Original Article

Combination of Metastatic Lymph Node Ratio and Carcinoembryonic Antigen Level for Predicting Prognosis of Stage III Colon Cancer after Curative Surgery

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Key Words
Stage-III colon cancer;
Carcinoembryonic antigen;
Lymph node ratio;
Overall survival;
Relapse-free survival

Background. The preoperative serum carcinoembryonic antigen (s-CEA) level has been proposed as a laboratory stage by The American Joint Committee on Cancer. The ratio of metastatic nodes to all examined lymph nodes (LNR) is another prognostic factor for stage III colorectal cancer. We assessed the combination of LNR and s-CEA for predicting the prognosis of stage III colon cancer.

Methods. Data of our cohort (N = 2205) that received a diagnosis of stage III colonic adenocarcinoma were collected from Chang Gung Memorial Hospital between 1995 and 2016. The s-CEA ≥ 5 ng/mL was defined as abnormal level. Based on the LNR, patients were divided into three subgroups: LNR1 (0.3-1.0), LNR2 (0.1-0.29), and LNR3 (< 0.1). We combined LNR and s-CEA level as a category to establish the six following groups: G1 (LNR1 with s-CEA ≥ 5.0), G2 (LNR1 with s-CEA < 5.0), G3 (LNR2 with s-CEA ≥ 5.0), G4 (LNR2 with s-CEA < 5.0), G5 (LNR3 with s-CEA ≥ 5.0), and G6 (LNR3 with s-CEA < 5.0).The Cox proportional hazard models and Kaplan-Meier analyses were used to investigate the independent factors associated with survival, including 5-year overall survival (OS) and 5-year relapse-free survival (RFS).

Results. G1 exhibited the worst OS and RFS, but G6 had the best survival. The G2 had significantly better RFS than G3 (60.0% vs. 48.4%, $p = .010$) although G2 had a significantly higher LNR, more poorly differentiated histology, and more stage IIIC colon cancer than G3. Both G2 and G5 with different LNR and s-CEA exhibited no difference in RFS and OS. In the multivariate Cox regression for survival, G3 like G1, male gender, stage IIIB and IIIC colon cancer, and no adjuvant chemotherapy were independent factors for poor prognosis.

Conclusions. Combination of s-CEA and the LNR may comprehensively predict the prognosis of stage III colon cancer and risk stratification, especially in stage IIIB and IIIC. When stage III colon cancer was in the same LNR group, the s-CEA level played a decisive role in RFS.

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Colorectal cancer is one of the most common cancers in Taiwan and globally.[1,2] For colorectal cancer treatment, en bloc resection involves removing the main tumor with a clear resection margin and adequately harvesting the lymph nodes associated with possible tumor drainage. The American Joint Committee on Cancer (AJCC) recommends properly harvesting and examining at least 12 lymph nodes to minimize the understaging risk.[3,4] In practice, even when achieving the lowest limit of the lymph node yield requirement, the total number of harvested lymph nodes still varies greatly and may depend on patient's age, the tumor locations, and surgical procedures. Therefore, given the effects of metastatic lymph nodes and the total lymph node yield, the ratio of metastatic to all examined lymph nodes (LNR) has been recommended as a factor for predicting the prognosis of stage III colorectal cancer. The LNR can be a key prognostic factor for colon cancer.[5,6] This finding usually implies a more advanced stage of colorectal cancer and worse prognosis.

In addition to metastatic lymph nodes, the preoperative serum carcinoembryonic antigen (s-CEA) level is a tumor marker secreted by many solid tumors. The s-CEA examination has mostly been used before cancer resection or in follow-up for colorectal cancer, lung cancer, and ovary cancer.[7-9] Elevated preoperative s-CEA level is a worse independent prognostic factor for colorectal cancer, either in overall survival (OS) or in relapse-free survival (RFS).[10-12] Some clinical researchers investigated whether the prognostic effect of elevated preoperative s-CEA levels similarly influences survival in the early and advanced stages of colorectal cancer. In 2011, Thirunavukarasu et al. reported a s-CEA–stage concept.[13,14] Lower OS was noted in stage I colon cancer with high preoperative s-CEA levels. The survival in stage IIIB colon cancer with normal s-CEA levels was also better than that in stage IIB or IIC with high s-CEA levels. Therefore, thes-CEA level may indicate more severe or potential risk of systemic organ involvement.

After reviewing these studies, we hypothesized that high LNR and high preoperative s-CEA levels can determine the potential extent or the severity of colorectal cancer. The combination of the preoperative s-CEA level and metastatic LNR may reflect the true involvement range of colorectal cancers. In this study, we investigated the s-CEA-LNR combination for predicting survival prognosis in stage III colon cancer. We were especially interesting to the prognostic role of this combination in stage IIIB and IIIC colon cancer.

Materials and Methods

Data collection

The inclusion criteria were stage III colon cancer after elective curative cancer resection; the exclusion criteria were emergent operation and no CEA data. Data for this study were initially obtained from 3034 patients with pathologic stage III colon cancer who underwent cancer surgery at Chang Gung Memorial Hospital between 1995 and 2016. The curative surgery was defined as that surgeon removed cancer with a safe margin and en bloc resection of tumor spreading route from body. We excluded 790 patients who received emergent surgery for cancer obstruction or perforation and 39 patients who did not have preoperative s-CEA data. We excluded rectosigmoid colon, since some of these patients receiving preoperative neoadjuvant therapy before cancer resection. Finally, we analyzed the data of 2205 patients for verifying our hypothesis. The data were collected prospectively and retrieved from the tumor registry of the colon and rectal surgery division. Follow-up data for survival were collected retrospectively from medical records and interviews. The last date of follow-up was February 28, 2020.

