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ORIGINAL ARTICLE

Prognosis of patients with gastric cancer and solitary lymph node metastasis

Chun-Qiu Chen, Xiao-Jiang Wu, Zhen Yu, Zhao-De Bu, Ke-Qiang Zuo, Zi-Yu Li, Jia-Fu Ji

Chun-Qiu Chen, Zhen Yu, Ke-Qiang Zuo, Department of General Surgery, Tenth People's Hospital of Shanghai, Tongji University, School of Medicine, Shanghai 200072, China
Xiao-Jiang Wu, Zhao-De Bu, Zi-Yu Li, Jia-Fu Ji, Department of Surgery, Beijing Cancer Hospital, Peking University School of Oncology, Beijing 100036, China
Author contributions: Wu XJ and Chen CQ contributed equally to the study design and writing of the manuscript, and should be considered as co-first authors; Yu Z performed the research and revised the manuscript for intellectual content; Zuo KQ performed the data analysis; Bu ZD and Li ZY collected the data; Ji JF supervised the entire research project and revised the manuscript for intellectual content; all authors have read and approved the final version of the manuscript.
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Correspondence to: Jia-Fu Ji, Professor, Department of Surgery, Beijing Cancer Hospital, Peking University School of Oncology, Fu-Cheng-Lu No. 52, Hai-Dian District, Beijing 100036, China. jiafuj@gmail.com
Telephone: +86-10-88196605 Fax: +86-10-88122437
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Abstract

AIM: To investigate the relationship of solitary lymph node metastasis (SLNM) and age with patient survival in gastric cancer (GC).

METHODS: The medical records databases of China's Beijing Cancer Hospital at the Peking University School of Oncology and Shanghai Tenth People's Hospital affiliated to Tongji University were searched retrospectively to identify patients with histologically proven GC and SLNM who underwent surgical resection between October 2003 and December 2012. Patients with distant metastasis or gastric stump carcinoma following resection for benign disease were excluded from the analysis. In total, 936 patients with GC + SLNM were selected for analysis and the recorded parameters of clinicopathological disease and follow-up (range: 13-2925 d) were collected. The Kaplan-Meier method was used to stratify patients by age (≤ 50 years-old, n = 198; 50-64 years-old, n = 321; ≥ 65 years-old, n = 446) and by metastatic lymph node ratio [MLR < 0.04 (1/25), n = 180; 0.04-0.06 (1/25-1/15), n = 687; ≥ 0.06 (1/15), n = 98] for 5-year survival analysis. The significance of intergroup differences between the survival curves was assessed by a log-rank test.

RESULTS: The 5-year survival rate of the entire GC + SLNM patient population was 49.9%. Stratification analysis showed significant differences in survival time (post-operative days) according to age: ≤ 50 years-old: 950.7 ± 79.0 *vs* 50-64 years-old: 1697.8 ± 65.9 *vs* ≥ 65 years-old: 1996.2 ± 57.6, all P < 0.05. In addition, younger age (≤ 50 years-old) correlated significantly with mean survival time (r = 0.367, P < 0.001). Stratification analysis also indicated an inverse relationship between increasing MLR and shorter survival time: < 0.04: 52.8% and 0.04-0.06: 51.1% *vs* ≥ 0.06: 40.5%, P < 0.05. The patients with the shortest survival times and rates were younger and had a high MLR (≥ 0.06): ≤ 50 years-old: 496.4 ± 133.0 and 0.0% *vs* 50-65 years-old: 1180.9 ± 201.8 and 21.4% *vs* ≥ 65 years-old: 1538.4 ± 72.4 and 37.3%, all P < 0.05. The same significant trend in shorter survival times and rates for younger patients was seen with the mid-range MLR group (0.04-0.06), but the difference between the two older groups was not significant. No significant differences were found between the age groups of patients with MLR < 0.04. Assessment of clinicopathological parameters identified age group, Borrmann type, histological type and tumor depth as the most important predictors of the survival rates and times observed for this study population.

CONCLUSION: GC patients below 51 years of age with MLR of SLNM above 0.06 have shorter life expec-

tancy than their older counterparts.

Key words: Gastric cancer; Solitary lymph node metastasis; Age; Metastatic lymph node ratio; Survival

Core tip: Among patients with gastric cancer and single lymph node metastasis, younger patients (≤ 50 years-old) tend to have less and shorter survival than their older counterparts; in particular, younger patients with the highest metastatic lymph node ratio have the worse prognosis.

