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ORIGINAL RESEARCH

Prognostic impact of the number of lymph nodes examined in different stages of colorectal mucinous adenocarcinoma

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Background: Mucinous adenocarcinoma (MC) is a special kind of colorectal adenocarcinoma that occurs more frequently in young patients and females, but the prognostic effect of lymph nodes in MC patients is unclear. This population-based study was conducted to analyze the prognostic value of the number of lymph nodes examined in different stages of colorectal MC.

Methods: We included 17,001 MC patients from the Surveillance, Epidemiology, and End Results program database between 2003 and 2013, of which 12,812 (75%) had >12 lymph nodes examined.

Results: Compared to the group with insufficient lymph nodes examined, patients with more lymph nodes (>12) examined tended to come from east and central America, were more frequently female and young, were diagnosed after 2008, had larger-sized tumors of less differentiated grade and in later stages, had not received radiation therapy and had more positive nodal status. Patients with more lymph nodes (>12) examined demonstrated significantly better survival than those with insufficient lymph nodes examined only in stages II and III (stage II: overall, $P<0.001$; cancer-specific, $P<0.001$; stage III: overall, $P=0.093$; cancer-specific, $P=0.032$), even though the overall ($P<0.001$) and cancer-specific survival ($P<0.001$) showed significant differences between the two groups. Both univariate (overall, HR=0.739, 95% CI=0.703–0.777, $P<0.001$; cancer-specific, HR=0.742, 95% CI=0.698–0.788, $P<0.001$) and multivariate (overall, HR=0.601, 95% CI=0.537–0.673, $P<0.001$; cancer-specific, HR=0.582, 95% CI=0.511–0.664, $P<0.001$) Cox proportional hazards models verified the association between >12 lymph nodes examined and better survival.

Conclusion: More number of lymph nodes (>12) examined significantly increased the survival probability of MC patients in stages II and III, but had no significant influence on patients in stages I and IV, indicating the effect of number of lymph nodes examined was a stage-dependent prognostic factor in clinical utility.

Keywords: number of lymph nodes examined, stages, mucinous carcinoma

Introduction

Colorectal cancer (CRC) is the second leading cause of cancer-related mortality in the USA.[1,2] Different histological subtypes have been reported to demonstrate distinct survival probabilities, clinical characteristics and response to clinical therapies.[3,4] According to the World Health Organization (WHO), mucinous adenocarcinoma (MC) is a special histological type of CRC with >50% of extracellular mucin within the tumor and is found in 1.6%–25.4% of CRC cases.[5,6] Compared to the non-mucinous adenocarcinoma (NMC), MC was reported to occur more frequently in younger and female patients.[7,8]

Besides, the survival probability of MC patients was believed to be worse than NMC patients considering the later-stage presentations of this kind of disease.[9–11]

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The number of metastatic lymph nodes is an important factor in staging criteria worldwide, one of which is the most popularly used TNM staging system.[12] Therefore, the number of lymph nodes examined has played an indispensable role in classifying the tumor stages, and different histological stages were often connected with distinct survival probabilities and treatment options.[13–15] However, the findings about the prognostic power of the number of lymph nodes examined were constantly inconsistent; some studies reported the number of lymph nodes examined as a good prognostic factor in CRC,[16–18] while others showed contradictory results.[19–21] Several studies had insufficient number of observed cases, and some were not taking stages into consideration. Furthermore, the prognostic effect of the number of lymph nodes examined in MC has not been well established.

Therefore, this population-based study was conducted to investigate the prognostic impact of the number of lymph nodes examined in different stages of MC.

Methods

Clinical dataset

The Surveillance, Epidemiology, and End Results (SEER)[22] is the largest cancer database in the USA, representing about 30% of the population. We included CRC cases diagnosed between 2003 and 2013 from 18 population-based cancer registries where the number of lymph nodes examined at the time of primary surgical resection was known. MC was defined according to the codes 8480 and 8481 of the International Classification of Diseases for Oncology, third edition. Characteristics of patients including age at diagnosis, geographical location, sex, race, year of diagnosis, tumor numbers, tumor size, tumor grade, American Joint Committee on Cancer (AJCC) stages, receipt of radiation therapy, nodal status and lymphadenectomy were used in the analysis. The lymph node ratio (LNR) was calculated as the number of positive lymph nodes divided by the total number of lymph nodes dissected. Patients with LNR higher than the median value of 0.17 were classified as "high" lymph node group, and the other patients were classified as "low" lymph node group. Patients were grouped into the following age categories: <50 years old, 50–65 years and >65 years old. The 18 registries were divided into three classes according to the geographical location as central (Metropolitan Detroit, Iowa, Kentucky, Utah and Louisiana), west (Alaska, Greater California, Hawaii, Los Angeles, New Mexico, San Francisco-Oakland SMSA, San Jose-Monterey and Seattle) and east (New Jersey, Metropolitan Atlanta, Rural Georgia and Greater Georgia). Patients were classified into four groups based on race as white, black, Asian or Pacific Islander and American Indian/Alaska Native (AI/AN). Tumor size was divided into two categories by cut-off of 5 cm. Tumor grade was characterized as well differentiated (G1), moderately differentiated, poorly differentiated and undifferentiated. TNM stages were reclassified into stage I, stage II, stage III and stage IV based on the criteria of the AJCC Staging Manual, 7th edition (2010). Patients with unknown ages, no available survival status, unknown follow-up survival times or undefined treatments were excluded from the analysis. The final analytic set consisted of 17,001 patients, for whom all the survival information was available.