The pathological data of each patient comprised the cancer type, grade, and the tumor, node, and metastasis (TNM) stage and they were restaged according to the *AJCC Cancer Staging Manual*, *8th Edition*. However, tumor deposit report was not obligatory included in pathology report before AJCC 7th edition (2010-2017), we excluded all tumor deposit data, and the N1c stage.

The T means depth of tumor penetration as the following descriptions: T1: into (but not through) sub-

mucosa; T2: into (but not through) muscularis propria; T3: through muscularis propria into subserosa; T4a: penetration of the visceral peritoneal layer; T4b: penetration or adhesion to adjacent organs. The N means lymph node status as the following conditions: N1a: involvement of one regional node; N1b: involvement of 2-3 regional nodes; N2a: involvement of 4-6 nodes; N2b: involvement of ≥ 7 nodes. Stage III colon cancer means that colon cancer with lymph nodal involvement regardless of the depth (T1-4) of tumor penetration. The substage of stage III colon cancer are divided into IIIA (T1/2 with N1 or T1N2a), IIIB (T3-4a/N1; T2-3/N2a; T1-2/N2b) and IIIC (T4a/N2a; T3-4a/N2b; T4b/N1-2). All blood samples were obtained on admission to surgery.

Definitions for high CEA and high LNR

A high preoperative s-CEA level is associated with poor prognosis.[15] Defining a high s-CEA level and high metastatic LNR was essential for this study. An elevated s-CEA level of > 5 ng/mL at the new diagnosis of colorectal cancer is widely accepted. Some interfering factors, including hepatic and biliary dysfunction, tumor differentiation in colorectal cancer, and smoking, can influence s-CEA serum data.[16,17] Fukuda reported that s-CEA levels were significantly higher among smokers (3.11 ± 1.8 ng/mL) than among non-smokers (2.14 ± 1.8 ng/mL). In the present study, we considered a s-CEA level of > 5 ng/mL as abnormal data.

As opposed to s-CEA levels, no recognized standard definition exists for a "high" LNR. Increased LNR is associated with decreased OS and DFS. The cut-off value for defining LNRs are quite different in previous studies, and stratified methods are not consistent (such as Mean, Medium, Quartiles, ROC curve analysis, Log rank analysis). In addition, the cut-off values vary in different studies or populations even under similar stratified method. Lymph node ratios from 0.1 to 0.4 are effective predictors of 5-year OS & DFS.[18,19] In one meta-analysis study, cut-off of less than 0.2 is examined in a single cut-off stratifying system with significant statistical power with little heterogeneity.[20] Also in the same study, the two cut-off values studies subdividing the patients into low risk, moderate risk, and high-risk LNR groups, have the highest pooled HR of 3.27 on OS and DFS.

Not only there is no unanimously agreed cut-off value for Lymph node ratio, but also there is no conclusion on how many cut-off values to take; there is one study that directly take four cut-off values from 0 to 1 and divide them into five equal parts, such as (Ng, 2009) (0-0.19, 0.2-0.39, 0.4-0.59, 0.6-0.79, 0.8-1);[43] another one divided the research sample into four equal quartiles (Hong, 2011) (< 0.037; 0.037-0.0723; 0.0723-0.1638; > 0.1638).[44] However, studies with many cut-off value groups may not necessarily have significant differences between each group.

According to (Lee, 2012) research,[19] they took a single cut-off value (0.05, 0.1, 0.15, 0.2, 0.25, 0.3, 0.35, 0.4) and conducted separate analyzes with overall survival (OS) or disease free survival (DFS). It showed any one from 0.1 to 0.4 will have significant significance as the cut off value, but 0.05; at the same time, in order to balance the number of people in each group, this article finally take two cut-off value, 0.15 and 0.3 (the number of people in the three groups was 80:44:30), and there are still significant difference in the correlation between OS and DFS under multiple variables; in addition, an interesting finding was obtained that patients with rectal cancer received neoadjuvant therapy, the OS and DFS of the ypN1 + LNR > 0.3 group were approximately equal to or slightly worse than those of the ypN2 + LNR 0.16-0.3 group. For further balance the case number between three groups, we choose two cut off values of 0.1 and 0.3 (the number of people in the three groups is 1080: 830:295).

Finally, we combined preoperative s-CEA levels and LNR groups to divide six subgroups with stage III colon cancer: G1 (LNR1 [0.3-1.0] with s-CEA ≥ 5), G2 (LNR1 [0.3-1.0] with s-CEA < 5), G3 (LNR2 [0.1-0.29] with s-CEA ≥ 5), G4 (LNR2 [0.1-0.29] with s-CEA < 5), G5 (LNR3 [< 0.1] with s-CEA ≥ 5), and G6 (LNR3 [< 0.1] with s-CEA < 5).

Statistical analysis

Bivariate associations between categorical vari-

ables were assessed using Pearson's chi-squared test. Significant risk factors associated with cancer relapse event were determined using logistic regression. Differences in OS were estimated using the Kaplan-Meier method, and a comparison was performed using a log-rank test. The primary outcome was the difference in 5-year OS between the six subgroups, and the secondary outcome was 5-year RFS. OS was defined as the interval between the date of cancer diagnosis and the time of death from any cause. The RFS was the length of time after curative surgery ended that the patient survived without any cancer relapse. The Cox regression model was used for multivariate analysis to compensate for confounding factors. All statistical analyses were performed using SPSS version 19 (SPSS, Chicago, IL, USA). All p values were two-tailed, and $p < 0.05$ was considered statistically significant.

