의학석사 학위논문

대장 신경내분비암에서 American Joint Committee on Cancer (AJCC) 암 병기 설정 매뉴얼 제 8 판에 따른 림프절 전이 개수의 예후에 대한 영향

Prognostic impact of the number of metastatic lymph nodes for colorectal neuroendocrine carcinoma using American Joint Committee on Cancer (AJCC) staging manual 8th edition

울산대학교대학원

의 학 과

황 영 현

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지 도 교 수　　임석병

이 논문을 의학석사 학위 논문으로 제출함

2018 년 12 월

울 산 대 학 교 대 학 원

의　학　과

황 영 현

황영현의 의학석사학위 논문을 인준함

심사위원장 박 인 자 (인)

심사위원　임 석 병 (인)

심사위원　김 찬 욱 (인)

울 산 대 학 교 대 학 원

2018 년　12 월

Abstracts

Introduction: In the AJCC staging manual, 8th edition, the regional lymph nodal stage (N) for colorectal neuroendocrine carcinoma (NEC) was categorized by the number of metastatic lymph nodes like adenocarcinoma. The aim of the study was to compare the nodal stage of AJCC Staging Manual 7th edition and that of 8th edition of the colorectal NEC with their oncologic outcomes.

Materials and Methods: Medical records were reviewed for a total of 26 patients diagnosed with colorectal NEC according to the World Health Organization's 2010 classification who underwent surgical resection between May 2000 and December 2014. The clinicopathologic characteristics of the patients and their 5-year overall survival were analyzed according to AJCC Staging Manual, 8th edition, criteria.

Results: Of 26 patients, 16 (61.5%) were N2, 4 were N1, and 6 were N0 categories. The median follow-up period was 9.5 (range 3.9-16.5) years. The 5-year OS rate of all patients was 49% and N2 was only independent poor prognostic factor for OS (P = 0.019).

Conclusion: The number of metastatic lymph nodes, as well as the presence of positive nodes, had prognostic significance. N category of AJCC staging manual 8th edition, which considers the number of metastatic lymph nodes, better reflects prognosis than the previous editions.

Keywords: neuroendocrine carcinoma, survival, lymph node, metastasis

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Introduction

Neuroendocrine carcinoma (NEC) of colorectum is a rare disease entity, accounting for <1% of all tumors of the large intestine [1]. It is characterized by its extreme aggressiveness and poor differentiation, which result in rapid clinical deterioration and poor oncologic outcomes. NEC has different biological and clinical features from neuroendocrine tumors (NET) [2, 3]. The differentiating characteristics of NEC were reflected in the World Health Organization (WHO) 2010 classification, which defined NECs as poorly differentiated neuroendocrine malignant neoplasms with mitotic counts >20 per 10 high-power fields (HPFs) and/or a Ki-67 index > 20%; other neuroendocrine neoplasms which did not satisfy the criteria for NEC are classified as G1/G2 NETs [4].

Ki-67 index and mitotic count are the main components for the strict diagnosis of NEC using the WHO 2010 classification. The Ki-67 index reflects high mitotic activity and helps to predict prognosis and to determine treatment direction for several digestive NET including NEC [5]. Ki-67 immunoreactivity is also an independent predictor for malignancy in endocrine tumors of the pancreas [6]. In ileal NET, Ki-67 index index > 2% is associated with lower progression free survival, and there was a correlation between Ki-67 index and mitotic count [7]. Mitotic count is an independent predictor of survival in pulmonary NET [8], and it is also one of the independent risk factors for distant metastasis in rectal NET [9]. Ki-67 index is also associated with the levels of Chromogranin A, a neuroendocrine secretory protein, which reflects the effect of the treatment and is used as a follow-up tool to identify recurrence [10].

Based on the WHO 2010 classification, a clinical need for a different staging system between NEC and NET has emerged. However, colorectal NEC and G1/G2 NET has been categorized with the same staging system until the American Joint Committee on Cancer (AJCC) Staging Manual 7th edition [11]. From the 8th edition of AJCC Staging Manual, different staging systems have been used for two types of tumors [12, 13]. The 8th edition of colorectal NET uses the same stage system of the 7th edition, which used size and depth of invasion for T-category and the presence of metastatic nodes for N-category (N0 or N1). The staging criteria for colorectal NEC from the 8th edition, however, shared the staging system of colorectal adenocarcinoma, which used depth of invasion for T-category and the number of metastatic lymph nodes for N-category (N0, N1, and N2) rather than relying only on the of the presence or absence of metastatic lymph nodes [13]. The shared staging system was based on the similarity