Survival analysis

Survival information included vital status, cause of death and survival time in years. Patients with unavailable survival information were excluded from the analysis. Overall survival and cancer-specific survival were both calculated. Patients who had died from causes other than CRC were marked as "dead" in the overall survival analysis, but "censored" in the cancer-specific survival analysis. The Kaplan–Meier method was used to generate survival curves in the study, and the log-rank test was applied to calculate the differences between the curves. HRs and their 95% CIs were estimated for each variate by univariate and multivariate Cox proportional hazards models with the R package "survival".

Statistical analysis

R version 3.3.2 (http://www.R-project.org/) was used to conduct all the statistical analyses in this work. The differences in clinicopathological characteristics between the group with <12 and the group with >12 lymph nodes examined were analyzed using Chi-square test. All tests conducted were two-sided, and the significant difference was considered at $P<0.05$.

Data availability

Data included in this analysis were downloaded from the SEER website (https://seer.cancer.gov/data/, SEER Incidence Data, 1973–2013). The data are freely available upon request from SEER by signing the "SEER Data-Use Agreement form". Our research does not contain any identifiable private information of the patients, so it is not within the scope of the Institutional Review Board review.

Results

Clinical and demographic characteristics of CRC patients

In this study, we included 17,001 patients with MC, of which three-quarter cases had met the criteria of 12 examined

lymph nodes. The clinicopathological characteristics of these patients are shown in Table 1. Cases from the western registries comprised nearly half of the population in both groups, while patients from eastern registries were more likely to have >12 lymph nodes examined (P=0.003). The numbers of female patients and male patients were basically equivalent to each other in the group with <12 lymph nodes examined, and in the group meeting the standard, females constituted

Table 1 Demographic and clinical characteristics of MC patients

Characteristics	<12 lymph nodes examined (N=4,189), n (%)	≥12 lymph nodes examined (N=12,812), n (%)	*P*-value
Registry			0.003
West	2,014 (48.1)	5,846 (45.6)	
East	1,090 (26.0)	3,670 (28.6)	
Central	1,085 (25.9)	3,296 (25.7)	
Sex			0.02
Male	2,070 (49.4)	6,065 (47.3)	
Female	2,119 (50.6)	6,747 (52.7)	
Age at diagnosis (years)			<0.001
<50	344 (8.2)	1,723 (13.4)	
50–65	1,201 (28.7)	3,937 (30.7)	
>65	2,644 (63.1)	7,152 (55.8)	
Race			0.11
White	3,392 (81.0)	10,576 (82.5)	
Black	506 (12.1)	1,413 (11.0)	
AI/AN	22 (0.5)	51 (0.4)	
Asian or Pacific Islander	269 (6.4)	772 (6.0)	
Year of diagnosis			<0.001
2004–2008	3,060 (73.0)	6,442 (50.3)	
2009–2013	1,129 (27.0)	6,370 (49.7)	
Tumor numbers			0.283
Single	3,674 (87.7)	11,318 (88.3)	
Multiple	515 (12.3)	1,494 (11.7)	
Tumor size (cm)			<0.001
≤5	2,590 (61.8)	5,779 (45.1)	
>5	1,599 (38.2)	7,033 (54.9)	
Tumor grade			<0.001
Well differentiated	580 (13.8)	1,350 (10.5)	
Moderately differentiated	2,725 (65.1)	8,427 (65.8)	
Poorly differentiated	801 (19.1)	2,646 (20.7)	
Undifferentiated	83 (2.0)	389 (3.0)	
TNM stage			<0.001
I	662 (15.8)	1,275 (10.0)	
II	1,465 (35.0)	4,879 (38.1)	
III	1,194 (28.5)	4,661 (36.4)	
IV	868 (20.7)	1,997 (15.6)	
Radiation			<0.001
Yes	554 (13.2)	1,105 (8.6)	
No	3,635 (86.8)	11,707 (91.4)	
Nodal status			<0.001
Negative	2,419 (57.7)	6,639 (51.8)	
Positive	1,770 (42.3)	6,173 (48.2)	
Lymphadenectomy			0.157
Yes	4,149 (99.0)	12,720 (99.3)	
No	40 (1.0)	92 (0.7)	
LNR			<0.001
High	1,180 (28.2)	3,108 (24.3)	
Low	3,009 (71.8)	9,704 (75.7)	