Results

Patient demographics

Among the 2205 patients, 869 patients (39.4%) had proximal colon cancer (cecum, ascending colon, liver flexure, and transverse colon), and 1336 patients (60.6%) had distal colon cancer (splenic flexure, descending colon and sigmoid colon). The mean follow-up period of the study patients was 64.5 months, and the maximal follow-up was 154 months. Adenocarcinoma was the most common histology type (91.1%). The mean age was 62.7 years (range: 22-99 years, standard deviation: 13.4). Approximately 29% of patients had abnormal preoperative s-CEA levels, and the mean s-CEA level of the cohort was 9.8 ng/mL (range: 0.5-270.0, standard deviation: 21.7). Moreover, 90% of patients had a yield of at least 12 lymph nodes, and the mean number of lymph nodes examined was 29.4 (range: 2-102, standard deviation: 16.6). The mean metastatic LNR of all patients was 0.15 (range: 0.01-1.0). Other categorical variables and their relative 5-year OS and RFS are displayed in Table 1. In the log-rank test, statistical survival differences were list for sex, age, cancer differentiation, pretreatment s-CEA level, the subgroup of stage III colon cancer, LNR, and postoperative adjuvant chemotherapy. Both s-CEA level and three different LNR groups were components for our target factor, and they were significantly associated with patient's survival. In logistic regression analysis, s-CEA level, LNR level and their combinations all were significantly associated with the event in colon cancer relapse (Table 2).

Survival

In the present study, the LNR and s-CEA combinations were possible to reflect the severity of stage III colon cancer. In a survival analysis using the Kaplan-Meier method, G1 demonstrated the worst 5-year OS and 5-year RFS, and G6 demonstrated the best 5-year OS and 5-year RFS (Fig. 1 and Fig. 2). However, G2 had significantly better 5-year RFS even their LNR was higher than G3 (60.0% vs. 48.4%, p = .010; Fig. 2). G2 exhibited a trend to better 5-year OS than G3 (63.3% vs. 57.0%, p = .144; Fig. 1). Similar statistical differences in survival were also observed between G4 and G5 for both OS (76.6% vs. 69.8%, p = .006; Fig. 1) and RFS (72.1% vs. 64.3%, p = .016; Fig. 2). Moreover, G2 and G5 with very different LNR demonstrated no differences in either RFS (p = .339, Fig. 2) or OS (p = .113, Fig. 1).

According to the best and the worst survival findings in G6 and G1, we further analyzed the differences in continuous variables between G2 and G3 and between G4 and G5. The mean s-CEA level and mean number of examined lymph node were significantly higher in G3 and G5 than those in G2 and G4 ($p <$ .001). The mean number of metastatic lymph nodes and mean LNR were higher in G2 and G4 than those in G3 and G5 ($p <$ .001) (Table 3). Regarding the cancer stage of the four subgroups, G2 and G4 had more cases of stage IIIC colon cancers (70.4% and 24%) than G3 and G5 (35.3% and 6.2%), respectively (Table 4). The percentage of colon cancer with poorly differentiated tumors was significantly higher in G2 than in G3 (17.6% vs. 9.2%, p = .036). However, the percentage of adjuvant chemotherapy was also higher in G2 than in G3 (84.5% vs. 75.7%, p = .025) and was likely a confounder for better RFS and OS in G2.

Because many confounders were present in the

Table 1. Clinicopathological characteristics and log-rank test results for influence of categorical variables on survival

Variables	Patients (n = 2205, %)	5-y OS (%)	*p*-value	5-y RFS (%)	*p*-value
Sex			0.012		0.036
Female	1093, 49.6%	75.4%		70.7%	
Male	1112, 50.4%	71.9%		66.0%	
Age			< 0.001		< 0.001
< 50 y/o	356, 16.4%	80.0%		72.1%	
50-64 y/o	816, 36.9%	80.0%		70.1%	
65-79 y/o	816, 36.9%	70.9%		67.6%	
≥ 80 y/o	217, 9.9%	48.4%		57.4%	
Tumor locations			0.028		0.076
Proximal colon	869, 39.4%	69.7%		66.1%	
Cecum	133, 6.0%				
Ascending	423, 19.2%				
Transverse	313,14.2%				
Distal colon	1336, 60.6%	76.1%		69.8%	
Splenic flexure	53, 2.4%				
Descending	234, 10.6%				
Sigmoid	1049, 47.6%				
HT			0.033		0.283
Adenocarcinoma	2008, 91.1%	74.3%		68.7%	
SR cell	26, 1.2%	51.0%		52.1%	
Mucinous	171, 7.8%	69.0%		65.0%	
HG, differentiation			0.004		< 0.001
Well	178, 8.1%	80.5%		77.6%	
Moderate	1788, 81.1%	73.7%		68.2%	
Poorly	239, 10.8%	67.0%		61.6%	
s-CEA			< 0.001		< 0.001
≥ 5 ng/mL	639, 29.0%	62.1%		53.5%	
< 5 ng/mL	1566, 71.0%	78.3%		74.3%	
ELN			0.012		0.115
≥ 12 nodes	1988, 90.2%	74.1%		69.0%	
< 12 nodes	217, 9.8%	69.5%		62.8%	
Pathology stage			< 0.001		< 0.001
Stage IIIA	192, 8.7%	91.3%		89.7%	
Stage IIIB	1522, 69.0%	75.8%		71.3%	
Stage IIIC	491, 22.3%	60.0%		50.8%	
LNR			< 0.001		< 0.001
LNR1: 0.3-1.0	295, 13.4%	58.8%		51.3%	
LNR2: 0.1-0.29	830, 37.6%	71.2%		65.3%	
LNR3: < 0.1	1080, 49.0%	79.6%		75.4%	
Adjuvant therapy*			< 0.001		< 0.001
ADT	1702, 77.2%	77.5%		70.2%	
OBS	410, 18.6%	57.3%		60.4%	

*: missing data, 93 patients (4.2%).