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INTRODUCTION

Gastric carcinoma (GC) is one of the most commonly diagnosed cancers in China. The elderly (65 years and older) represent over one-half of these cases, and occurrence of GC in individuals younger than 40-years-old is relatively rare (approximately 5% of total reported cases)[1,2]. Studies of age-related GC progression and prognosis have yielded inconsistent findings. The collective data in the literature indicate both distinctly unfavorable outcomes for the younger patient population (citing more advanced disease at diagnosis and/or faster disease progression) and a seemingly paradoxical favorable overall survival (with early disease stage cases possibly providing a confounding subgroup effect); in addition, other studies have demonstrated a lack of age-related impact on GC prognosis[3-8].

Regardless of patient age, lymph node metastasis is a well-established critical prognostic factor and predictor of recurrence in GC. Histological detection of metastatic lymph nodes (MLNs) is strongly correlated with a high risk of recurrence, and this is an especially critical clinical finding for patients diagnosed in the early stages of GC to help design effectively robust, but safe, clinical management strategies[9-12]. While calculation of the metastatic lymph node ratio (MLR; single positive lymph nodes per total number of lymph nodes harvested) improves the sensitivity of predicting GC recurrence, minimizing the number of lymph node dissection is necessary to reduce the corresponding side effects, such as lymphedema[13-15].

A major clinical challenge in GC evaluation is determining the appropriate extent of lymph node dissection that is capable of detecting single lymph node metastasis (SLNM). The gastric lymphatic drainage system is particularly complex, and not all cases of SLNM are localized to the perigastric node area and are detectable by standard D2 lymphadenectomy. MLR, however, can help to overcome this limitation.

In this study, the differential prognostic features of younger and older GC patients with SLNM were investigated using MLR to gain further insights into the particular clinicopathological features and surgical outcomes of these two patient populations.

MATERIALS AND METHODS

Patients

The clinical records databases of two large metropolitan hospitals - Beijing Cancer Hospital of the Peking University School of Oncology, and the Shanghai Tenth People's Hospital Affiliated to Tongji University - were searched retrospectively to identify patients with histologically proven GC and SLNM who underwent resection surgery between October 2003 and December 2012. Patient records were selected for study inclusion according to the following eligibility criteria: available histological and pathological data related to diagnosis, including total number of resected lymph nodes. Of the 965 patients identified, 29 were excluded from analysis according to the presence of distant metastasis or development of gastric stump tumors following resection for benign disease.

In total, 936 patients with GC + SLNM were selected for analysis and the recorded parameters of clinicopathological disease and follow-up were collected. The patients were stratified by age (≤ 50, 50-64, and ≥ 65 years-old) and by MLR [< 0.04 (1/25) with > 25 lymph nodes sampled, 0.04-0.06 (1/25-1/15) with 15-25 lymph nodes sampled, and ≥ 0.06 (1/15) with ≥ 15 lymph nodes sampled].

Statistical analysis

All statistical analyses were carried out by the SPSS statistical software package, version 13.0 (SPSS Inc., Chicago, IL, United States). The Kaplan-Meier method, determined the overall and subgroups' 5-year survival rates, with the "event" endpoint being defined as death by any cause. The significance of differences between the various survival curves was assessed by a log-rank test. The chi-square test was used to evaluate differences between the clinicopathological disease and follow-up categorical variables. A P-value of < 0.05 was set as the threshold for statistical significance.

RESULTS

Characteristics of GC + SLNM patients

The study population's demographic and clinicopathological characteristics related to diagnosis and treatment, and stratified by age, are presented in Table 1. The median age was 68.6 years old (range: 26-86 years), with a relatively similar representation among the three age groups (20.5%, ≤ 50 years-old; 33.3%, 50-64 years-old; 46.2%, ≥ 65 years-old) but with a remarkably high proportion

Table 1 Characteristics of gastric cancer + solitary lymph node metastasis during clinical management, stratified by age *n* (%)