of molecular characteristics between colorecctal NEC and colorectal adenocarcinoma [14]. Significant mutations in TP53, APC, KRAS, and BRAF gene were found in NEC and adenocarcinoma, but not in NET [14]. Furthermore, colorectal NEC and NET showed different biology and oncologic outcomes. We previously reported that tumor differentiation among NEC patients was poorer than in the G1/G2 NET group (% of poorly differentiated tumor, 70% vs 7%; $P < 0.001$) [2]. The 5-year overall survival (OS) rate of the NEC group was also significantly poorer than G1/G2 NET group ($P = 0.02$) [2]. However, compared with NET, there have been few reports focusing on NEC due its low incidence and because the strict pathologic definition of NEC using mitotic count and Ki-67 index was defined recently.

The nodal status in NET/NEC has been reported to have a profound effect upon on oncologic outcomes; for example, the presence of metastatic lymph nodes has been associated with subsequent development of distant metastasis in rectal carcinoids [15]. In a population-based analysis using Surveillance, Epidemiology, and End Results (SEER) data to evaluate survival of patients with colorectal NEC, prognosis in resected cases worsened as the number of metastatic lymph nodes increased [16]. In the AJCC Staging Manual 8th edition, the regional lymph nodal stage for colorectal NEC is categorized not only by the presence of metastatic lymph node, but also by the number of metastatic lymph nodes [13]. Like adenocarcinoma, lymph node stage of the colorectal NEC is N1 when 1 to 3 regional lymph nodes are positive, and N2 when 4 or more regional nodes are positive [13]. The aim of the present study was to compare the nodal stage of AJCC 7th and that of AJCC 8th of the colorectal NEC with their oncologic outcomes.

Materials and Methods

Patients

We retrospectively reviewed medical records of 26 patients who underwent surgical resection for colorectal NEC at Asan Medical Center in Seoul, Korea, between May 2000 and December 2014. The data including clinical (age, gender, location of tumor, site of metastasis, surgical curability, chemotherapeutic regimen, radiation therapy), pathological (differentiation, Ki-67 index, mitotic count, depth of tumor, number of harvested lymph nodes, number of metastatic lymph nodes, the presence of lymphovascular invasion, the presence of perineural invasion, the status of resected margins, and growth type), and follow-up (recurrence, survival status) variables were investigated. Patients were excluded from the study if they were (i) over 85 or under 18 years of age; (ii) had tumors located in areas other than colon or rectum; (iii) synchronous colorectal carcinoma with other histology; (iv) Ki-67 index <20% and mitotic count <20/10 HPF; (v) unavailable pathologic T or N staging; (iv) or follow-up less than 6 months. Surgery included right hemicolectomy, left hemicolectomy, Hartmann's operation, total colectomy, low anterior resection, lowest anterior resection, and abdominoperineal resection. Surgery without curative intent was classified as palliative. After surgery, all the patients underwent protocol-based follow-up with clinical examinations, chest radiography, complete blood counts, blood chemistry tests, abdominopelvic computed tomography (CT) and either colonofiberoscopy or sigmoidofiberoscopy.

Patients suspected of recurrence were examined according to the suspected site with imaging studies using CT, magnetic resonance imaging, and/or positron emission tomography. The survival status and date of death was confirmed by follow-up. This study was approved and exempted from informed consent by the institutional review board of Asan Medical Center (registration no: 2018-1125).

Diagnosis of neuroendocrine carcinoma

The diagnosis of NEC was made according to the WHO 2010 classification (mitotic count >20/10 HPF and/or Ki-67 index >20%) [4] and tumor nodal staging was made according to the 8th edition of AJCC Staging Manual [13]. Differences in staging system for colorectal NET and NEC in AJCC Staging Manual, 7th and 8th editions [11-13], are described in Table 1. The presence

and number of metastatic lymph nodes were identified by using pathologic report. The event of OS was defined as death and the primary outcome of the present study was OS. The event of recurrence-free survival (RFS) was defined as recurrence, and death was considered as censoring. Well- and moderately-differentiated lesions were grouped together and compared with poorly differentiated lesions. T1 and T2 were grouped together and compared with T3 and T4 groups. Tumor size was dichotomized at 5 cm according to the mean and median tumor size of patients. The Ki-67 index was dichotomized at 30% and the mitotic count at 40 per 10 HPF, which was close to the patients' median.