OS: overall survival; RFS: relapse-free survival; HT: histology type; SR cell: Signet ring cell carcinoma; HG: histology grade; s-CEA: serum carcinoembryonic antigen; ELN: examined lymph node; LNR: the ratio of metastatic nodes to all examined lymph nodes; ADT: adjuvant therapy after surgery; OBS: observation after surgery.

cohort, a multivariate Cox regression model was used to identify independent factors for OS and RFS, such as sex, age at diagnosis, tumor location, histology, and grade, examined lymph node, substages of stage III

Table 2. The association between s-CEA and relapse risk/LNR and relapse risk/LNR plus s-CEA and relapse risk from logistic regression analysis

Target factor	OR (95% CI)	*p* value
s-CEA		
≥ 5 ng/mL	1	
< 5 ng/mL	0.402 (0.331-0.489)	< 0.001
LNR		
LNR 1	1	
LNR 2	0.588 (0.447-0.774)	< 0.001
LNR 3	0.333 (0.254-0.438)	< 0.001
LNR plus s-CEA Subgroups		
G1	1	
G2	0.306 (0.182-0.512)	< 0.001
G3	0.520 (0.315-0.858)	0.011
G4	0.189 (0.119-0.302)	< 0.001
G5	0.246 (0.150-0.402)	< 0.001
G6	0.118 (0.074-0.188)	< 0.001

OR (95% CI): odds ratio 95% confidence interval; s-CEA: serum carcinoembryonic; RFS: relapse-free survival; LNR: the ratio of metastatic nodes to all examined lymph nodes; LNR 1: 0.3-1.0; LNR 2: 0.1-0.29; LNR 3: < 0.1; G1: LNR 1 (0.3-1.0) + s-CEA (≥ 5); G2: LNR 1 (0.3-1.0) + s-CEA (< 5); G3: LNR 2 (0.1-0.29) + s-CEA (≥ 5); G4: LNR 2 (0.1-0.29) + s-CEA (< 5); G5: LNR 3 (< 0.1) + s-CEA (≥ 5); G6: LNR 3 (< 0.1) + s-CEA (< 5).

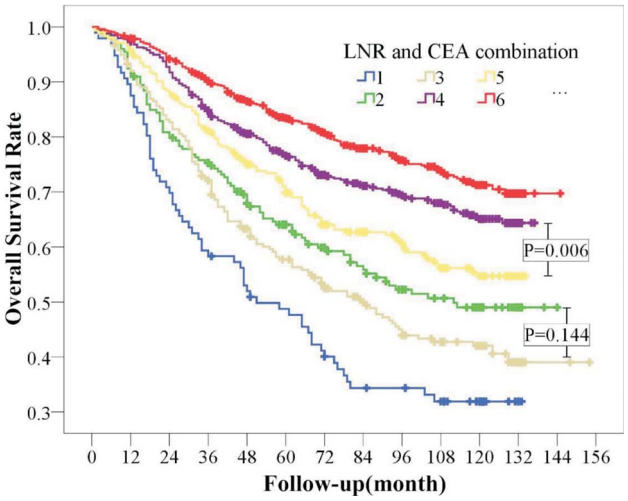

Fig. 1. In OS analysis, G1 had the worst survival and G6 had the best survival; G2 had a trend to better OS than G3 even G2 had more poor prognostic factors; G4 also had significant better OS than G5 even G5 had lower LNR than G4. The G2 and G5 with very different LNR level demonstrated no differences in their OS. G1: LNR1 (0.3-1.0) and CEA (≥ 5) (Blue line); G2: LNR1 (0.3-1.0) and CEA (< 5) (Green line); G3: LNR2 (0.1-0.29) and CEA (≥ 5) (Grey line); G4: LNR2 (0.1-0.29) and CEA (< 5) (Purple line); G5: LNR3 (< 0.1) and CEA (≥ 5) (Yellow line); G6: LNR3 (< 0.1) and CEA (< 5) (Red line).

colon cancer, and G1-G6 groups (Table 5). Several clinicopathological characteristics were identified as independent prognostic factors in the analysis. For OS, these independent, positive prognostic factors included female gender; age younger than 65 years; distal colon cancer; non-signet ring cell type; stage IIIA colon cancer; administration of adjuvant chemotherapy; and subgroups G2, G4, G5, and G6. For RFS, the independent negative prognostic factors were male gender; stage IIIB and IIIC colon cancer; no administration of adjuvant chemotherapy; and subgroups G1 and G3.

Discussion

In the TNM cancer staging system, the major difference between stages I/II and III colorectal cancer is the presence of lymph node metastasis in stage III. When lymph node metastasis occurs, colorectal cancer is usually considered more severe and advanced status. Generally, the pathological stage is a strong predictor for colorectal cancer patient survival. In addition to stage IV, stages IIIC which is defined as high-

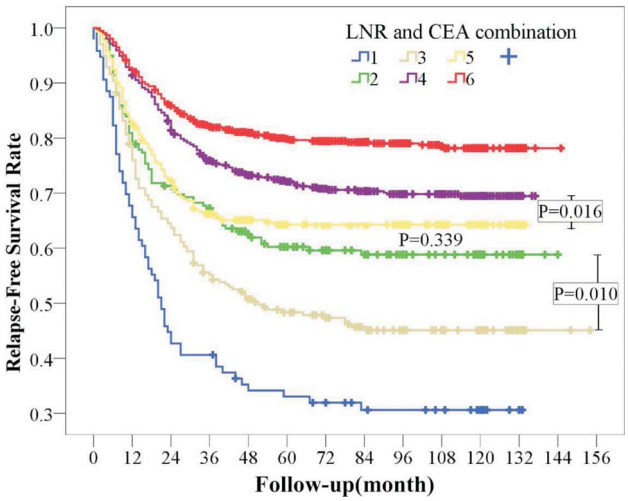

Fig. 2. In RFS analysis, G1 had the highest relapse risk and G6 had the lowest relapse risk; G2 had better RFS than G3 even G2 had more poorly prognostic factors; G4 also had significant better RFS than G5 even G5 had lower LNR than G4. Moreover, G2 and G5 with very different LNR level demonstrated no differences in their RFS.