Parameter	Age (yr)			All patients (*n* = 965)
	≤ 50 (*n* = 198)	50-64 (*n* = 321)	≥ 65 (*n* = 446)	
Sex				
Male	117 (59.1)	207 (64.5)	272 (61.0)	596 (61.8)
Female	81 (40.9)	114 (35.5)	174 (39.0)	369 (38.2)
Tumor location				
Upper stomach	15 (7.6)	28 (8.7)	40 (9.0)	83 (8.6)
Middle stomach	79 (39.9)	131 (40.8)	183 (41.0)	393 (40.7)
Lower stomach	104 (52.5)	162 (50.5)	223 (50.0)	489 (50.7)
Gross type (Borrmann)				
Ⅰ	5 (2.5)	10 (3.1)	19 (4.3)	34 (3.5)
Ⅱ	51 (25.8)	59 (18.4)	103 (23.1)	213 (22.1)
Ⅲ	78 (39.4)	182 (56.7)	205 (45.9)	465 (48.2)
Ⅳ	64 (32.3)	70 (21.8)	119 (26.7)	253 (26.2)
Histological type				
High differentiation	1 (0.5)	2 (0.6)	4 (0.9)	7 (0.7)
Moderate differentiation	27 (13.6)	79 (24.6)	119 (26.7)	225 (23.3)
Low differentiation	170 (85.9)	240 (74.8)	323 (72.4)	733 (76.0)
Tumor status				
T1	16 (8.1)	29 (9.1)	42 (9.4)	87 (9.0)
T2	36 (18.2)	53 (16.5)	87 (19.5)	176 (18.2)
T3	75 (37.9)	125 (38.9)	194 (43.5)	394 (40.8)
T4	71 (35.8)	114 (35.5)	123 (27.6)	308 (32.0)
Metastasis lymph node ratio				
≥ 0.06	12 (6.1)	32 (10.0)	54 (12.1)	98 (10.2)
0.04-0.06	155 (78.3)	230 (71.7)	302 (67.7)	687 (71.2)
< 0.04	31 (15.6)	59 (18.3)	90 (20.2)	180 (18.6)
Postoperative chemotherapy				
No	4 (2.0)	11 (3.4)	29 (6.5)	43 (4.5)
Yes	194 (98.0)	310 (96.6)	417 (93.5)	922 (95.5)
Surgery				
Subtotal gastric resection	113 (57.1)	181 (56.4)	238 (53.4)	532 (55.1)
Total gastrectomy	85 (42.9)	140 (43.6)	208 (46.6)	433 (44.9)

in the mid MLR (0.04-0.06) group (71.2%). The median number of dissected lymph nodes was 24.3 (range: 5-71) and almost all patients received postoperative chemotherapy (with similar representation among the three age groups). The three age groups also showed statistically similar ($P > 0.05$) patient distribution for sex and tumor location, gross (Borrmann) type, histological (differentiation) type and status.

GC + SLNM patient outcome and predictors of survival

The study population's demographic and clinicopathological characteristics related to follow-up, stratified by age, are presented in Table 2. Twenty-nine of the patients were lost to follow-up and were excluded from further analysis. For the remaining overall study population, the median follow-up was 957 d (range: 13-2925 d) and the 5-year survival rate was 49.9%. Comparative analysis of the survival curves indicated significant differences among groups according to age (all three categories), Borrmann type (Ⅰ *vs* Ⅱ *vs* Ⅲ *vs* Ⅳ), histological type (high *vs* moderate *vs* low), and tumor depth (T1 *vs* T2 *vs* T3 *vs* T4) (all $P < 0.0001$); thus, all four of these variables were characterized as important predictors of survival.

Correlation of age with survival of GC + SLNM patients

Comparative analysis of the cumulative survival rates between the age categories (≤ 50 years-old: 950.7 ± 79.0, 50-64 years-old: 1697.8 ± 65.9, and ≥ 65 years-old: 1996.2 ± 57.6) showed statistically significant differences among all three (≤ 50 *vs* 50-64, $P < 0.001$; ≤ 50 *vs* ≥ 65 $P < 0.001$; 50-64 *vs* ≥ 65, $P = 0.020$) (Figure 1). The group of patients ≥ 65 years old had the best survival, and younger age (≤ 50 years-old) was found to correlate significantly with mean survival time ($r = 0.367$, $P < 0.001$) (Figure 2).