Statistical analysis

Data were reported as median ± interquartile range for continuous variables and as frequency (%) for categorical variables. OS and RFS were calculated using the Kaplan–Meier method, and the log-rank test was used to compare the differences among survival curves in univariate analyses. The potential prognostic factors identified in univariate analysis were further analyzed by multivariate analysis using a Cox regression model, and hazard ratios (HR) were calculated at 95% confidence intervals (CI). A P-value <0.05 was considered statistically significant for all analyzes, and all calculations were carried out using SPSS software (version 25.0, IBM Corp., Armonk, New York, USA).

Results

Patient characteristics

From May 2000 to December 2014, a total of 26 patients were diagnosed with colorectal NEC based on the WHO 2010 classification at Asan Medical Center. The median Ki-67 index was 33% and mitotic count was 38/10 HPF. Clinicopathologic characteristics for all patients are listed in Table 2. The median age at surgery was 66.9 years and the median tumor size was 5.0cm. Of the 26 patients, 10 (38.5%) had tumors located at rectum, 16 (65%) had poorly differentiated tumors, and 18 (69.2%) underwent surgery with curative intent (16 cM0 category, 2 cM1 category).

Of 26 patients with colorectal NEC, 6 with negative nodes were classified as N0 by both AJCC 7th and 8th edition. The remaining 20 patients with positive nodes were classified as N1 according to the AJCC Staging Manual, 7th edition, and divided into N1 (n=4) and N2 (n=16) according to AJCC Staging Manual, 8th edition.

Twelve (46.2%) had distant metastasis at time of surgery. In Table 3, clinicopathologic characteristics according to the regional lymph node status (N0, N1, and N2) were compared, but there were no significant difference.

Survival and recurrence

The median follow-up time was 9.5 (range 3.9~16.5) years. The 5-year OS rate for all 26 patients was 49%. The results of univariate and multivariate analysis for OS are listed in Table 4. From the univariate analysis for OS, N-category (P = 0.009), distant metastasis (P = 0.04) and tumor differentiation (P = 0.057) were selected for the multivariate analysis. In the multivariate analysis, N2 (HR=18.7, 95% C.I 1.6-214.7 P = 0.019) was the only independent factor for poor OS. 5 year OS rate of N0 category was significantly higher than N2 (P = 0.003), but the comparisons between N0 and N1 (p=0.23) and N1 and N2 (p=0.21) were not significantly different (Fig 1).

Poor differentiation trended toward poorer OS (HR 3.9 95% CI 0.8-7.5) without statistical difference (p=0.052). Adjuvant chemotherapy or radiation therapy did not affect OS rate.

5-year OS rate according to AJCC Staging Manual, 7th edition, nodal status were compared, and N0 had significantly higher OS rate than N1 (Fig 1, P = 0.011). Of 18 patients who underwent surgery with curative intent, 9 developed recurrence during follow-up and their 5-

year RFS rate was 52.9%.

Table 1. Differences in AJCC Staging Manual, 7th and 8th editions, in colorectal NEC.

Colorectal NET in AJCC Staging Manual, 7th and 8th edition Colorectal NEC in AJCC Staging manual, 7th edition and colorectal NET in AJCC staging manual 8th edition are staged according to this staging system		Colon and rectum in AJCC Staging Manual, 8th edition Colorectal NEC in AJCC Staging Manual, 8th edition is staged according to this staging system	
Primary Tumor (T)			
T0	No evidence of primary tumor	T0	No evidence of primary tumor
T1	Tumor invades lamina propria or submucosa and size 2 cm or less	Tis	Carcinoma in situ, intramucosal carcinoma
T1a	Tumor size less than 1 cm in greatest diamension	T1	Tumor invades the submucosa
T1b	Tumor size 1-2 cm in greatest dimension	T2	Tumor invades the muscularis propria
T2	Tumor invades muscularis propria or size more than 2 cm with invasion of lamina propria or submucosa	T3	Tumor invades through the muscularis propria into pericolorectal tissues
T3	Tumor invades through the muscularis propria into the subserosa, or into non-peritonealized pericolic or perirectal tissues	T4	Tumor invades the visceral peritoneum or invades or adheres to adjacent organ or structure
T4	Tumor invades peritoneum or other organs	T4a	Tumor invades through the visceral peritoneum
		T4b	Tumor directly invades or adheres to adjacent organs or structures
Regional Lymph Nodes (N)			
N0	No regional lymph node metastasis has occurred	N0	No regional lymph node metastasis
N1	Regional lymph node metastasis	N1	One to three regional lymph nodes are positives
		N2	Four or more regional nodes are positive
Distant Metastases (M)			
M (-)	No distant metastases	M0	No distant metastasis by imaging
M (+)	Distant metastasis	M1	Metastasis to one or more distant sites or organs or peritoneal metastasis is identified
M1a	Metastasis confined to liver	M1a	Metastasis to one site or organ is identified without peritoneal metastasis
M1b	Metastasis in at least one extrahepatic site	M1b	Metastasis to two or more sites or organs is identified without peritoneal metastasis
M1c	Both hepatic and extrahepatic metastases	M1c	Metastasis to the peritoneal surface is identified alone or with other site or organ metastasis
Prognostic Stage Groups			
Stage 0	Tis N0 M (-)	Stage 0	Tis N0 M0

