not but observe LN metastases as earlier events; and because hematogenous metastasis has not been resectable for a long time and caused death, we could not but regarded as a final stage. That is, LN metastasis and hematogenous metastasis are not a way station and a final destination in the progression of CRC, but only independent events and, accordingly, the effects of survival decreases are independent each, if resected. We could notice it by the far lower survival curve of N2bM1 than N2aM1 or N1M1 (N2b

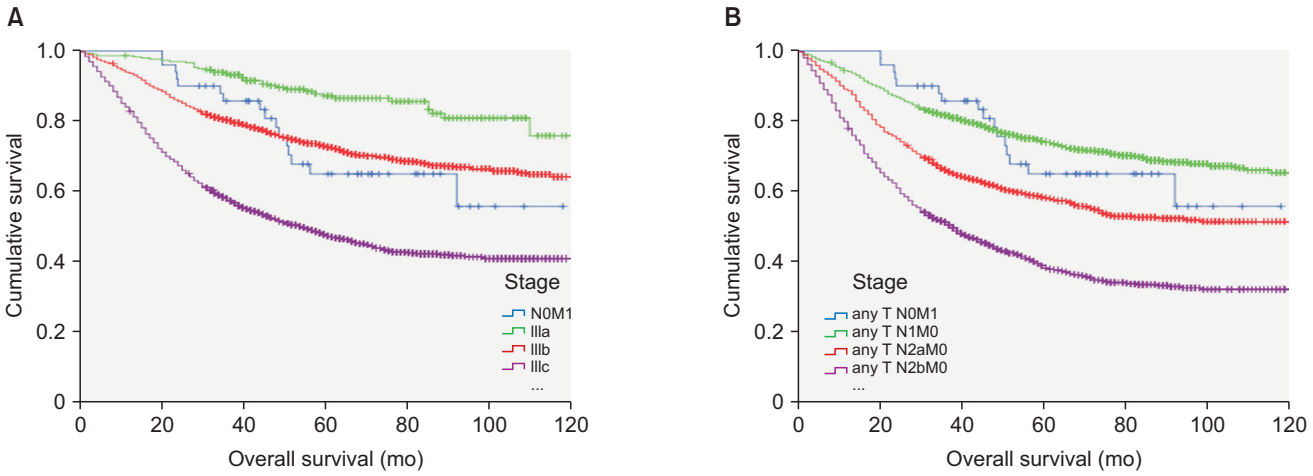

Fig. 4. Kaplan-Meier survival curves of patients of N0M1 with curative resection and of stage III. (A) Overall survivals (OSs) of N0M1 (n = 50) with stage IIIA (n = 298), IIIB (n = 2,633), and IIIC (n = 2,521). The 5-year OS's of anyTN0M1, stage IIIa, IIIb, and IIIc were 64.9% ± 7.5%, 87.2% ± 2.2%, 73.2% ± 0.9%, and 47.6% ± 1.1% each (P < 0.001 for anyTN0M1 *vs.* stage IIIa; P = 0.774 for anyTN0M1 *vs.* stage IIIb; P = 0.002 for anyTN0M1 *vs.* stage IIIc, Log-rank test). (B) OSs of N0M1 with stage III according to N stage only. The 5-year OS's of anyTN1M0 (n = 2,932), anyTN2aM0 (n = 1,143), and anyTN2bM0 (n = 1,377) were 74.9% ± 0.9%, 58.3% ± 1.5%, and 38.7% ± 1.4% each (P = 0.587 for anyTN0M1 *vs.* anyTN1M0; P = 0.063 for anyTN0M1 *vs.* anyTN2aM0; P < 0.001 for anyTN0M1 *vs.* anyTN2bM0).

is the poorer and major determinant than M1 from Fig. 3B) and by the similar curve of N2aM1 and N1M1 (nonsignificant difference of M1 from N1 or N2a) in patients with curative resection. However, in patients with palliative resection, the effect of N stage is masked by the unresected M1 and the survival curves have different patterns. As the N+M0 patients have hematogenous metastasis sometime if not treated, N0M1 patients will get LN metastasis too, so it is impossible to know which of the LN or hematogenous metastasis was first in N+M1 patients. However, observation of details in rare cases like N0M1 would broaden our understanding of the mechanism of LN metastasis and hematogenous metastasis and would provide important clues to CRC progression.

This study has weakness of enrolling small number of patients and of not showing the disease specific survivals. Therefore, further study with large scale is necessary.

In conclusion, LN metastasis is an important prognostic factor in stage IV CRC by hematogenous metastasis. However, the effect of survival decrease is determined by the resection of metastases as well. N stage progression accumulates pathologically poor prognostic factors. AnyTN0M1 with curative resection has equivocal survival to anyTN2aM0 and is potentially curable stage. Therefore, active metastasectomy was recommended, if resectable, when advanced LN metastases were not determined.

CONFLICTS OF INTEREST

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

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