Abbreviations: MC, mucinous adenocarcinoma; AI/AN, American Indian/Alaska Native; LNR, lymph node ratio.

more than males (P=0.02). More than half of the CRC patients were diagnosed at ages >65 years old, and patients >65 years old tended to have less lymph nodes examined than young people (P<0.001). More than 80% of patients were white, while only <1% were AI/AN in both groups. Cases with <12 lymph nodes examined were more likely diagnosed at the former half of the studied time interval (P<0.001). The proportion of tumors with sizes <5 cm in group with >12 lymph nodes examined was significantly higher than that of the other group (P<0.001). Well-differentiated tumors comprised 13.8% in the less examined group, but only 10% in the well-examined group (P<0.001), and the cases in the well-examined group were more likely to be in stage II or later of the pathological processes (P<0.001). Patients treated with radiation were less in number in the well-examined group than the other group (P<0.001), but most patients met the standard of 12 lymph nodes examined. More patients had positive nodal status in the well-examined group than in the less examined group in our dataset (P<0.001). Not surprisingly, patients with >12 lymph nodes examined had lower LNR than patients with inadequate examined lymph nodes (P<0.001). To reduce the bias that might be caused by the imbalance of sample sizes in the two groups, we repeated the analysis by randomly sampling equivalent numbers of patients in the two conditions. We found all the covariates were significantly different between the well-examined (≥12 lymph nodes) group and the group with inadequate (<12) retrieved lymph nodes (Table S1).

Insufficient lymph nodes examined as a poor prognostic factor in stage II and III patients

The group with <12 lymph nodes examined had both significantly worse overall (P<0.001) and cancer-specific survival probability (P<0.001) in our dataset (Figure 1). Among patients in different tumor stages, insufficient lymph nodes examined indicated worse overall and cancer-specific survival rates in stage II patients (overall, P<0.001; cancer-specific, P<0.001), and worse cancer-specific survival rate in stage III patients (overall, P=0.093; cancer-specific, P=0.032), while the number of lymph nodes examined had no significant influence on survival of patients with stage I and IV MC (stage I: overall, P=0.196; cancer-specific, P=0.796; stage IV: overall, P=0.917; cancer-specific, P=0.798). Specific information is listed in Table 2 and Figure 2.

Univariate and multivariate analysis

Univariate Cox proportional hazards analyses were conducted on all the clinical factors to explore their effect on the overall and cancer-specific survival. Both the overall survival and cancer-specific survival showed that the group with more lymph nodes (≥12) examined demonstrated better survival than the group with insufficient lymph nodes examined (HR=0.739, 95% CI=0.703–0.777, P<0.001; HR=0.742, 95% CI=0.698–0.788, P<0.001). In our analysis, age at diagnosis, race, tumor numbers, tumor size, tumor grade, AJCC stages, radiation therapy, nodal status and

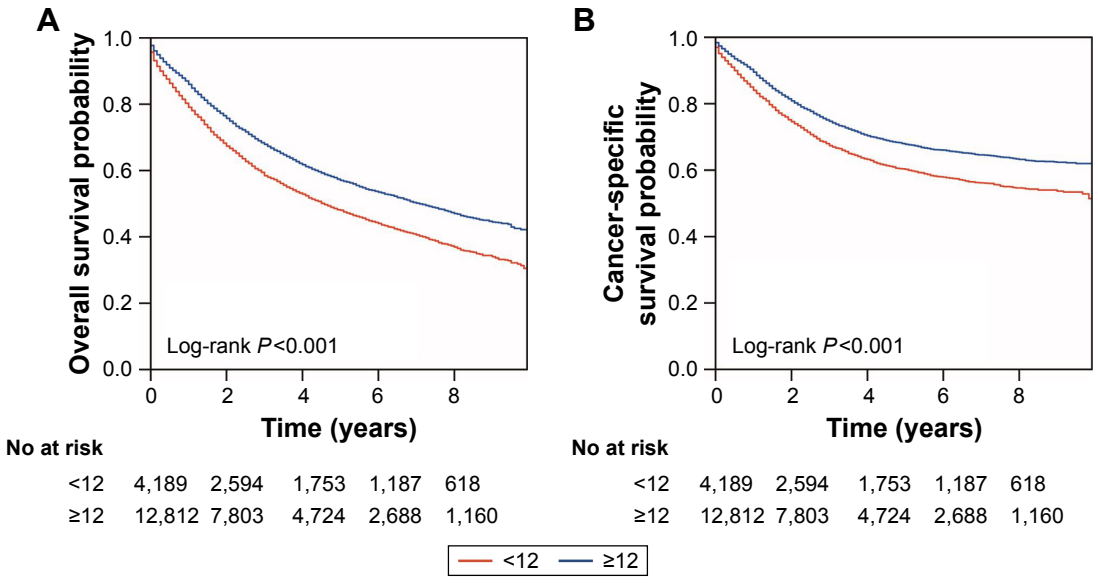


Figure 1 The (**A**) overall and (**B**) cancer-specific survival probability of MC patients with sufficient (≥12) and insufficient number of lymph nodes examined (<12).
Abbreviation: MC, mucinous adenocarcinoma.