Stage I	T1	N0	M (-)	Stage I	T1, T2	N0	M0
Stage IIA	T2	N0	M (-)	Stage IIA	T3	N0	M0
Stage IIB	T3	N0	M (-)	Stage IIB	T4a	N0	M0
Stage IIIA	T4	N0	M (-)	Stage IIC	T4b	N0	M0
Stage IIIB	Any T	N1	M (-)	Stage IIIA	T1-T2	N1/N1c	M0
Stage IV	Any T	Any N	M (+)		T1	N2a	M0
				Stage IIIB	T3-T4a	N1/N1c	M0
					T2-T3	N2a	M0
					T1-T2	N2b	M0
				Stage IIIC	T4a	N2a	M0
					T3-T4a	N2B	M0
					T4b	N1-N2	M0
				Stage IVA	Any T	Any N	M1a
				Stage IVB	Any T	Any N	M1b
				Stage IVC	Any T	Any N	M1c

NEC, neuroendocrine carcinoma; AJCC, American Joint Community on Cancer

Table 2. Clinicopathologic characteristics of all patients.

Features		
Age (median, [IQR], years)		66.9 [14]
Sex (n, (%))	Male	18 (69.2)
	Female	8 (30.8)
Location (n, (%))	Colon	16 (61.5)
	Rectum	10 (38.5)
Growth type (n, (%))	Expanding	5 (19.2)
	Infiltrative	21 (80.8)
Differentiation (n, (%), 2 missing)	WD+MD	8 (33.3)
	PD	16 (66.7)
Tumor size (median, [IQR], cm)		5.0 [3.4]
Ki-67 index (median, [IQR], %)		33 [43]
Mitotic count (median, [IQR], per 10 HPF)		38 [36]
Lymphovasular invasion (n, (%))	No	5 (19.2)
	Yes	21 (80.8)
Perineural invasion (n, (%))	No	20 (76.9)
	Yes	6 (23.1)
Surgical curability	Curative	18 (69.2)
	Palliative	8 (30.8)
T stage (n, (%))	I	3 (11.5)
	II	1 (3.8)
	III	20 (76.9)
	IV	2 (7.7)
N stage (n, (%))	0	6 (23.1)
	I	4 (15.4)
	II	16 (61.5)
Distant metastasis (n, (%))	No	14 (53.8)
	Yes	12 (46.2)
Follow-up period (median, [IQR], months)		114 [68]

IQR, interquartile range; WD, well differentiated; MD, moderately differentiated; PD, poorly differentiated; HPF, high power field.

Table 3. Clinicopathologic characteristics according to regional lymph node status