Table 3. Analysis of variance results on different combinations of LNR and s-CEA levels

	ELN (Mean/SD)	*p*	PLN (Mean/SD)	*p*	LNR (Mean/SD)	*p*
G1, n = 96	19.7/11.9		9.5/5.9		0.50/0.17	
G2, n = 199	20.1/11.7	< 0.001	9.2/5.8	< 0.001	0.48/0.17	< 0.001
G3, n = 238	27.2/15.6		4.4/2.5		0.17/0.06	
G4, n = 592	24.4/13.6	< 0.001	3.9/2.4	< 0.001	0.16/0.05	< 0.001
G5, n = 305	34.9/17.3		1.6/1.0		0.05/0.02	
G6, n = 775	35.3/17.2		1.6/0.9		0.05/0.02	
	Age (Mean/SD)	*p*	s-CEA (Mean/SD)	*p*		
G1, n = 96	64.8/13.0		32.4/41.3			
G2, n = 199	63.4/13.8	0.605	2.8/1.6	< 0.001		
G3, n = 238	63.2/14.2		28.3/38.2			
G4, n = 592	62.1/13.5	0.439	2.7/1.5	< 0.001		
G5, n = 305	64.4/12.9		25.1/28.3			
G6, n = 775	61.9/13.2		2.5/1.5			

s-CEA: serum carcinoembryonic antigen; ELN: examined lymph node; LNR: the ratio of metastatic to examined lymph nodes; PLN: metastatic lymph node; SD: standard deviation.
G1: LNR1 (0.3-1.0) and s-CEA (≥ 5) (Blue line in figure). G2: LNR1 (0.3-1.0) and s-CEA (< 5) (Green line in figure).
G3: LNR2 (0.1-0.29) and s-CEA (≥ 5) (Grey line in figure). G4: LNR2 (0.1-0.29) and s-CEA (< 5) (Purple line in figure).
G5: LNR3 (< 0.1) and s-CEA (≥ 5) (Yellow line in figure). G6: LNR3 (< 0.1) and s-CEA (< 5) (Red line in figure).

Table 4. Statistical differences between combinations of LNR and CEA levels

	Stage IIIA (n = 192)	Stage IIIB (n = 1522)	Stage IIIC (n = 491)	*p*-value	ELN ≥ 12 (n = 1988)	ELN < 12 (n = 217)	*p*-value
G1, n = 96	0	19	77		69	27	
%	0.0%	19.8%	80.2%		71.9%	28.1%	
G2, n = 199	2	57	140	< 0.001	145	54	< 0.001
%	1.0%	28.6%	70.4%		72.9%	27.1%	
G3, n = 238	3	151	84		207	31	
%	1.3%	63.4%	35.3%		87.0%	13.0%	
G4, n = 592	57	393	142	< 0.001	502	90	< 0.001
%	9.6%	66.4%	24.0%		84.8%	15.2%	
G5, n = 305	15	271	19		301	4	
%	4.9%	88.9%	6.2%		98.7%	1.3%	
G6, n = 775	115	631	29		764	11	
%	14.8%	81.4%	3.7%		98.6%	1.4%	
	HG 1 (n = 178)	HG 2 (n = 1788)	HG 3 (n = 239)	*p*-value	ADT (n = 1702)	OBS (n = 410)	*p*-value
G1, n = 96	2	75	19		78	15	
%	2.1%	78.1%	19.8%		83.9%	16.1%	
G2, n = 199	11	153	35	0.036	163	30	0.025
%	5.5%	76.9%	17.6%		84.5%	15.5%	
G3, n = 238	14	202	22		174	56	
%	5.9%	84.9%	9.2%		75.7%	24.3%	
G4, n = 592	48	481	61	0.997	460	109	0.626
%	8.1%	81.5%	10.3%		80.8%	19.2%	
G5, n = 305	25	248	32		228	59	
%	8.2%	81.3%	10.5%		79.4%	20.6%	
G6, n = 775	78	626	70		608	132	
%	10.1%	80.9%	9.0%		82.2%	17.8%	

LNR: the ratio of metastatic nodes to examined lymph nodes; ELN: examined lymph node; ADT: adjuvant therapy after surgery; OBS: observation after surgery; HG 1: well-differentiated; HG 2: moderate differentiated; HG 3: poorly differentiated.
G1: LNR1 (0.3-1.0) and s-CEA (≥5) (Blue line in figure). G2: LNR1 (0.3-1.0) and s-CEA (< 5) (Green line in figure).
G3: LNR2 (0.1-0.29) and s-CEA (≥ 5)(Grey line in figure). G4: LNR2 (0.1-0.29) and s-CEA (< 5) (Purple line in figure).
G5: LNR3 (< 0.1) and s-CEA (≥ 5) (Yellow line in figure). G6: LNR3 (< 0.1) and s-CEA (< 5) (Red line in figure).

