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Original Article

Exploration of the optimal lymph node count retrieved for patients with node-negative colonic mucinous cancer

Shifeng Teng[1*], Kai Xu[1*], Jun Yao[1*], Xianwen Zhang[1], Mingming Li[1], Yanyan Zhang[1], Weigang Zhang[1], Haolu Wang[2], Xiaowen Liang[2], Xinxing Li[1], Zhiqian Hu[1]

[1]*Department of General Surgery, Changzheng Hospital, The Second Military Medical University, Shanghai, China;* [2]*Therapeutics Research Centre, The University of Queensland Diamantina Institute, The University of Queensland, Translational Research Institute, Brisbane, Australia.* [*]*Equal contributors.*

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Abstract: This study aims to explore the effect of lymph node (LN) count retrieved on the survival of patients with node-negative colonic mucinous adenocarcinoma (MAC). All registered patients with colon cancer from the Surveillance, Epidemiology, and End Results Program (SEER) database were collected for analysis in this study. X-tile plots were used to find the optimal cutoff values of LN counts in MAC patients. Based on these numbers, patients were divided into high, middle and low risk subsets in terms of colon cause specific survival (CCSS). Chi-square (χ^2) test was applied to analyze the effect of LN count on CCSS. Chi-square (χ^2) test was applied to analyze the clinicopathologic parameters in different LN subgroups. Univariate survival analysis and multivariate Cox proportional hazards model were used to assess the risk factors affecting survival. A total of 17,280 patients with node-negative colonic MAC between 1988 and 2013 were included. Based on the LN count, all patients were stratified into high (1-7), middle (8-17), and low (>18) risk subsets, and their 5-year CCSS rates were 80.8%, 85.0% and 89.5%, respectively. We found that the LN counts of each subset was an independently prognostic factor using multivariate Cox analysis (HR=0.765, 95% CI=0.702-0.833; HR=0.518, 95% CI=0.465-0.577. P<0.001). Our study demonstrated that the LN count was an independent prognostic factor for MAC. The higher the LN counts retrieved, the longer the survival would be. The longest CCSS was observed in patients with more than 17 LNs.

Keywords: Lymph node, (LN), colon cancer, (CC), mucinous adenocarcinoma (MAC), colon cancer specific survival (CCSS)

Introduction

Colorectal cancer is the third most commonly diagnosed cancer in both men and women worldwide. In 2014, 135,430 cases of colorectal cancer was diagnosed in the United States [1]. Mucinous adenocarcinoma (MAC) is a distinct form of colorectal cancer found in 10-15% of patients [2, 3]. MAC differs from other types of colorectal cancer in terms of clinical and histopathological characteristics [4]. It has long been associated with an inferior response to treatment compared with adenocarcinoma. The debate concerning the prognostic implications of MAC in patients is ongoing and it is still considered an unfavourable and unfamiliar subtype of the disease [5-7].

The pathological TNM stage is used to make prognosis prediction and treatment plans for patients with colorectal cancer. The number of LNs retrieved is a fundamental parameter in most pathological staging systems. The American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) guideline have suggested that 12 regional LNs is the minimal number for colorectal cancer resection [8, 9]. However, colorectal cancer is a heterogeneous disease. The epidemiological, morphology, molecular characteristics are significantly different in pathological types [10-13]. The aim of this study was to assess the association between LN count and the survival of MAC patients, to investigate the prognosis value of LN count and other clinico-