Features		N0 (n=6)	N1 (n=4)	N2 (n=16)	P-value
Age (median, [IQR], years)		63 [17]	67.5 [27]	69.0 [14]	0.51
Sex (n, (%))	Male	4 (66.7)	3 (75.0)	11 (68.8)	0.96
	Female	2 (33.3)	1 (25.0)	5 (31.3)	
Location (n, (%))	Colon	5 (83.3)	2 (50.0)	9 (56.3)	0.45
	Rectum	1 (16.7)	2 (50.0)	7 (43.8)	
Growth type (n, (%))	Infiltrative	5 (83.3)	3 (75.0)	13 (81.3)	0.95
	Expanding	1 (16.7)	1 (25.0)	3 (18.8)	
Differentiation (n, (%))	WD+MD	3 (50.0)	1 (33.3)	4 (26.7)	0.59
	PD	3 (50.0)	2 (66.7)	11 (73.3)	
Tumor size (median, [IQR], cm)		3.4 [3.5]	4.5 [6.0]	5.25 [2.7]	0.43
Ki-67 index (median, [IQR], %)		38.5 [58]	65.0 [42]	32.0 [44]	0.16
Mitotic count (median, [IQR], per 10 HPF)		30 [62]	56 [NC]	36 [22]	0.23
Lymphovasular invasion (n, (%))	No	1 (16.7)	1 (25.0)	3 (18.8)	0.95
	Yes	5 (83.3)	3 (75.0)	13 (81.3)	
Perineural invasion (n, (%))	No	5 (83.3)	4 (100.0)	11 (68.8)	0.38
	Yes	1 (16.7)	0 (0.0)	5 (31.3)	
Surgical curability	Curative	5 (83.3)	4 (100.0)	9 (56.3)	0.17
	Palliative	1 (16.7)	0 (0.0)	7 (43.8)	
T stage (n, (%))	I	1(16.7)	1 (25.0)	1 (6.3)	0.82
	II	0 (0.0)	0 (0.0)	1 (6.3)	
	III	4 (66.7)	3 (75.0)	13 (81.3)	
	IV	1 (16.7)	0 (0.0)	1 (6.3)	
Distant metastasis (n, (%))	No	5 (83.3)	3 (75.0)	6 (37.5)	0.1
	Yes	1 (16.7)	1 (25.0)	10 (62.5)	
Follow-up period (median, [IQR], months)		128.5 [98]	116.0 [81]	114.0 [53]	0.84

IQR, interquartile range; WD, well differentiated; MD, moderately differentiated; PD, poorly differentiated; NC, not calculated; HPF, high power field

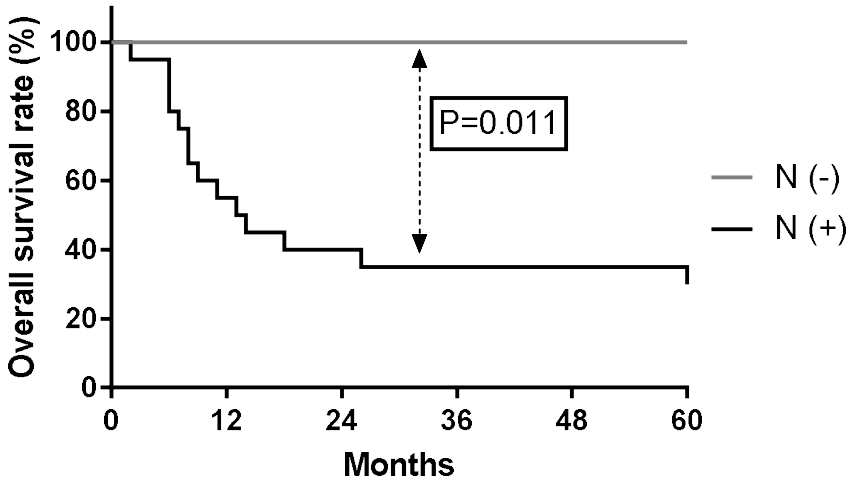
Table 4. Univariate and multivariate analysis of overall survival.

Variables		Univariate analysis		Multivariate analysis		
		5-year OS rate (%)	P-value	HR	95% C.I.	P-value
Sex	Male	61.1	0.11			
	Female	20.0				
Size	<5 cm	65.2	0.15			
	≥5 cm	35.7				
Location	Colon	41.9	0.9			
	Rectum	60				
Differentiation	WD/MD	73.3	0.057	ref		
	PD	31.3		3.943	0.758-7.526	0.052
Ki-67 index (%)	<30	37.5	0.23			
	≥30	51.5				
Mitotic count (per 10 HPF)	<40	27.3	0.24			
	≥40	57.9				
LVI	No	40.0	0.99			
	Yes	51.2				
PNI	No	55.0	0.31			
	Yes	27.3				
Growth type	Infiltrative	41.5	0.21			
	Expanding	80.0				
Surgical curability	Curative	60.0	0.13			
	Palliative	25.0				
T stage	T1-2	75.0	0.13			
	T3-4	44.2				
N stage	N0	100	0.009	ref		
	N1	75.0		9.714	0.766-123.134	0.079
	N2	25.0		18.681	1.625-214.730	0.019
Distant metastasis	No	70.4	0.04	ref		
	Yes	25.0		3.943	0.988-15.735	0.14
Chemotherapy	No	44.4	0.56			
	Yes	51.5				
Radiation therapy	No	42.2	0.76			
	Yes	100				