Table 2 Five-year survival in different stages of CRC patients with or without lymphadenectomy

	Overall survival			Cancer-specific survival		
	<12 lymph nodes examined	≥12 lymph nodes examined	*P*-value	<12 lymph nodes examined	≥12 lymph nodes examined	*P*-value*
Stage I	0.793 (0.041)	0.823 (0.039)	0.196	0.93 (0.024)	0.931 (0.031)	0.796
Stage II	0.591 (0.014)	0.713 (0.008)	<0.001	0.762 (0.013)	0.857 (0.006)	<0.001
Stage III	0.486 (0.049)	0.529 (0.013)	0.093	0.56 (0.052)	0.643 (0.013)	0.032
Stage IV	0.156 (0.053)	0.101 (0.03)	0.917	0.208 (0.065)	0.115 (0.034)	0.798
All	0.480 (0.008)	0.570 (0.005)	<0.001	0.602 (0.008)	0.678 (0.005)	<0.001

Note: *Based on log-rank test.
Abbreviation: CRC, colorectal cancer.

LNR all showed significant prognostic value for both overall and cancer-specific survival, while lymphadenectomy only demonstrated significant prognostic value for cancer-specific survival (Table 3). Including all these clinical characteristics with prognostic value from the univariate analysis into a multivariate Cox proportional hazards model, we found that the number of no less than 12 lymph nodes examined was an independent predictor of both better overall (HR=0.601, 95% CI=0.537–0.673, $P<0.001$) and cancer-specific survival (HR=0.582, 95% CI=0.511–0.664, $P<0.001$). Higher