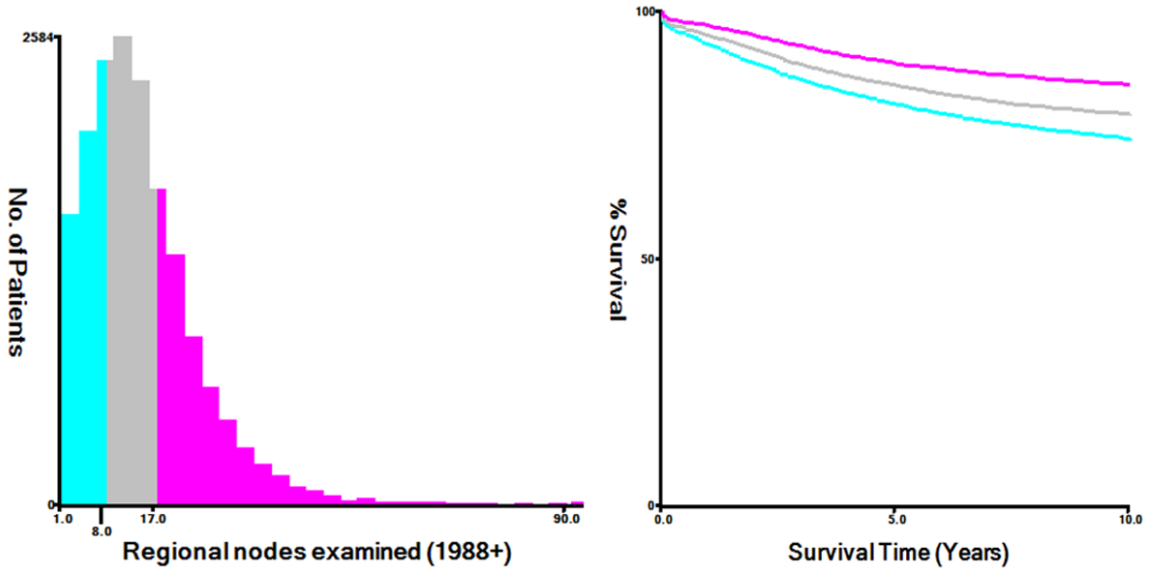

Figure 1. X-tile analysis of survival data from the SEER registry. X-tile analysis was performed using data from SEER database. The samples from patients with colon cancer was equally divided into three different sets. X-tile plots of the training sets are shown in the left panels, with plots of matched validation sets shown in the smaller inset. The optimal cut-point highlighted by the black circle in the left panels is shown on a histogram of the entire cohort (middle panels), and a Kaplan-Meier plot (right panels). *P* values were determined using the cutoff point defined in the training set and applying it to the validation set. **Figure 1** shows the optimal cutoff points for the lymph node negative patients (number of 8 and 17, χ^2=152.3636, P<0.001).

pathologic characteristics in patients without LN metastasis, and to find the optimal LN count should be retrieved.

Materials and methods

Ethics statement

The current study was based on the SEER database, which is an authoritative source of information on cancer incidence and survival in the United States. All relevant data were obtained from SEER. Requests for data access can be sent by following the instructions on the website (Surveillance Research Program, National Cancer Institute SEER*Stat software, www.seer.cancer.gov/seerstat; Version 8.3.2). Permission to access the research data files were obtained with the reference number 10263-Nov2015. The study contained no personal identifying information and required no informed consent. Anonymous patient's data were extracted from online SEER registries, which require no further institutional review approval prior to use.

Date selection

The SEER program has collected clinical data from 17 population-based cancer registries that represent approximately 30% of US population [14]. The SEER Stat software (SEER*Stat 8.3.2) was used to identify patients who were diagnosed with CC (C19.9/20.9) from 1988 to 2013. Patients who were diagnosed with MAC (8480/3 and 8481/3) were more than 18 years old, and have gone through surgical resection were included. Patients were excluded if he or she had more than one primary cancer, had LN metastasis, or had unknown cause of death or unknown survival records.

Age, gender, race, grade, tumor T stage, regional LN retrieval, demographic and clinicopathologic variable of included patients were analyzed in this study. The primary clinical characteristic of this study was CCSS. Data of patients who died from other causes or who were alive on the date of their last follow-up were censored. T stage classification was based on the criteria of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual (the 7th edition, 2010).