Table 5. Multivariate Cox regression for OS and RFS of stage III colon cancer

Variables	HR (95% CI) for OS	*p* value	HR (95% CI) for RFS	*p* value
Sex				
Female	1		1	
Male	1.258 (1.089-1.453)	0.002	1.226 (1.054-1.426)	0.008
Age				
< 50 y/o	1		1	
50-64 y/o	1.144 (0.889-1.471)	0.295	1.170 (0.923-1.483)	0.194
65-79 y/o	1.759 (1.385-2.233)	< 0.001	1.237 (0.979-1.565)	0.075
≥ 80 y/o	3.016 (2.281-3.988)	< 0.001	1.389 (1.023-1.885)	0.035
Tumor locations				
Proximal colon	1		1	
Distal colon	0.846 (0.725-0.988)	0.034	0.876 (0.745-1.030)	0.108
Histology type				
Adenocarcinoma	1			
SR cell	2.130 (1.215-3.734)	0.008	1.275 (0.693-2.346)	0.435
Mucinous	1.020 (0.771-1.349)	0.889	1.027 (0.773-1.364)	0.856
HG, differentiation				
Well	1			
Moderate	1.159 (0.864-1.555)	0.325	1.294 (0.933-1.793)	0.122
Poorly	1.265 (0.878-1.823)	0.206	1.428 (0.965-2.113)	0.075
ELN				
≥ 12 nodes	1		1	
< 12 nodes	1.089 (0.860-1.380)	0.479	1.133 (0.877-1.463)	0.338
Pathology stage				
Stage IIIA	1		1	
Stage IIIB	1.736 (1.208-2.494)	0.003	2.784 (1.725-4.493)	< 0.001
Stage IIIC	2.410 (1.603-3.623)	< 0.001	4.404 (2.637-7.355)	< 0.001
LNR with CEA				
G1	1		1	
G2	0.591 (0.427-0.819)	0.002	0.449 (0.322-0.627)	< 0.001
G3	0.799 (0.579-1.103)	0.173	0.777 (0.563-1.072)	0.124
G4	0.431 (0.315-0.589)	< 0.001	0.384 (0.281-0.526)	< 0.001
G5	0.592 (0.416-0.842)	0.004	0.560 (0.390-0.803)	0.002
G6	0.359 (0.255-0.505)	< 0.001	0.324 (0.229-0.459)	< 0.001
Post operation				
ADT	1		1	
OBS	1.997 (1.686-2.365)	< 0.001	1.489 (1.230-1.803)	< 0.001

HR (95% CI): hazard ratio and 95% confidence interval; OS: overall survival; RFS: relapse-free survival; HT: histology type; SR cell: Signet ring cell carcinoma; HG: histology grade; ELN: examined lymph node; LNR: the ratio of metastatic nodes to all examined lymph nodes; ADT: adjuvant therapy after surgery; OBS: observation after surgery.
G1: LNR1 (0.3-1.0) + s-CEA (≥ 5). G2: LNR1 (0.3-1.0) + s-CEA (< 5). G3: LNR2 (0.1-0.29) + s-CEA (≥ 5).
G4: LNR2 (0.1-0.29) + s-CEA (< 5). G5: LNR3 (< 0.1) + s-CEA (≥ 5); G6: LNR3 (< 0.1) + s-CEA (< 5).

risk stage III colon cancer have the worst survival rates of 37%.[21] The stage IIIC colon cancer is composed of a greater number of metastatic lymph nodes and its' high LNR is partially associated with apical lymph node metastasis which was an independent factor for OS and RFS. However, the apical lymph node metastasis only accounted 8.6% of stage IIIC colon cancer in Ishii's report.[22] Therefore, we considered s-CEA, another factor for combination in the present study, to evaluate prognosis of stage III colon cancer, especially for stage IIIB and IIIC disease. In 2006, a similar study focused on prognosis of stage IIIB and IIIC colon cancer was reported by Johnson et al. They supported the findings regarding the relationship of

number of negative lymph nodes and survival in stage III colon cancer.[23] Both number of negative lymph nodes and number of positive lymph nodes demonstrated an independent effect in patients with stage IIIB and IIIC colon cancer. As the number of negative lymph nodes identified increased, patient's survival also improved. However, in their study, the stage IIIA colon cancer still had the best prognosis, and no association was noted between their target-prognostic factor and survival.

Furthermore, the LNR is the combination of positive number and total number of examined lymph nodes. In many studies, the LNR is considered more reliable and superior to the TNM node (TNM-N) stage as a prognostic factor for stage III colorectal cancer.[24-27] In one meta-analysis, the reported cut off values for the LNR varied widely between 5% and 25% (mean: 13.2%, median: 11.5%), and a higher LNR resulted in worse survival.[28] During surgical resection, the metastatic lymph nodes are removed; the nodes can be removed more easily when they are closer to the colon cancer location. Therefore, the distribution of metastatic lymph nodes is critical for the prognosis of colon cancer. However, the TNM-N stage is dependent on the number of metastatic nodes. The LNR is also based on the number of metastatic nodes and the total yield of lymph nodes. In the *Japanese General Rules for Clinical and Pathologic Studies on Cancer of the Colon, Rectum, and Anus*, node metastases are classified into four grades based on their distribution: n (−), n1-pericolic nodes (+), n2-intermediate nodes (+), and n3-nodes at the root of major vessels (+).[29] Kobayashi et al. reported that metastatic lymph nodes on major vessels or at the root of major vessels are poor prognostic factors that are independent of the TNM-N2 stage.[30] Lymph node metastasis at the apical site poses a risk to patients with stage III colon cancer because patients with node metastasis along the inferior mesenteric artery exhibit a high incidence of tumor relapse. Such different location of node metastases may not really reflect in LNR. These distributions of metastatic lymph nodes probably interfered and caused the differences in RFS and OS between G2 and G3 or might have led to the similarities in RFS between G2 and G5.