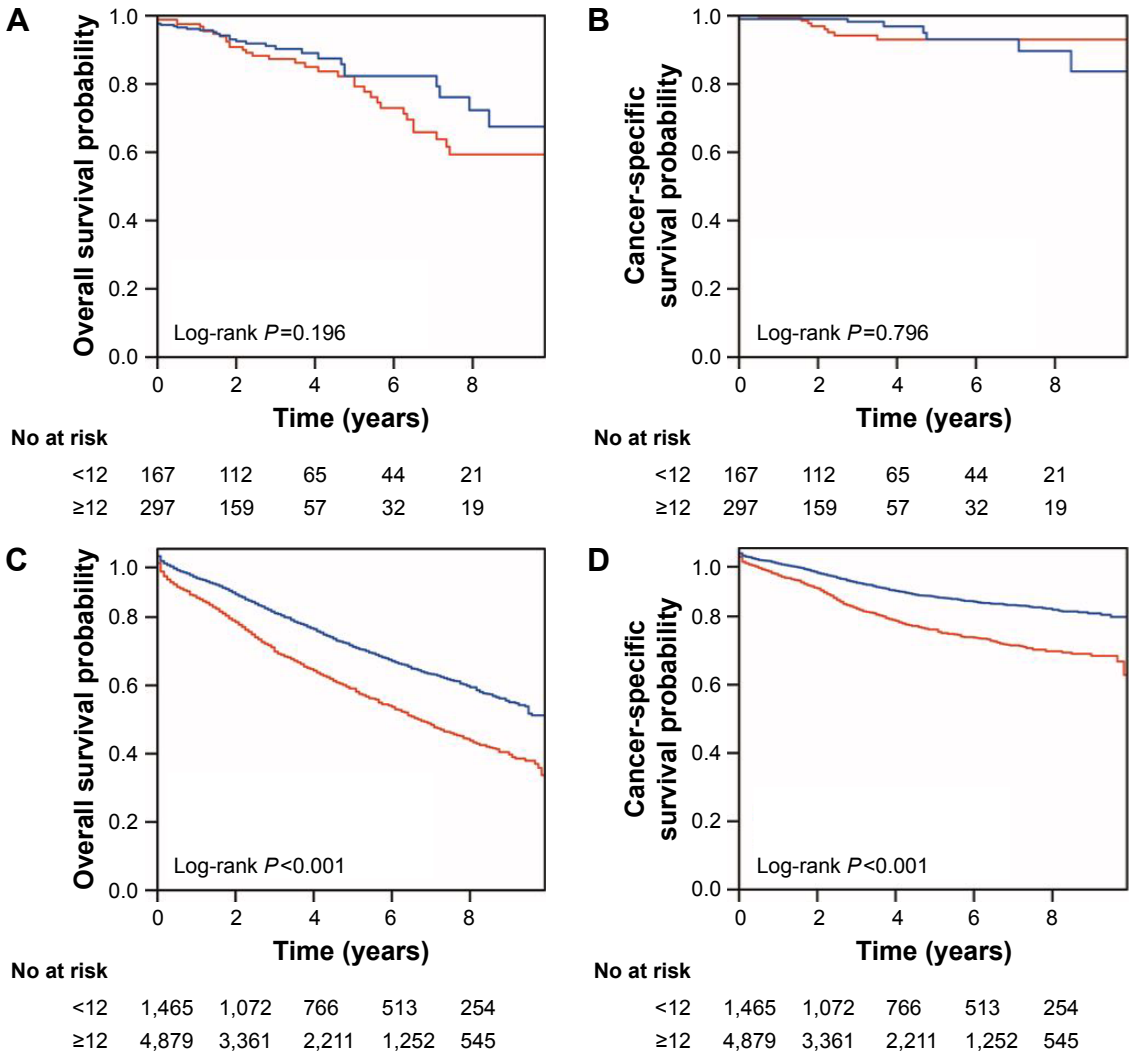


Figure 2 (*Continued*)

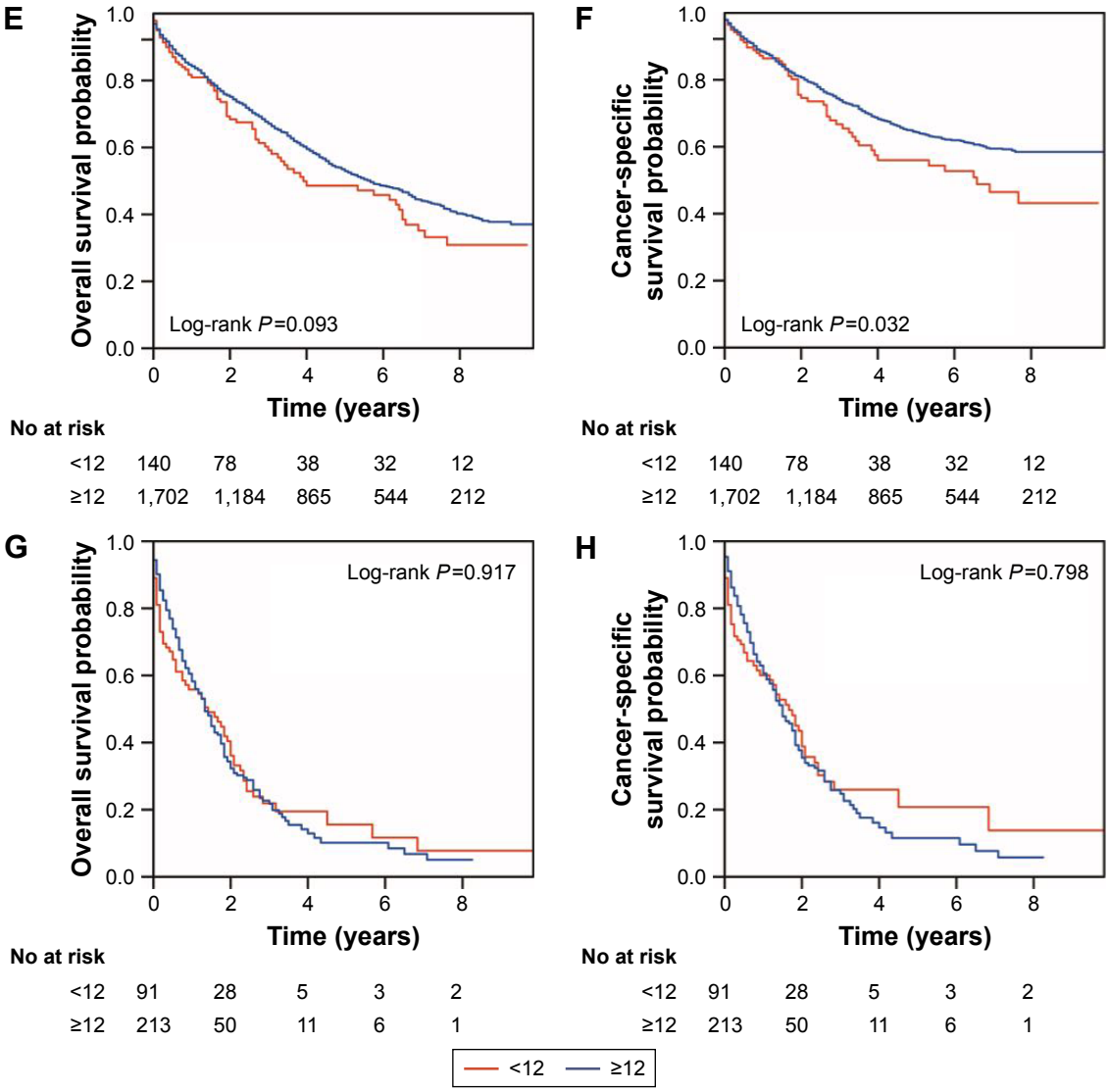


Figure 2 The overall and cancer-specific survival rates in different stages of MC patients with or without sufficient number of lymph nodes examined: (**A** and **B**) stage I, (**C** and **D**) stage II, (**E** and **F**) stage III and (**G** and **H**) stage IV.
Abbreviation: MC, mucinous adenocarcinoma.

