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Extent of Serosal Changes Predicts Peritoneal Recurrence and Poor Prognosis After Curative Surgery for Gastric Cancer

Yue Kang, MD, Shenglong Li, MS, Qinghong Ge, MS, Xinran Liu, MS, Zhenyu Yang, MS, Yingwei Xue, MD, and Fujing Wang, MD

Abstract: To investigate whether the width of gastric serosal lesions in advanced gastric cancer patients have a predictive value for peritoneal recurrence and the 5-year survival rate.

A total of 1109 patients with advanced noncardia primary gastric adenocarcinoma, who underwent curative gastrectomy between January 1997 and December 2007, were included. Data about tumor size, longitudinal tumor location, resection type, serum albumin concentration, lymphatic/venous invasion, lymph node metastasis status, lesion size, histological and Borrmann type of tumor, as well as the recurrence rate and width of the gastric serosal lesions were collected and analyzed.

The peritoneal recurrence rate in patients with gastric serosal lesions $\leq$3 cm was lower than in patients with gastric serosal lesions >3 cm. Multivariate analyses of the 5-year survival rate variables for all patients revealed significant correlations with serum albumin concentrations (HR 1.382, $P = 0.002$, 95% CI 1.123–1.701), width of serosa changes (HR 1.377, $P = 0.020$, 95% CI 1.053–1.802), depth of invasion (HR 1.529, $P < 0.001$, 95% CI 1.288–1.814), and lymph node metastasis (HR 1.551, $P < 0.001$, 95% CI 1.420–1.694), whereas for recurrent patients only serum albumin concentrations (HR 2.000, $P < 0.001$, 95% CI 1.425–2.805), width of serosa changes (HR 1.867, $P = 0.002$, 95% CI 1.248–2.793), and lymph node metastasis (HR 1.521, $P < 0.001$, 95% CI 1.249–1.852) correlated with the 5-year survival rate.

Gastric serosal lesions >3 cm may indicate a high risk for peritoneal recurrence and serve as additional indicators for preventive postoperative adjuvant chemotherapies in patients with advanced gastric cancer.

(*Medicine* 94(42):e1750)

Abbreviations: HIPC = hyperthermic intraperitoneal chemotherapy, PLC = peritoneal lavage cytology.

INTRODUCTION

Gastric cancer is the third most common cause of cancer-related death, with the highest mortality rates in East Asia, including China. Approximately 60% of gastric cancers are diagnosed in these regions.[1] The main treatment for gastric cancer is surgery but peritoneal recurrence is the most frequent pattern of metastasis even after curative resection.[2,3] Since the prognosis of patients with peritoneal recurrence is dismal and the median survival time is only about 6 months, the identification of patients at high-risk of peritoneal recurrence is crucial to allow proper treatment strategies to be developed.

Over the last 20 years, peritoneal lavage cytology (PLC) has been the standard method used to detect peritoneal micrometastasis. However, the sensitivity of PLC for metastasis prognosis has been reported to be only 18%–50% and not all patients with positive peritoneal cytology will eventually develop a peritoneal recurrence. However, even patients with negative peritoneal cytology have developed peritoneal recurrence after curative resection.[4,5] Other authors have noted that test execution variations might be the reason for the poor diagnostic accuracy of PLC.[6] Therefore, additional approaches to identify definitively peritoneal metastasis are needed.

As up to 50% of patients with serosal invasion are known to develop peritoneal recurrence, even after curative resections,[7] the present retrospective study was carried out to investigate the correlation between the magnitude of serosal changes and the incidence of peritoneal recurrence in order to determine the high-risk factors for peritoneal metastasis.