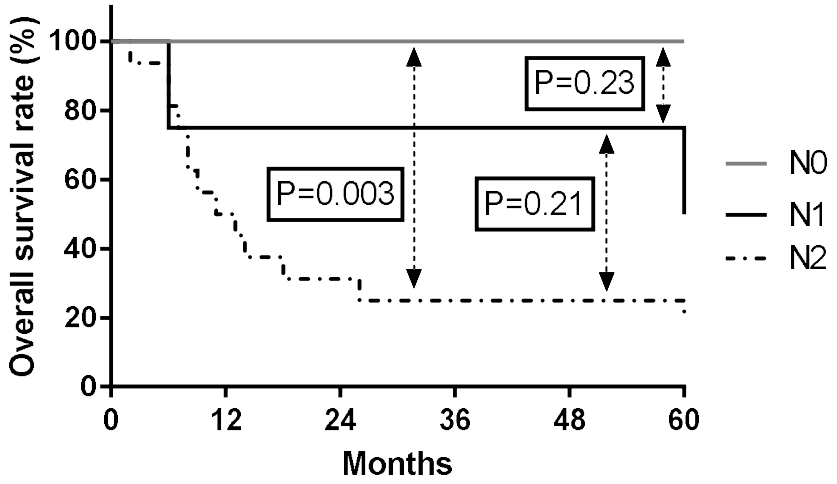
WD; well differentiated, MD; moderate differentiated, PD; poorly differentiated, LVI; lymphovascluar invasion, PNI; perineural invasion, HR, hazard ratio; CI, confidence interval; OS, overall survival

Figure 1. 5-year overall survival curves according to the regional lymph node stage. (A) AJCC Staging Manual, 7th edition. (B) AJCC Staging Manual, 8th edition

(A)



(B)



Discussion

Our study investigated the definition changes of colorectal NEC nodal stage in between the AJCC Staging Manual, 7th to 8th editions. For initial diagnosis prior to staging, we strictly applied the WHO 2010 classification definition of NEC strictly, and then analyzed the association between the number of metastatic lymph nodes and OS. The main finding of the present study is that 5-year OS rate was significantly low when 4 or more regional nodes are positive (N2 category in AJCC 8th edition). Using the AJCC Staging Manual, 7th edition, which determined stage only by the presence or absence of metastatic lymph nodes, the difference of 5-year OS between N0 and N1 was also significant (p=0.011). However, N0-N1 comparison in AJCC 8th edition was not different (p=0.23). Although N1 cases (1-3 nodes were positive) in AJCC 8th criteria was also N1 (node-positive) in AJCC 7th criteria, the poor oncologic effect of positive node (1-3 nodes) cannot be persisted. Furthermore, we could not tell the difference in 5-year OS rate between N2 and N1 cases (AJCC 8th criteria).

There were only 4 patients staged as N1 category and comparisons between N1 and the other subgroups could not make a difference with statistical significance. However, 5-year OS rate showed a tendency to decrease from N0 to N1 and N2. If there were more N1 cases from multi-center study or population based study, statistically significant differences in OS between N1 and N2 categories could be expected. Considering our findings, AJCC Staging Manual, 8th edition, for staging colorectal NEC, which follows the staging system of adenocarcinoma and classifies colorectal NEC according to the number of metastatic lymph nodes, appears to be more helpful in predicting poor prognosis than the AJCC 7th edition. In terms of colorectal adenocarcinoma, minimum number of harvested lymph nodes for accurate staging has been known as 12 [17]. However, no research has been conducted on the minimum number of lymph node for accurate staging for colorectal NEC. In small bowel NET, there was a study that patients with 4 or more positive lymph nodes showed decreased 3-year RFS compared with 1-3 positive lymph nodes or no lymph node metastasis when more than 8 lymph nodes were harvested [18]. Further investigation into the appropriate minimum number of harvested lymph nodes will be needed for colorectal NEC.

N2 had lower OS rate than N0 but OS rate of N1 was not significantly lower than N0. Compared to previous studies, this study was a single center study to firmly adhere maintained definition of NEC.

The 5-year OS rate of the present study was 49%, which was higher than the previous studies (16.3-21.4%) [16, 19]. One of the causes was that the proportion of cases with distant metastasis of present study was lower than in the others studies (46.2% vs. 57.9-62.1%). Another possible explanation is that our study included patients who underwent surgery, not endoscopic resection and the more radical treatment could contribute to high OS rate.