Correlation of MLR with survival of GC + SLNM patients

Comparative analysis of the cumulative survival rates between the MLR categories (< 0.04: 1527.0 ± 67.6, 0.04-0.06: 1851.1 ± 1527.0, and ≥ 0.06: 1352.1 ± 111.8) indicated that high MLR was associated with shorter survival (0.04-0.06 *vs* ≥ 0.06, $P = 0.030$; < 0.04 *vs* ≥ 0.06 $P = 0.028$). Comparison of the lower MLR categories showed no significant difference between the two (< 0.04 *vs* 0.04-0.06, $P = 0.681$). The high MRL group also showed a significantly lower 5-year survival rate than the other two groups (< 0.04: 52.8%, 0.04-0.06: 51.1%, and ≥ 0.06: 40.5%) (Figure 3).

Age-based stratification analysis of the MLR categories indicated that the younger patients with higher MLR had the shortest survival rate (Figure 4). In particular, the cumulative survival curves for patients with MLR of ≥

Table 2 Characteristics of gastric cancer + solitary lymph node metastasis during follow-up, stratified by age

Parameter	All patients (n = 936)	5-yr survival	P value
Age (yr)			< 0.0001
⩽ 50	188	29.10%	
50-64	311	55.00%	
⩾ 65	437	56.60%	
Borrmann type			< 0.0001
Ⅰ	33	92.40%	
Ⅱ	208	90.00%	
Ⅲ	455	40.40%	
Ⅳ	240	19.20%	
Histological type			< 0.0001
High differentiation	7	100.00%	
Moderate differentiation	215	74.60%	
Low differentiation	714	42.00%	
Tumor status			< 0.0001
T1	84	94.80%	
T2	170	82.10%	
T3	382	40.20%	
T4	300	30.40%	

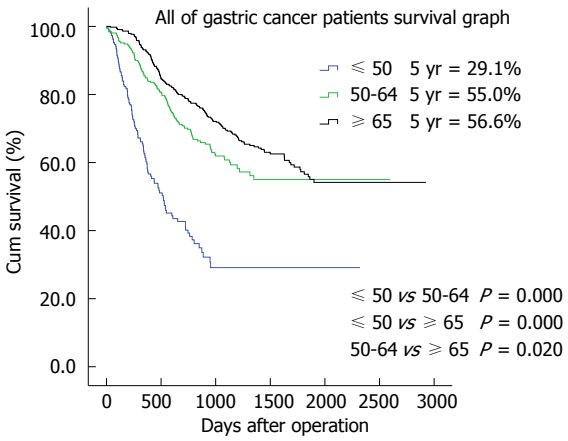

Figure 1 Cumulative survival of patients with gastric cancer + solitary lymph node metastasis according to age category.

0.06 (⩽ 50: 496.4 ± 133.0, 50-65: 1180.9 ± 201.8, and ⩾ 65: 1538.4 ± 72.4) were significantly different among the three age categories (⩽ 50 *vs* 50-65, P = 0.03; ⩽ 50 *vs* ⩾ 65, P = 0.000; 50-65 *vs* ⩾ 65, P = 0.005). The 5-year survival rates followed a similar trend: ⩽ 50, 0.0%; 50-65, 21.4%; > 65, 37.3% (Figure 4A). The cumulative survival curves for patients with MLR of 0.04-0.06 (⩽ 50: 847.3 ± 85.1, 50-65: 1410.1 ± 53.4, and ⩾ 65: 2140.7 ± 68.1) were also significantly different from the lowest age category (⩽ 50 *vs* 50-65, P = 0.000; ⩽ 50 *vs* ⩾ 65, P = 0.000); however, no difference was observed between the two older groups. The 5-year survival rates followed a similar trend: ⩽ 50, 23.9%; 50-65: 60.0%; ⩾ 65: 66.0%) (Figure 4B). The cumulative survival curves of patients with MLR of < 0.04 showed no significant differences among the age categories, and the 5-year survival rates were also similar (⩽ 50: 50.8%, 50-65: 56.3%, and ⩾ 65: 46.0%) (Figure 4C).

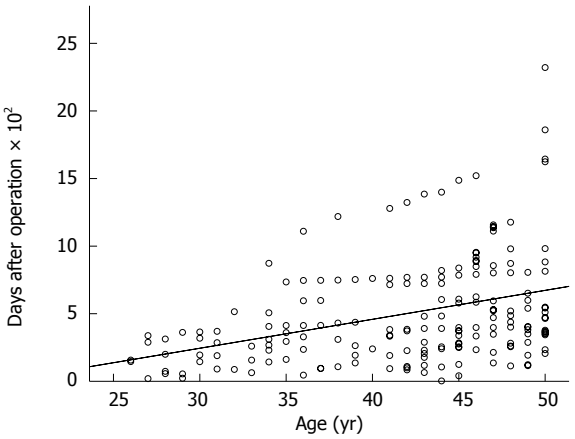

Figure 2 Correlation between age (⩽ 50 years-old) and mean survival days after surgery in patients with gastric cancer + solitary lymph node metastasis (r = 0.367; P < 0.001).