Patients and Methods

A cohort of 1109 patients with advanced stage, primary noncardia gastric adenocarcinoma[8] were operated on (gastrectomy) between January 1997 and December 2007 in the Department of General Surgery of the Second Affiliated Hospital of Harbin Medical University. Patient pathological and operation reports together with subsequent follow-up clinical evaluation examination data were stored on our outpatient clinical computer database and available to us from remote terminals as required. The majority of the patients underwent total or partial gastrectomy together with a D2 lymphadenectomy performed by experienced surgeons, which closely followed the operation guidelines of the Japanese Research Society for Gastric Cancer.[9] The exclusion criteria for analysis were gastric stump cancer or synchronous malignancy, tumors of the esophagogastric junction, any form of chronic inflammatory disease, the number of lymph nodes retrieved was <15, a definitive M1 classification, and peritoneal recurrence records that were erroneous. It is an indisputable fact that micrometastases are found in the peritoneal cavity of all PT4b stage cancers, and therefore these patients were excluded from the present study. All patients provided written informed consent for the study,

Editor: Neil Merrett.
Received: June 3, 2015; revised: September 10, 2015; accepted: September 15, 2015.
From the Department of General Surgery, The Second Affiliated Hospital of Harbin Medical University (YK, SL, XL, FW); Department of Internal Medicine, Orthopedic Hospital of Harbin (QG); Intensive Care Unit, The Second Affiliated Hospital of Harbin Medical University (ZY); and Department of Gastroenterologic Surgery, The Tumor Hospital of Harbin Medical University, Harbin, China (YX).
Correspondence: Fujing Wang, Yue Kang, Department of General Surgery, The Second Affiliated Hospital of Harbin Medical University, No. 246, Xue Fu Road, Harbin 150086, China (e-mail: wangfujing-hyd@163.com).
YK and SL contributed equally to this work.
This work was supported by the Postdoctoral Science Foundation of Heilongjiang Province (No. LBH-Z14136).
The authors have no conflicts of interest to disclose.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000001750

which was approved by the Research Ethics Committee of Harbin Medical University.

Extent of Serosal Invasion

The Japanese Classification of Gastric Carcinoma[27] was used as a guide to measure the width of the serosal invasion. Briefly, the entire serous membrane was visualized by opening the resected stomach along the lesser or greater curvature. The largest macroscopical change in the serosal surface was determined as the measurement (serosal invasion width) used in subsequent analysis. The changes were characterized thus: S0, no change (n = 770); Sn, maximum diameter of change ≤3 cm (n = 113); and Sw, maximum diameter of changes >3 cm (n = 226).

Follow-Up

All patients underwent periodic follow-up examinations and were assessed every 3 months during the first 2 years after surgery, then every 6 months for 3 years and afterwards yearly. During follow-up, patients were evaluated by physical examination, serum tumor markers (carcinoembryonic antigen, CA19-9 and CA125), endoscopy, chest radiography, abdominopelvic ultrasonography, and computed tomography. Survival duration was calculated from the time of surgery to death or the last follow-up date (December 31, 2011). The median follow-up duration was 52.2 months (range 3.8–119.4).

Peritoneal recurrence was determined by positive cytologic findings of ascitic fluid or by reoperative biopsy. Abdominal ultrasonography and computed tomography were performed for suspected clinical recurrence or because of an increase in tumor markers above pathological levels. The proof of peritoneal recurrence usually required sequential imaging that demonstrated progression of metastatic lesions. In rare situations, peritoneal recurrence was detected by the appearance of clinical signs such as intraabdominal mass or intractable intestinal obstruction. Tumors involving the ovaries (Kruchenberg tumors) and Douglas metastases detected clinically or radiologically were counted as peritoneal recurrences. Although some patients had multiple recurrence episodes, only the initial site of peritoneal recurrence was taken into consideration for statistical evaluations.

Statistical Analyses

SPSS (version 19.0; SPSS, Inc., Chicago, IL) was used for all statistical analyses. Data presented as percentages were compared using a Chi-square test; comparisons of 5-year survival rates with different variables among subgroups were analyzed using a log-rank Chi-square test; multivariate analysis was carried out to establish the hazard ratio with different variables. The Cox proportional hazard regression model was used to determine the optimal cutoff threshold for gastric lesion size. *P*-values <0.05 were considered to be statistically significant.