ages (>65 years old), tumor grades including moderately differentiated, poorly differentiated and undifferentiated, stages II and IV and positive nodal status were all significantly associated with worse overall and cancer-specific survival ($P<0.001$, respectively). On the other hand, Asian ethnicity (overall, HR=0.848, 95% CI=0.730–0.984, $P=0.03$; cancer-specific, HR=0.844, 95% CI=0.707–1.006, $P=0.059$), higher tumor numbers (overall, HR=0.883, 95% CI=0.795–0.981, $P=0.021$; cancer-specific, HR=0.683, 95% CI=0.590–0.790, $P<0.001$) and lower LNR (overall, HR=0.834, 95% CI=0.759–0.916, $P<0.001$; cancer-specific, HR=0.743, 95% CI=0.668–0.825, $P<0.001$) were associated with better survival probabilities. The detailed results of multivariate analysis are shown in Table 4.

Discussion

In this population-based study, we analyzed 17,001 MC patients with available information on the number of lymph nodes examined from SEER. Of all the tumors, 9.4% were MC, similar to the proportion reported in previous literature irrespective of the histological stages.[5,6] In our study, the number of lymph nodes examined (≥12) was associated independently with better overall and cancer-specific survival in MC in both the univariate and multivariate Cox proportional hazards models in a stage-dependent manner, where it acted as a good prognostic factor for stage II and III MC patients, while not for those in the other two stages.

MC is a distinct subtype of colorectal adenocarcinoma that requires special attention despite its low occurrence. MC has a

Table 3 Univariate analysis of the population for overall and cancer-specific survival

Characteristics	N	Overall		Cancer-specific	
		5-year survival (%)	*P*-value	5-year survival (%)	*P*-value
Registry			0.051		0.078
West	7,860	0.555		0.657	
East	4,760	0.544		0.669	
Central	4,381	0.533		0.648	
Sex			0.345		0.986
Male	8,135	0.545		0.651	
Female	8,866	0.548		0.665	
Age at diagnosis (years)			<0.001		<0.001
<50	2,067	0.623		0.653	
50–65	5,138	0.627		0.672	
>65	9,796	0.489		0.653	
Race			0.005		0.003
White	13,968	0.546		0.664	
Black	1,919	0.527		0.62	
AI/AN	73	0.466		0.543	
Asian or Pacific Islander	1,041	0.588		0.665	
Tumor numbers			<0.001		<0.001
Single	14,992	0.542		0.645	
Multiple	2,009	0.581		0.751	
Tumor size (cm)			<0.001		<0.001
≤5	8,369	0.578		0.7	
>5	8,632	0.515		0.617	
Tumor grade			<0.001		<0.001
Well differentiated	1,930	0.641		0.754	
Moderately differentiated	11,152	0.566		0.683	
Poorly differentiated	3,447	0.446		0.546	
Undifferentiated	472	0.42		0.487	
TNM stage			<0.001		<0.001
I	1,937	0.751		0.928	
II	6,344	0.682		0.833	
III	5,855	0.524		0.617	
IV	2,865	0.145		0.168	
Radiation			0.008		0.008
Yes	1,659	0.545		0.596	
No	15,342	0.547		0.666	
Nodal status			<0.001		<0.001
Negative	9,058	0.676		0.825	
Positive	7,943	0.402		0.474	
Lymphadenectomy			0.09		0.03
Yes	16,869	0.547		0.659	
No	132	0.443		0.516	
LNR			<0.001		<0.001
High	1,874	0.32		0.38	
Low	6,504	0.6		0.73	
No of lymph nodes examined			<0.001		<0.001
<12	4,189	0.48		0.602	
≥12	12,812	0.57		0.678	

Abbreviations: AI/AN, American Indian/Alaska Native; LNR, lymph node ratio.

propensity to exhibit a worse-differentiated grade and a higher likelihood of lymph node metastasis according to previous studies.[7,23–25] The production of mucus under pressure allows the cancers to separate tissue planes in the bowel wall and more frequently gain access to the regional lymph.[26] Therefore, lymph node retrieval is important in this subtype of CRC.