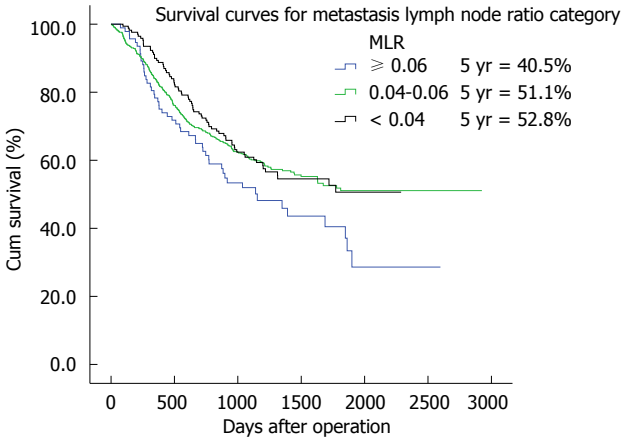

Figure 3 Survival curves for patients with gastric cancer + solitary lymph node metastasis according to metastatic lymph node ratio category. Survival is shown to be inversely associated with the ratio of positive nodes to lymph nodes harvested during surgery.

DISCUSSION

Some studies have indicated that a younger age of diagnosis may correspond to worse prognosis of GC[16]. From a histological perspective, GC in younger patients is more likely to be diffuse type, rather intestinal or mixed, and with disseminated morphology[17-19]. These features may underlie a more aggressive behavior of GC in this patient population or merely reflect a trend in diagnosis being made at a later disease state[4]; nevertheless, both of these issues are associated with poorer prognosis and may help to explain a key pathological difference between younger and older GC patients.

As cited in the Introduction, the collective research to date has yet to define the precise age-related epidemiological and clinicopathological characteristics of GC. For example, in a study of old and young GC patients matched by tumor stage, Moreira *et al*[20] found that younger age was associated with a more favorable out-