Statistical analyses

The LNs cutoff values were determined by using the X-tile program, which identified the cutoff value with the minimal *P* values from log-

Table 1. Univariate analysis of the influence of different LN count on CSS in node-negative MAC patients

Total NLNs	No.	3-year CCS	5-year CCS	Log rank χ^2 test	*P* value	Total NLNs	No.	3-year CCS	5-year CCS	Log rank χ^2 test	*P* value
<2	220	82.1	74.0	25.326	<0.001	<14	8706	87.5	82.9	101.424	<0.001
≥2	17060	89.6	85.5			≥14	8574	91.6	88.0		
<3	567	83.3	78.5	29.912	<0.001	<15	9529	87.6	83.0	109.650	<0.001
≥3	16713	89.7	85.6			≥15	7751	91.9	88.4		
<4	1057	84.0	79.7	26.777	<0.001	<16	10307	87.7	83.2	107.548	<0.001
≥4	16223	89.8	85.7			≥16	6937	92.2	88.7		
<5	1604	85.3	80.1	39.113	<0.001	<17	11049	87.8	83.4	103.564	<0.001
≥5	15676	89.9	85.9			≥17	6231	92.5	89.1		
<6	2245	85.8	80.7	52.154	<0.001	<18	11708	87.9	83.5	108.915	<0.001
≥6	15035	90.0	86.1			≥18	5572	92.9	89.4		
<7	2922	85.6	80.7	76.846	<0.001	<19	12276	88.1	83.7	103.201	<0.001
≥7	14358	90.3	86.3			≥19	5004	92.9	89.5		
<8	3669	85.7	80.8	91.003	<0.001	<20	12793	88.2	83.9	98.005	<0.001
≥8	13611	90.5	86.6			≥20	4487	93.1	89.7		
<9	4451	86.1	81.2	100.611	<0.001	<21	13310	88.3	84.1	87.172	<0.001
≥9	12829	90.7	86.9			≥21	3970	93.4	89.7		
<10	5251	86.3	81.6	109.119	<0.001	<22	13755	88.5	84.3	73.196	<0.001
≥10	12029	90.9	87.1			≥22	3525	93.4	89.6		
<11	6122	86.8	82.2	98.544	<0.001	<23	14169	88.6	84.5	63.079	<0.001
≥11	11158	91.0	87.2			≥23	3111	93.4	89.4		
<12	6927	87.0	82.4	108.656	<0.001	<24	14516	88.8	84.6	53.915	<0.001
≥12	10353	91.2	87.4			≥24	2764	93.1	89.4		
<13	7862	87.2	82.7	109.289	<0.001	<25	14829	88.8	84.7	48.737	<0.001
≥13	9418	91.4	87.7			≥25	2451	93.4	89.5		

rank χ^2 statistics for the categorical LNs in terms of CCSS [15, 16]. Baseline characteristics were compared using the χ^2 test for nominal variables. The actual survival rate was generated by using Kaplan-Meier analysis. The Cox proportional hazard regression model was used to identify the variables that could independently influence survival. Hazard ratios (HRs) and 95% confidence intervals were calculated, with an HR of <1.0 indicating survival benefit. All *P* values were two-sided. P<0.05 was considered statistically significant.

Results

Patient characteristics

From SEER database, we identified 17,280 patients with colon cancer in total including 7,641 males and 9,639 females diagnosed with MAC from 1988 to 2013. The median age at diagnosis was 73 years (range from 19 to 106 years old). The median survival time was 68 months.

Identification of the optimal cutoff values of LN

X-tile was used to determine the optimal LN cutoff values for CCSS. The maximal χ^2 log-rank value of 152.3636 was achieved when applying 8 and 17 as the cutoff values (**Figure 1**, P<0.001). All included MAC patients can be divided into three subgroups with significant differences in 5-year CCSS using 8 and 17 as the cutoff values.

To assess the influence of different LN count on CCSS we further analyzed the number of retrieved LN counts from 2 to 25. The 5-year CCSS was calculated for patients with N (cutoff point of LNs number) or more nodes and less than N nodes were calculated. With the LN count increased from 2 to 25, the 5-year CSS rate increased from 84.0% to 89.5%. After the number of 17, the survival rates were roughly equal (**Table 1**). In addition, sex (P=0.005), age (P<0.001), race (P=0.001), primary site (P< 0.001), tumor grade (P<0.001), and T stage (P<0.001) were different among three subgroups (**Table 2**).