Positive lymph node assessment is critical for staging and to determine the need for adjuvant chemotherapy for

Table 4 Cox proportional hazards model of the population for overall and cancer-specific survival

	Overall			Cancer-specific		
	HR	**95% CI**	***P*-value**	**HR**	**95% CI**	***P*-value**
Age at diagnosis (years)						
<50						
50–65	1.123	1.026–1.229	0.011	1.094	0.994–1.203	0.067
>65	2.280	2.098–2.477	<0.001	1.717	1.569–1.879	<0.001
Race						
White						
Black	1.073	0.997–1.154	0.058	1.13	1.038–1.231	0.005
AI/AN	1.371	0.978–1.921	0.067	1.481	0.999–2.196	0.051
Asian or Pacific Islander	0.826	0.743–0.919	<0.001	0.876	0.774–0.991	0.036
Tumor numbers						
Single						
Multiple	0.918	0.856–0.985	0.017	0.72	0.653–0.794	<0.001
Tumor size (cm)						
≤5						
>5	1.129	1.076–1.185	<0.001	1.203	1.135–1.275	<0.001
Tumor grade						
Well differentiated						
Moderately differentiated	1.19	1.097–1.291	<0.001	1.204	1.085–1.335	<0.001
Poorly differentiated	1.463	1.337–1.601	<0.001	1.563	1.397–1.748	<0.001
Undifferentiated	1.653	1.419–1.925	<0.001	1.813	1.519–2.163	<0.001
TNM stage						
I						
II	1.357	1.229–1.499	<0.001	2.413	1.992–2.923	<0.001
III	1.131	0.977–1.309	0.099	2.967	2.379–3.698	<0.001
IV	4.164	3.631–4.775	<0.001	12.736	10.291–15.763	<0.001
Radiation						
Yes						
No	1.055	0.973–1.143	0.195	0.954	0.872–1.043	0.302
Nodal status						
Negative						
Positive	1.994	1.784–2.228	<0.001	2.103	1.863–2.373	<0.001
LNR						
High						
Low	0.834	0.759–0.916	<0.001	0.743	0.668–0.825	<0.001
No of lymph nodes examined						
<12						
≥12	0.737	0.7–0.775	<0.001	0.712	0.669–0.758	<0.001

Abbreviations: AI/AN, American Indian/Alaska Native; LNR, lymph node ratio.

patients with colon cancer.[27,28] Thus, an adequate number of lymph nodes needs to be examined. The evaluation of at least 12 lymph nodes was first recommended in the 1990 Working Party Report to the World Congresses of Gastroenterology, and then reiterated by a National Cancer Institute-sponsored panel of experts to ensure adequate sampling.[29–32]

Our findings were consistent with several previous studies that an increased number of lymph nodes evaluated was associated with improved survival among patients with stage II colon cancer.[18,27,33] While for stage III diseases, our results showed more number of lymph nodes examined significantly increased the cancer-specific survival, but the other studies found this prognostic value only existed in node-positive group.[17,34–36] This might be caused by the different cut-offs of lymph nodes examined in previous studies. For example, Chang et al evaluated the prognostic effect of lymph nodes examined with the cut-off of 7,[32] and Gumus et al separated the population with 9 lymph nodes examined.[36] Moreover, in our dataset, three-quarter patients had been evaluated for >12 lymph nodes, which was much higher than the proportion reported earlier, where a population-based study suggested that only 37% of colon cancer patients had adequate lymph node evaluation (at least 12 nodes examined),[27] indicating the increased retrieval of lymph nodes in recent years.

Multivariate analysis confirmed the prognostic value of the number of lymph nodes retrieved (Table 4), while the overall survival showed that stage III disease was associated with a slightly better survival than stage II disease; this might probably have been due to the fact that there were cases of death from other causes rather than CRC, since for the cancer-specific survival, stage III patients had significantly larger HR than the stage II group.

The examination of lymph nodes also correlated closely with the surgical procedures and the quality of surgeons in clinical practice.[27] Relatively little is known about the factors that influence the adequacy of lymph node evaluation. Our data indicated that the number of lymph nodes examined was affected by many clinical characteristics, such as the geographic location – patients from eastern America were more likely to have sufficient lymph nodes examined than the west or central registries. Besides, females with MC were examined for more lymph nodes than males, and more lymph nodes were evaluated in younger patients (≤65 years old). Patients diagnosed after 2008 evidently had increased number of lymph nodes examined, suggesting the improvement in health care and pathological practice, which agreed with the previous report that lymph node retrieval was correlated with surgeon factors like procedure volume.[22,37] Tumor factors (tumor size, grade, stage) also had great influence on the number of lymph nodes examined based on our analysis. We observed that more lymph nodes were evaluated in MC patients with not well-differentiated tumors and stage II and III diseases. This phenomenon was also reported in several other studies, but the reason for the association was unclear.[38,39] It is possible that with the increased number of lymph nodes examined, the probability to retrieve positive lymph nodes will increase, as the positive lymph nodes play an important role in tumor staging. However, the LNR in the well-examined group was significantly lower than that of the patients with inadequate lymph nodes retrieved, and LNR also served as an independent prognostic factor in our analysis, suggesting the necessity of consideration of LNR in staging and diagnosis in clinical practice. Radiation therapy was also associated with the number of lymph nodes examined based on our data – patients receiving the radiation therapy were less likely to have sufficient lymph nodes examined, while radiation itself was not an independent prognostic factor, indicating that the number of lymph nodes should be taken into consideration when considering the radiation therapy in clinical utility.