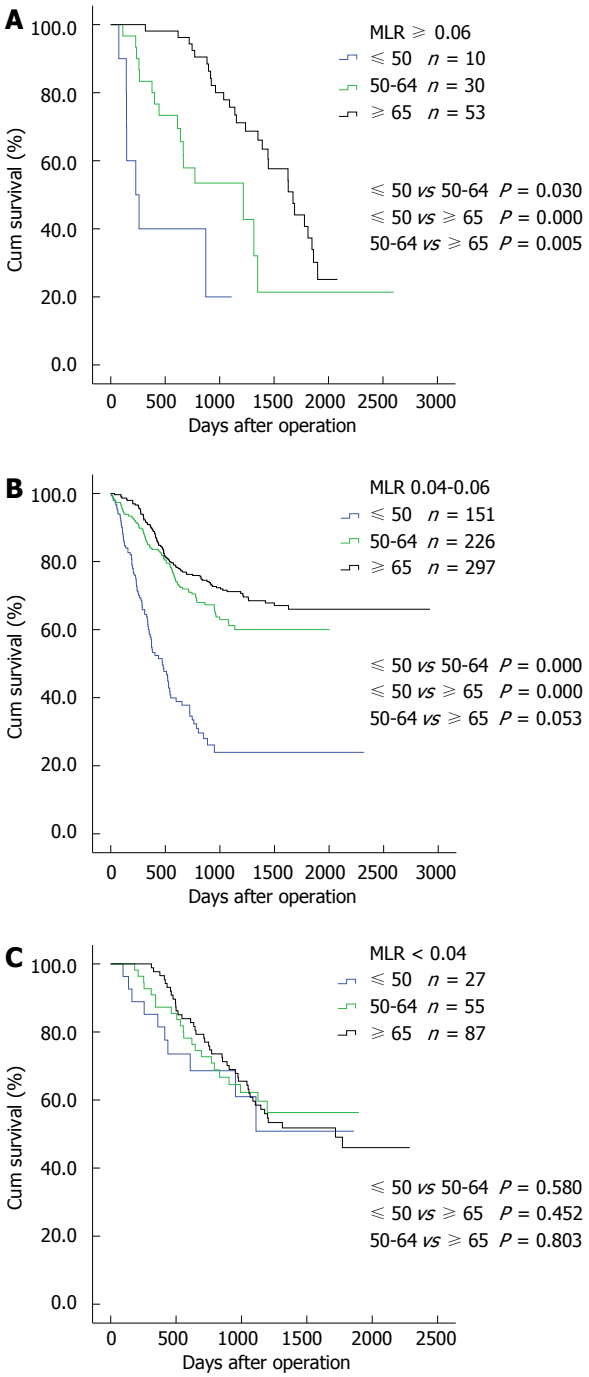

Figure 4 Cumulative survival of patients with gastric cancer + solitary lymph node metastasis and different metastatic lymph node ratio according to age category. A: $P < 0.05$ for comparisons among all three groups; B: Younger patients have significantly worse survival than the two older patient groups ($P < 0.01$); C: There are no significant differences among the three groups. Cumulative survival of patients with metastatic lymph node ratio (MLR) ⩾ 0.06 (A), 0.04-0.06 (B), and < 0.04 (C) by age.

come. Similarly, in a study of elderly and middle-aged GC patients matched for tumor extension, Kitamura *et al*[21] found that older age was associated with poorer overall survival and death within 30 d after surgery. Indeed, the increased risk of complications and death from surgery in general is well recognized, and a study of surgically-treated GC patients showed markedly better 5-year post-operative survival at all tumor stages[22].

It has been reported that younger (middle-aged) patients have better prognosis following curative resection of stage I tumors than their elderly counterparts[6]. Other reports, however, have demonstrated that younger age provides no benefit to survival when the GC is present in more advanced stages and that the most important prognostic factor in young patients is advanced nodal involvement[23-25]. Regardless of whether or not there is a distinctive malignant trait related to age, a key means towards improving survival rates is early diagnosis and timely application of curative resection.

The results from the current study confirmed the view that the relationship between GC prognosis and patient age is complicated. In general, the mean age of GC diagnosis falls within the 5th decade of life and cases younger than 50 years old are relatively rare[26,27]; however, by searching a large patient database we were able to analyze a patient population that equally represented young and old GC sufferers. The current study population showed a poorer prognosis for younger (⩽ 50 years old) patients, as evidenced by both cumulative and 5-year survival rates. Moreover, the younger patients had fewer surgery-related complications (data not shown) that may have benefited their recovery and prognosis.

Another important finding for the current study's population of patients with GC + SLNM was the relationship between age and mean survival days after surgery. The younger patients, who also had more aggressive tumors by histological analysis, survived for a significantly shorter duration following the resection treatment. This finding agrees with another study of GC patients that found diffuse cancers more likely to occur in younger patients and to be associated with poorer prognosis.

Depth of invasion and presence of MLNs are well-established and essential prognostic factors of GC[28], and nodal involvement is considered an especially significant clinical finding in early GC. Ten-year overall survival in node-positive patients has been reported at 27%, compared to the estimated 92% for node-negative patients[29]. Incomplete removal of MLNs, which harbor residual tumor cells, represents an increased risk of disease spread or recurrence. Indeed, studies of post-gastrectomy survival in GC patients have shown that survival rates improve in conjunction with number of lymph nodes removed for examination[30-32].

The benefit of lymphadenectomy was related to extent; however, it remains to be precisely determined. Both the Union for International Cancer Control and the American Joint Commission for Cancer have recommended that at least 15 lymph nodes be examined for correct assessment node metastatic status in GC (7th edition TNM system). Moreover, dissection of ⩾ 15 lymph nodes in resections with curative intent has been reported to significantly improve prognosis of patients with GC + MLN[33]. Yet, while the useful prognostic impact of this lower-limit criteria has been validated in several large clinical studies[34,35], no study to date has systematically

evaluated the risk to benefit ratio of precise numbers of lymph nodes for GC or its myriad of histological parameters.

The association of SLNM with depth of tumor invasion and its prognostic significance in GC are well established. Furthermore, it is generally accepted that GC patients with SLNM have a worse survival rate than those without SLNM (zero positive lymph nodes). The estimates of GC cases with single nodal metastasis distributed beyond the perigastric area range from 12.6%-29.0%, and it is hypothesized that this feature may be related to (caused by) complicated lymphatic drainage from the stomach[36-38]. However, a comparative study of patients with and without skip metastasis after standard D2 lymphadenectomy found no significant difference in survival between the two groups[39]. Sentinel node mapping with a visible tracer or radio-guided approach has limited accuracy in GC patients. Therefore, the current study evaluated the age-related 5-year survival rates of follow-up GC + SLNM patients using an array of clinicopathological parameters, and found that Borrmann type, histological type, and tumor status were significantly different among the groups and were related to patient survival.