The G1 and G6 in the present study had extreme LNRs, and the significant differences in RFS or OS were equally extreme. Regarding the high LNR associated with poor prognosis, the trend of survival paradox was found between G2 and G3; it was also present between G4 and G5. G2 had a high LNR like G1, but RFS and OS in G2 were better than those in G1 and G3. G2 also demonstrated many negative factors, such as a lower lymph node yield, inadequate lymph node harvests (< 12 lymph nodes), more metastatic lymph nodes, poorly differentiated adenocarcinoma, and more cases of stage IIIC colon cancer. The lower mean s-CEA level and higher administration rate of postoperative adjuvant chemotherapy were the only two positive factors in G2. To this extent, is the survival impact from LNR and s-CEA level equal for stage III colon cancer? Another interesting finding was that the RFS of G2 and G5 did not significantly differ. Compared with G5, G2 was exhibited more poor prognostic factors. Therefore, the preoperative s-CEA level was probably a key predictor of prognostic differences between G2 and G3 and between G2 and G5.

The s-CEA is secreted by many solid tumors, including 90% of colorectal cancers.[7] In many published reports, regarding biological functions, s-CEA is involved in colon cancer cell adhesion, innate immunity, tumor cell attachment to metastatic organ, and disease progression.[31-33] The s-CEA level probably increased with the CEA expression in proliferative colorectal cancer. A high preoperative s-CEA level related to the tumor burden and the biological behavior of tumors has been identified as an independent prognostic factor for OS and disease-free survival in both stage II and III colorectal cancer. According to the early days studies for stage III colorectal cancer, the argument for different prognostic determinant was the association between abnormal s-CEA level and number of metastatic lymph nodes. A study by the Gastrointestinal Tumor Study Group concluded that s-CEA > 5 ng/mL was associated with cancer relapse risk for colorectal cancer with one to four metastatic lymph nodes.[34] Moertal, et al. studied 272 patients with curative surgery for colorectal cancer at Mayo clinic. The s-CEA level showed an independent prognostic determinant only in patients with four or more metastatic lymph

nodes.[35] In 2011, Thirunavukarasu et al. proposed including C-stage colon cancer in the conventional TNM staging system.[13] They observed that stage I colon cancer with abnormal s-CEA levels had a worse prognosis than stage IIIA colon cancer with normal s-CEA levels. Similarly, patients with TNM-N1 cancer stage (1-3 lymph node metastases) with abnormal s-CEA levels had a higher risk of overall mortality than those with TNM-N2a cancer stage (4-6 metastatic lymph nodes) with normal s-CEA levels. Abnormal s-CEA level was a stronger factor for poor prognosis than the TNM-N1 and N2a stages (except for the N2b stage in their study).

Our result like Thirunavukarasu's observation showed that G2 and G4 respectively had better OS than G3 and G5 (G2 and G4 had higher LNRs but normal s-CEA levels; by contrast, G3 and G5 had lower LNRs and abnormal s-CEA level). Regarding RFS, G2 and G5 had very different LNRs and s-CEA levels but had a similar survival curve. Zhang et al. ever suggested the optimal minimal number of examined lymph nodes for colon cancer patients with abnormal s-CEA level.[36] The 18-node standard could be regarded as an alternative to 12-node standard recommended by the ASCO and NCCN guidelines. In our study, 98.7% of G5 patients who had abnormal s-CEA reached the 12-node standard recommended by the ASCO and NCCN guidelines. However, 85.2% of G5 patients still met the 18-node standard recommended by Zhang's report and this percentage was higher than Zhang's data base. The high s-CEA levels of G5 probably neutralize the survival benefit resulting from a lower LNR because the preoperative high s-CEA level is partially related to the tumor burden and possible occult metastasis. The abnormal CEA level was a decisive survival factor in all six subgroups in our analysis.

In our cohort, 90.2% of patients had lymph node yields of ≥ 12, and 77.2% of them received postoperative 5-fluorouracil-based adjuvant chemotherapy. The percentage of adequate lymph node yield and the administration of adjuvant chemotherapy were comparable to contemporary data from specialist centers and were also not lower than those reports from national cohorts, including the Surveillance, Epidemiology, and End Results program or Medicare-linked databases.[37-39] The reasonable rates of adequate lymph node yield and adjuvant chemotherapy administration could decrease the confounding effects in our study. However, in the study, 22.8% of patients (18.6% without adjuvant chemotherapy and 4.2% were missing data) had no data to prove the administration of adjuvant chemotherapy. In fact, it still was a deviation from standardized guidelines. Therefore, we further analyzed the RFS between the six subgroups with and without postoperative adjuvant chemotherapy. In pairwise comparison for RFS between G1-G6 with or without adjuvant chemotherapy, the significant RFS differences between G1-G6 were noted in those with adjuvant chemotherapy. However, the survival difference was neutralized when patients did not receive adjuvant chemotherapy (Table 6).