To our knowledge, the large number of patients from national population-based data in our study avoided the biases from single-institution experiences or limited sample sizes. However, we noticed that several limitations still need further comment. First, considering the retrospective nonrandomized nature of SEER, individual pathological diagnosis was not feasible to review in a large population size, so the variations caused by different pathologists may lead to misclassification of patients. Second, the different criteria used by registries or surgical methods used for the lymph nodes evaluation may slightly affect the results of our analysis. Furthermore, despite that we included as many potential clinical cofactors in our analysis as feasible, there were limited information on surgical and treatment options such as the procedure strategy, specimen adequacy and chemotherapy dose or duration, which may lead us to overlook the influences of these factors in prognosis besides the number of lymph nodes examined. Further randomized large-scale trial in the Chinese population is needed to obtain more definitive conclusion and give more clues for the treatment of Chinese patients. In summary, lymph nodes retrieval was associated with geographic location, and more number of lymph nodes was examined in female patients, who were at younger ages, diagnosed after 2008, had larger-sized tumors of less-differentiated grade and in later stages, less likely to have radiation therapy, more positive lymph nodes and lower LNR. The increased number of lymph nodes examined (≥12) significantly improved the survival probability of MC patients in a stage-dependent manner. Although the number of lymph nodes examined was not associated with better survival for stage I and IV patients, it remained an independently good prognostic factor for MC patients in stages II and III.

Author contributions

YM, YQL and JJG conceived and designed the project. YM and YQL collected and analyzed data. YM and YQL wrote the manuscript. NL, YZL, YZ, BL, KNH, SJ revised the manuscript. All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work. All the authors approved the final manuscript.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary material

Table S1 Demographic and clinical characteristics of MC patients with balanced sample sizes

Characteristics	<12 lymph nodes examined (N=4,189), n (%)	≥12 lymph nodes examined (N=4,189), n (%)	*P*-value
Registry			<0.001
West	2,014 (48.1)	1,832 (43.7)	
East	1,090 (26.0)	1,340 (32.0)	
Central	1,085 (25.9)	1,017 (24.3)	
Sex			0.005
Male	2,070 (49.4)	1,942 (46.4)	
Female	2,119 (50.6)	2,247 (53.6)	
Age at diagnosis (years)			<0.001
<50	344 (8.2)	959 (22.9)	
50–65	1,201 (28.7)	1,352 (32.3)	
>65	2,644 (63.1)	1,878 (44.8)	
Race			0.008
White	3,392 (81.0)	3,504 (83.6)	
Black	506 (12.1)	419 (10.0)	
AI/AN	22 (0.5)	15 (0.4)	
Asian or Pacific Islander	269 (6.4)	251 (6.0)	
Year of diagnosis			<0.001
2004–2008	3,060 (73.0)	480 (11.5)	
2009–2013	1,129 (27.0)	3,709 (88.5)	
Tumor numbers			0.002
Single	3,674 (87.7)	3,765 (89.9)	
Multiple	515 (12.3)	424 (10.1)	
Tumor size (cm)			<0.001
≤5	2,590 (61.8)	797 (19.0)	
>5	1,599 (38.2)	3,392 (81.0)	
Tumor grade			<0.001
Well differentiated	580 (13.8)	258 (6.2)	
Moderately differentiated	2,725 (65.1)	2,820 (67.3)	
Poorly differentiated	801 (19.1)	915 (21.8)	
Undifferentiated	83 (2.0)	196 (4.7)	
TNM stage			<0.001
I	662 (15.8)	116 (2.8)	
II	1,465 (35.0)	1,634 (39.0)	
III	1,194 (28.5)	2,055 (49.1)	
IV	868 (20.7)	384 (9.2)	
Radiation			<0.001
Yes	554 (13.2)	136 (3.2)	
No	3,635 (86.8)	4,053 (96.8)	
Nodal status			<0.001
Negative	2,419 (57.7)	1,775 (42.4)	
Positive	1,770 (42.3)	2,414 (57.6)	
Lymphadenectomy			0.009
Yes	4,149 (99.0)	4,170 (99.5)	
No	40 (1.0)	19 (0.5)	
LNR			<0.001
High	1,180 (28.2)	694 (16.6)	
Low	3,009 (71.8)	3,495 (83.4)	

Abbreviations: MC, mucinous adenocarcinoma; AI/AN, American Indian/Alaska Native; LNR, lymph node ratio.

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