Table 2. Demographic and characteristics of patients with node-negative MAC cancer

	LN subgroup							
	1-7		8-17		>17			
	N=3669		N=8039		N=5572			
	N	%	N	%	N	%	χ^2 Value	*P* Value
Sex							10.425	0.005
Male	1702	46.4	3543	44.1	2396	43.0		
Female	1967	53.6	4496	55.9	3176	57.0		
Age							206.859	<0.001
<60	539	14.7	1363	17.0	1408	25.3		
≥60	3130	85.3	6676	83.0	4164	74.7		
Race							18.947	0.001
White	3102	84.5	6888	85.7	4686	84.1		
Black	386	10.5	724	9.0	525	9.4		
Other	181	5.0	427	5.3	361	6.5		
Primary site							578.404	<0.001
Right colon	2266	61.8	6082	75.7	4611	82.8		
Left colon	1360	37.1	1807	22.5	871	15.6		
Colon NOS	43	1.2	150	1.9	90	1.6		
Grade							53.918	<0.001
High/Moderate	2822	76.9	6305	78.5	4408	79.1		
Poor/Anaplastic	489	13.3	1136	14.1	842	15.1		
Unknown	358	9.8	598	7.4	322	5.8		
T Stage							318.251	<0.001
T1	396	10.8	446	5.5	196	3.5		
T2	728	19.8	1412	17.6	768	13.8		
T3	2035	55.5	5122	63.7	3845	69.0		
T4	510	13.9	1059	13.2	763	13.7		

Identifying the survival risk factors in LN subsets

The clinicopathologic factors, including age (P<0.001), primary site (P<0.001), race (P= 0.006), tumor grade (P=0.004), T stage (P< 0.001), LNs (P<0.001) were correlated with survival by univariate analysis (**Table 3**). Multivariate Cox regression analysis revealed that age, primary site, grade, T stage and LN counts were independent prognostic factors of CCSS in MAC patients. LN counts (>18) indicated longer survival period (HR=0.518, 95% CI=0.465-0.577, P<0.001, **Table 3**).

Discussion

Colorectal cancer is a heterogeneous disease. Epidemiological, morphology, molecular characteristics alters amongst different pathological types, especially between MAC and non-MAC patients [17, 18]. As a rare histopathological sub-type of CC, MAC is characterized with prominent mucin production, and consisted about 3.9% to 19% in all types of colorectal cancer [19-22]. As previous studies reported, the MAC patients has worse prognosis than the non-MAC patients [20, 22, 23]. Therefore, it is necessary to develop specialized treatments for MAC with focus on the lymph node count retrieved.

According to Union for International Cancer Control (UICC)/American Joint Committee on Cancer (AJCC) system, a minimum of 12 LNs retrieved is required for tumor staging, and this LN count retrieved is also associated with a better outcome in patients after surgery [24, 25]. However, as an important pathological factor, the relationship between lymph count and prognosis still need to be studied. As previous studies reported, with the increase of tumor infiltration, MAC patients tend to have more LN metastasis [26]. Therefore, a sufficient number of LNs retrieved could improve the accuracy of TNM staging and patient's prognosis.

If the number of LN retrieved is insufficient, the TNM staging system could not make accurate survival prediction. Recent reports confirmed that a number of 12 LNs is baseline in CC patients. However, as a distinct form of colorectal cancer, the optimal LN count retrieved should be treated different for MAC patients.

In this study, we revealed that LN count was an independent prognostic factor for node negative colonic MAC. To find the optimal LN count retrieved, LN count from 2 to 25 was analyzed respectively. We found that the number of total

Table 3. Univariate and multivariate analyses of the survival of node-negative colonic MAC patients