Findings of our research present eminent signifi-

Table 6. Pairwise comparison for RFS between G1-G6 with adjuvant chemotherapy

Groups/*p* value	G1	G2	G3	G4	G5	G6
G1		< 0.000	0.026	< 0.000	< 0.000	< 0.000
G2	< 0.000		0.016	0.004	0.456	< 0.000
G3	0.026	0.016		< 0.000	0.001	< 0.000
G4	< 0.000	0.004	< 0.000		0.029	0.007
G5	< 0.000	0.456	0.001	0.029		< 0.000
G6	< 0.000	< 0.000	< 0.000	0.007	< 0.000	

Pairwise comparison for RFS between G1-G6 without adjuvant chemotherapy

Groups/*p* value	G1	G2	G3	G4	G5	G6
G1		0.003	0.006	< 0.000	0.001	< 0.000
G2	0.003		0.411	0.135	0.815	0.037
G3	0.006	0.411		0.002	0.231	< 0.000
G4	< 0.000	0.135	0.002		0.131	0.409
G5	0.001	0.815	0.231	0.131		0.024
G6	< 0.000	0.037	< 0.000	0.409	0.024	

cance in our clinical practice. After the LNR and s-CEA combination with six subgroups formation for stage III colon cancer, except G1, the other five groups all included stage IIIA, IIIB and IIIC disease. Our results demonstrated the remarkable value from the combination of s-CEA and LNR to predict prognosis of stage III colon cancer, especially for stage IIIB and IIIC colon cancer. Of the 2205 colon cancer patients enrolled, only 29% had elevated s-CEA, and the most patients had s-CEA < 5 ng/mL, including patients with poor tumor biology, patients with a high rate of positive lymph nodes, and patients with poor prognosis. In fact, nearly 70% of normal s-CEA patients still rely on the lymph node ratio to determine prognosis. However, in either the pairwise comparison for RFS between G2 and G3 or pairwise comparison for RFS between G2 and G5, we confirmed that the high s-CEA level had worse prognosis than the different LNR.

This study has some limitations. First, our study had a small sample size, used a retrospective study design, and collected data from a single center. Furthermore, the total of 2205 patients enrolled in the study spans a near period of 30 years. The level of diagnosis and treatment of colon cancer, especially in clinical diagnosis and treatment, has developed significantly, including advances in the level of clinicopathologic evaluation. For example, in the new era of complete mesocolon excision (CME), it may not be appropriate to mix colectomies performed over a period of more than 20 years. Postoperative adjuvant therapy for colon cancer has also made remarkable progress since 1995, and the adjuvant therapy strategy has also improved greatly after 30 years. We can't avoid the bias of patient selection within the exceedingly long-time span and a retrospective design. Second, no data were available for microsatellite instability high (MSI/dMMR) status, which is a key variable of stage II colorectal cancer. However, the lack of data was acceptable because the prognostic effect of MSI/dMMR status is controversial for patients with stage III colon cancer who have received postoperative adjuvant chemotherapy.[40-42] Third, tumor deposit data was not included in our study. Tumor deposit is a poor prognosis factor that N1c is isolated since AJCC 7th edition, but it could not be calculated into lymph node ratio according to the definition. Recently, there is new concept that the number of tumor deposit should be included into number of lymph node metastases, to improve the prognostic accuracy.[45] It is involving not only N1c, but all I-III stage with tumor deposits — just like other poor prognostic factor such as perineural invasion, or lymphovascular invasion, and further study is indicated. Finally, the treatment in this study was limited to surgical resection treatment; more detail surgical types, including CME concept, laparotomy, laparoscopy-assisted surgery, or robotic surgery, were not clear due to data resource limitations.

Conclusions

Based on the observations in our study, we recommended that the combination of s-CEA and the LNR comprehensively predicted the prognosis of stage III colon cancer. When the LNR was equal in stage III colon cancer, the preoperative s-CEA level played a decisive role in 5-year RFS and 5-year OS.

Ethics Statement

Appropriate approval for this observational study was obtained from the Institutional Review Board of the Chang Gung Medical Foundation (201701456B0).

Consent for Publication

Owing to retrospective nature of study design, the requirement for informed consent was waived by the board.

Data Availability Statement

Our raw data for the analysis of this study will be made available after anonymous information and all authors' agreement.

Competing Interests

The authors declare that they have no competing interests.

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Author Contribution

Ho and Hung have full access to all data of this study and take responsibility for the data integrity and analysis accuracy. Study concept and design: Kuo. Acquisition, analysis, and interpretation of data: Hung, You, Chin, and Kuo. Drafting of this manuscript: Chin, Hung, and Kuo. Critical revision of this manuscript: Chin and You. Statistical analysis: Chin and Kuo. Study supervision: Kuo. All authors contributed to the article and approved this submitted version.

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原　著

綜合轉移淋巴結比率與癌胚抗原指數與第三期結腸癌根治性手術預後的相關性

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目的　癌胚抗原指數 (CEA) 對結腸癌病患預後有影響，而轉移淋巴結比率 (LNR) 對結腸癌第三期病人手術預後也有顯著影響；透過分組比較找出預後較差病患，可提供臨床治療決策的參考。

方法　回溯性研究分析於 1995 年 1 月至 2016 年 12 月間，於長庚紀念醫院接受根治性手術病診斷第三期之結腸癌病人，共 2205 人。依照 CEA 及 LNR 分為六組，分析比較五年存活率 (OS) 及五年無復發存活率 (RFS)。

結果　六組裡，G1 的存活率 (OS & RFS) 最差，而 G6 最好；雖然 G2 相較 G3 有較高的 LNR、較不好的組織分化、較多的 IIIc 期病患，但 RFS 顯著較好。而 G2 與 G5 比較，雖然 CEA 與 LNR 完全不同，但 OS 或 RFS 並沒有顯著差異。綜合分析下，男性、IIIb and IIIc、沒有接受輔助化療、及高 CEA 的 G1 & G3 組都是預後不好的獨立因子。

結論　綜合 CEA 及 LNR 可以更完整將第三期病患分組，得到更準確的預後；而其中若 LNR 相近，CEA 對於 RFS 更關鍵。

關鍵詞　第三期大腸癌、癌胚抗原指數、轉移淋巴結比率、存活率、無復發存活率。