MLR calculation is considered a simpler and (possibly) more effective method for prognosing patients with GC who undergo curative or radical resections[40-42], compared to the conventional lymph node staging systems. In particular, MLR could supplement the conventional N staging system when a limited number of lymph nodes are obtained, thus providing more accurate prognostic stratification in advanced GC[40,43-45]. Herein, as in some related previous studies, MLR was shown to be a better prognostic factor than the other clinicopathological parameters examined; however, no consensus has been made on the optimal categorization of MLR, as each study has used different standardization. In the current study, the GC + SLNM patients were categorized according to the number of harvested lymph nodes, and the data indicated that 5-year survival rates were associated with SLNM per lymph node harvested. Specifically, younger patients with MLR $\geqslant$ 0.06 and 0.06-0.04 had lower survival than older patients.

As discussed above, young adults may be more likely to present for diagnosis at an advanced disease stage. In the absence of an effective predictive marker, surveillance endoscopy of patients with positive family histories seems to be the only way to detect early stage GC. Such patients should also be educated on the signs and symptoms of GC, and more attention should be paid to younger patients with upper gastrointestinal symptoms, to improve their rate of early diagnosis. Multivariate analyses have indicated that younger patients undergoing curative resection have longer survival[46]. As D2 lymphadenectomy leads to the examination of more nodes, and improves prognostic accuracy in patients with or without MLNs[47], wider use of D2 lymphadenectomy may be essential for patients with GC, especially those of younger age.

In conclusion, among the GC + SLNM patients examined in this study, younger patients tended to have shorter survival than their older counterparts. In particular, younger patients with the highest MLR had the worst prognosis. Thus, the field should strive towards improving earlier detection rates for GC patients to help improve prognosis of these patients. For younger patients, who may be at greater risk of disease-related mortality but at less risk of surgery-related morbidities, D2 lymphadenectomy may be considered because it allows sampling of many more lymph nodes.

COMMENTS

Background

The current data on age-related differential prognoses for gastric cancer (GC) is inconsistent. This study was designed to investigate the potential age-related differences in survival of GC patients with solitary lymph node metastasis (SLNM) and to determine the clinical efficacy of metastatic lymph node ratio (MLR) as a more sensitive predictor of GC recurrence than traditional histopathological parameters.

Research frontiers

Among the patients with GC + SLNM examined in this study, the younger patients ($\leqslant$ 50-years-old) experienced greater mortality and shorter survival times than the older patients. In particular, the younger patients with the highest MLR had the worst prognosis.

Innovations and breakthroughs

Overall and 5-year survival rates of patients with GC and SLNM are lower in patients $\leqslant$ 50-years-old. Thus, efforts should be made to diagnose these cases earlier, and more sensitive intraoperative prognostic methods, such as calculating the MLR, should be applied. The younger age of these patients translates to their general better health and good candidacy for uncomplicated recovery from surgery, thus allowing for the realization of benefit from the more accurate surgical prognosis methods.

Applications

Strategies to improve earlier detection of GC should be devised and implemented, especially targeting the younger patient population. To achieve more accurate prognosis in this patient population, methods that allow for sampling of more lymph nodes, such as D2 lymphadenectomy, should be applied.

Terminology

Gastric carcinoma is usually detected at a later disease stage in younger individuals, and this fact may have cause a shorter survival time. It is generally accepted that GC patients with SLNM have a worse survival rate than those without SLNM. MLR is considered a simpler and more effective method for prognosing patients with GC who undergo curative or radical resections. D2 lymphadenectomy is considered when sampling many more lymph nodes.

Peer review

The authors thoroughly explained the problem of prognostic value of examined lymph node count in GC cases with SLNM, with respect to patient age. They have described, in detail, their data based on clinicopathological parameters and sufficiently discussed the implications of their findings in relation to the collective body of literature on this topic. The study showed that there is an age-related component to cumulative and 5-year survival of these cases, with younger age ($\leqslant$ 50-years-old) and higher MLR status being predictive of less and shorter survival.

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