In terms of colorectal NET, tumor size has been well known as a prognostic factor [15, 20]. However, to our knowledge, there has been no study on the association between tumor size and prognosis of NEC. In the study of NET, the tumor size was divided by 1cm or 2cm [16, 21]. In the present study, the median tumor size was 5.0 cm, which was larger than that of NETs. There were no patients with tumor size smaller than 1cm and 3 patients had tumors that were 1-2 cm. If the threshold for tumor size was determined at 1cm or 2cm, the analysis was impossible because of small number of the cases with small tumors less than 2cm. Tumor size (>5.0 cm) did not affect OS (P = 0.15) or lymph node metastasis (P = 0.25). NEC usually has a very rapid tumor growth, and thus the tumor size itself does not appear to have a significant impact on prognosis.

The present study has some limitations. As a single center study of a relatively rare disease, the number of cases was too small to draw concrete conclusion about prognostic factors in the survival analysis. Therefore, a sufficient number of cases strictly identified according to WHO 2010 definition for colorectal NEC should be collected by multi-center or population-based studies in order to identify prognostic factors with greater certainty. In addition, as a retrospective study, there could be a selection bias or misclassification and it was difficult to evaluate reasoning behind treatment decision. However, because of the extremely low incidence (2.0 per million person-years) [3] of colorectal NEC, it is difficult to implement a prospective study. Large scaled multi-center studies are needed to overcome these shortcomings.

Conclusion

The number of metastatic lymph nodes, as well as the presence of positive nodes, had prognostic significance. N category of AJCC Staging Manual, 8th edition, which divided according to the number of metastatic lymph nodes, reflects the prognosis better than previous editions.

References

1. Bernick PE, Klimstra DS, Shia J, Minsky B, Saltz L, Shi W, et al. Neuroendocrine carcinomas of the colon and rectum. Dis Colon Rectum. 2004;47:163-9.
2. Lee JL, Yu CS, Kim M, Hong SM, Lim SB, Kim JC. Prognostic impact of diagnosing colorectal neuroendocrine carcinoma using the World Health Organization 2010 classification. Surgery. 2014;155:650-8.
3. Dasari A, Shen C, Halperin D, Zhao B, Zhou S, Xu Y, et al. Trends in the Incidence, Prevalence, and Survival Outcomes in Patients With Neuroendocrine Tumors in the United States. JAMA Oncol. 2017;3:1335-42.
4. Bosman FT, Carneiro F, Hruban RH. WHO classification of tumours of the digestive system. Lyon: IARC Press; 2010.
5. Vilar E, Salazar R, Perez-Garcia J, Cortes J, Oberg K, Tabernero J. Chemotherapy and role of the proliferation marker Ki-67 in digestive neuroendocrine tumors. Endocr Relat Cancer. 2007;14:221-32.
6. Pelosi G, Bresaola E, Bogina G, Pasini F, Rodella S, Castelli P, et al. Endocrine tumors of the pancreas: Ki-67 immunoreactivity on paraffin sections is an independent predictor for malignancy: a comparative study with proliferating-cell nuclear antigen and progesterone receptor protein immunostaining, mitotic index, and other clinicopathologic variables. Hum Pathol. 1996;27:1124-34.
7. Dhall D, Mertens R, Bresee C, Parakh R, Wang HL, Li M, et al. Ki-67 proliferative index predicts progression-free survival of patients with well-differentiated ileal neuroendocrine tumors. Hum Pathol. 2012;43:489-95.
8. Travis WD, Rush W, Flieder DB, Falk R, Fleming MV, Gal AA, et al. Survival analysis of 200 pulmonary neuroendocrine tumors with clarification of criteria for atypical carcinoid and its separation from typical carcinoid. Am J Surg Pathol. 1998;22:934-44.
9. Park CH, Cheon JH, Kim JO, Shin JE, Jang BI, Shin SJ, et al. Criteria for decision making after endoscopic resection of well-differentiated rectal carcinoids with regard to potential lymphatic spread. Endoscopy. 2011;43:790-5.
10. Massironi S, Rossi RE, Casazza G, Conte D, Ciafardini C, Galeazzi M, et al. Chrom

ogranin A in diagnosing and monitoring patients with gastroenteropancreatic neuroen docrine neoplasms: a large series from a single institution. Neuroendocrinology. 201 4;100:240-9.

11. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Andy Trotti I. AJCC cancer staging manual Seventh Edition. New York Dordrecht Heidelberg London:: Springer; 2010.

12. Edge SB, Brookland RK, Jessup JM, Greene FL, Brierley JD, Byrd DR, et al. AJCC cancer staging manual Eighth Edition. AG Switzerland: Springer International Publis hing; 2017.

13. Edge SB, Brookland RK, Jessup JM, Greene FL, Brierley JD, Byrd DR, et al. AJCC cancer staging manual Eighth Edition. AG Switzerland: Springer International Publis hing; 2017.

14. Takizawa N, Ohishi Y, Hirahashi M, Takahashi S, Nakamura K, Tanaka M, et al. Mol ecular characteristics of colorectal neuroendocrine carcinoma; similarities with aden ocarcinoma rather than neuroendocrine tumor. Hum Pathol. 2015;46:1890-900.

15. Shields CJ, Tiret E, Winter DC, International Rectal Carcinoid Study G. Carcinoid tu mors of the rectum: a multi-institutional international collaboration. Ann Surg. 2010; 252:750-5.

16. Shafqat H, Ali S, Salhab M, Olszewski AJ. Survival of patients with neuroendocrine carcinoma of the colon and rectum: a population-based analysis. Dis Colon Rectum. 2015;58:294-303.

17. Sjo OH, Merok Ma Fau - Svindland A, Svindland A Fau - Nesbakken A, Nesbakken A. Prognostic impact of lymph node harvest and lymph node ratio in patients with co lon cancer.

18. Zaidi MY, Lopez-Aguiar AG, Dillhoff M, Beal E, Poultsides G, Makris E, et al. Prog nostic Role of Lymph Node Positivity and Number of Lymph Nodes Needed for Acc urately Staging Small Bowel Neuroendocrine Tumors. JAMA Surg. 2018.

19. Kang H, O'Connell JB, Leonardi MJ, Maggard MA, McGory ML, Ko CY. Rare tumo rs of the colon and rectum: a national review. Int J Colorectal Dis. 2007;22:183-9.

20. Yangong H, Shi C, Shahbaz M, Zhengchuan N, Wang J, Liang B, et al. Diagnosis an

d treatment experience of rectal carcinoid (a report of 312 cases). Int J Surg. 2014;12: 408-11.

21. Gleisner AL, Mogal H, Dodson R, Efron J, Gearhart S, Wick E, et al. Nodal status, n umber of lymph nodes examined, and lymph node ratio: what defines prognosis after resection of colon adenocarcinoma? Journal of the American College of Surgeons. 2 013;217:1090-100.

대장 신경내분비암에서 American Joint Committee on Cancer (AJCC) 암 병기 설정 매뉴얼 제 8 판에 따른 림프절 전이 개수의 예후에 대한 영향

서론: AJCC 암 병기 설정 매뉴얼 제 8 판에서 대장 직장 신경내분비암의 국소 림프절 병기는 선암과 같이 전이 림프절의 수에 따라 분류된다. 이 연구의 목적은 대장 직장 신경내분비암에서 AJCC 암 병기 설정 매뉴얼 제 7 판과 제 8 판의 림프절 병기에 따른 종양학적 결과를 비교하는 것이다.

대상 및 방법: 2000 년 5 월부터 2014 년 12 월까지 26 명의 환자가 WHO 2010 분류에 따라 대장 직장 신경내분비암 진단 하 외과적 절제술을 시행 받았다. 환자의 임상 병리학적 특징과 5 년 전체 생존율을 AJCC 암 병기 설정 매뉴얼 제 8 판에 따라 분석하였다.

결과: 환자 26 명 중 N2 가 16 명 (61.5 %), N1 이 4 명, N0 가 6 명이었다. 추적 관찰 기간의 중앙값은 9.5 (범위 3.9-16.5)년 이었다. 모든 환자의 5 년 생존률은 49 % 였고 N2 는 전체생존률의 나쁜 독립적 예후 인자였다 (P = 0.019).

결론: 전이 림프절의 존재 여부뿐 만 아니라 개수도 예후에 영향을 미쳤다. 전이성 림프절의 수에 따라 분류 된 AJCC 암 병기 설정 매뉴얼 제 8 판의 N 카테고리는 이전 판보다 예후를 더 잘 반영하였다.

중심단어: 신경내분비암, 생존, 림프절, 전이