Parameter	Characteristic	3-year CCS	5-year CCS	Univariate analysis		Multivariate analysis	
				Log rank χ^2 test	*P* value	HR (95% CI)	*P* value
Sex				0.369	0.544		NI
	Male	89.8	85.5				
	Female	89.2	85.2				
Age				162.145	<0.001		
	<60	94.1	90.3			Reference	
	≥60	88.4	84.2			1.779 (1.626-1.947)	<0.001
Primary site				78.447	<0.001		
	Right colon	90.0	86.4			Reference	
	Left colon	88.0	82.4			1.278 (1.203-1.375)	<0.001
	Colon NOS	81.7	74.3			1.741 (1.425-2.127)	<0.001
Race				10.160	0.006		
	White	89.3	85.4			Reference	
	Black	88.8	83.1			1.069 (0.969-1.181)	0.184
	Others	92.0	87.5			0.820 (0.713-0.943)	0.005
Grade				10.885	0.004		
	High/Moderate	89.7	85.7			Reference	
	Poor/Anaplastic	88.1	84.2			1.094 (1.006-1.189)	0.036
	Unkown	88.2	83.1			1.163 (1.046-1.293)	0.005
T Stage				777.370	<0.001		
	T1	96.2	94.4			Reference	
	T2	94.3	92.0			1.398 (1.138-1.717)	0.001
	T3	89.7	85.6			2.470 (2.049-2.976)	<0.001
	T4	78.4	70.8			5.002 (4.125-6.065)	<0.001
N0.of LNs				145.853	<0.001		
	1-7	85.7	80.8			Reference	
	8-17	89.1	85.0			0.765 (0.702-0.833)	<0.001
	>18	92.9	89.5			0.518 (0.465-0.577)	<0.001

NI: not included in the multivariate survival analysis.

LN evaluated was associated with CCSS in MAC patients. The more LNs retrieved, the better prognosis would be. There was a 15.1% increase in survival rate in 5 years patients with ≥17 LN retrieved compared to those with <2 LN retrieved, and a 1.7% increase compared to those with ≥12 LN retrieved. After the number of 17, the survival rates were roughly equal. Therefore, the number of 17 is the minimal number of LN should be retrieved. This may explained the phenomenon of lymphatic micrometastasis. As a key etiology of recurrence and metastasis after resection of CC [27, 28], lymphatic micrometastasis is taking more and more attentions in current clinic practice. Because LN micrometastasis is common in nodes which have a size from 0.2 mm to 2.0 mm, it is very difficult to find lymphatic micrometastasis during the operation. Therefore, increasing the retrieve LNs can reduce the residual micrometastases, and improve the prognosis of MAC.

In this study, we found that LN count retrieved was associated with the survivals in node-negative colonic MAC patients. Patients diagnosed with MAC could decrease their risk of death by examine additional LN (up to 17 LN). It provided more accurate prognostic information than the traditional 12 lymph nodes examination for MAC patients. Therefore, in the current clinical practice, if the preoperative pathological examination confirms colonic MAC, surgeons are suggested to increase the lymph node dissected scope, including ileocolic vascular lymph nodes, superior mesenteric vein surface lymph nodes. If tumor resection showed high T stage,

and LN dissection number is less than 17, postoperative chemotherapy may take into consideration. This additional indicator might produce substantial improvements in the quality of postoperative care and prognosis for colonic MAC patients.

This study has several limitations. Firstly, the SEER database does not include details of therapeutic information such as chemotherapy, targeted therapy, immunotherapy, metastasis or recurrence, which may also affect patients' prognosis. Secondly, operative approaches, surgeons and pathologists would affect the detective rate of total LN counts, which was not recorded in SEER [10]. Despite these limitations, SEER remains a valuable resource to analyze trends and patterns in patient characteristics, tumor features, cancer treatments, and survival outcomes

In conclusion, our study demonstrated that the LN count was an independent prognostic factor for MAC. The higher the LN counts retrieved, the longer the survival would be. The longest CCSS was observed in patients with more than 17 LNs.

Address correspondence to: Xinxing Li and Zhiqian Hu, Department of General Surgery, Changzheng Hospital, The Second Military Medical University, 415 S. Fengyang Road, Shanghai 200003, China. Tel: +86 21 81885591; Fax: +86 21 63520020; E-mail: xingxin123456@sina.com (XXL); huzhiq163@163.com (ZQH)

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