RESULTS

Threshold Size of Gastric Lesion

To determine the survival rates, changes in the serosal width threshold were calculated at 1 cm interval. The Cox proportional hazard regression model indicates that the optimal cutoff point is given by the largest Chi-square score determined. The most significant difference in survival rates was at the threshold value of 3 cm (Chi-square 136.486, $P < 0.0001$, HR 3.079, 95% CI 2.550–3.719) (Table 1).

TABLE 1. Chi-Square Score and Hazard Ratio According to the Extent of Serosal Changes Calculated Using the Cox Proportional Hazard Regression Model

Threshold	Chi-square	*P*	HR	95% CI
1	50.456	<0.0001	1.920	1.604–2.298
2	113.387	<0.0001	2.713	2.258–3.260
3	136.486	<0.0001	3.079	2.550–3.719
4	129.376	<0.0001	2.939	2.441–3.540
5	90.971	<0.0001	2.423	2.020–2.907

95% CI = 95% confidence interval, HR = hazard ratio.

TABLE 2. Gastric Cancer Parameters and Peritoneal Recurrence Rates

Variable	Total Number of Patients	Number Of Recurrence Patients	Recurrence Percentage, %	*P*
Age, years				0.064
<60	636	112	17.6	
≥60	473	110	23.3	
Sex				1
Male	800	160	20.0	
Female	309	62	20.1	
Tumor size, cm				<0.001
<7	869	110	12.7	
≥7	240	112	46.7	
Borrmann type				<0.001
I/II	299	101	33.8	
III/IV	810	121	14.9	
Resection type				<0.001
Subtotal	886	100	11.3	
Total	223	122	54.7	
Longitudinal location				<0.001
Other	875	128	14.6	
Entire	234	94	40.2	
Serum albumin, g/L				<0.001
≤3.5	286	153	53.5	
>3.5	823	69	8.4	
Histologic type				0.711
Differentiated	482	93	19.3	
Undifferentiated	627	129	20.6	
Lymphatic/venous invasion				<0.001
Negative	1,003	143	14.3	
Positive	106	79	74.5	
Lymph node metastasis				<0.001
pN0	433	9	2.1	
pN1	190	53	27.9	
pN2	208	50	24.0	
pN3	278	110	39.6	
Width of serosa changes (cm)				<0.001
≤3 cm	883	63	7.1	
>3 cm	226	159	70.4	

TABLE 3. Predictive Specificity, Sensitivity, and Accuracy Levels of Serosa Lesion Size, Lymph Node Metastasis, and Serum Albumin Concentrations for Predicting Peritoneal Recurrence

	Peritoneal Recurrence				
	Negative	**Positive**	**Specificity, %**	**Sensitivity, %**	**Accuracy, %**
Width of serosa changes, cm			92.4	71.6	88.3
≤3 cm	820	63			
>3 cm	67	159			
Lymph node metastasis			47.8	95.9	94
Negative	424	9			
Positive	463	213			
Serum albumin, g/L			85	68.9	81.8
>3.5	754	69			
≤3.5	133	153			
Combined			98	77	93.8

TABLE 4. Associations Between Clinicopathologic Parameters and the Width of Serosal Changes in Patients With Advanced Gastric Cancer Who Underwent Curative Gastrectomy

		Width of Serosal Changes			
		S0 (n = 770)	**Sn (n = 113)**	**Sw (n = 226)**	
Variable	**n**	**n (%)**	**n (%)**	**n (%)**	***P***
Age, years					0.067
<60	636	458 (72)	63 (10)	115 (18)	
≥60	473	312 (66)	50 (10.6)	111 (23.4)	
Sex					0.575
Male	800	557 (69.6)	77 (9.6)	166 (20.8)	
Female	309	213 (68.9)	36 (11.7)	60 (19.4)	
Tumor size, cm					<0.001
<7	869	663 (76.3)	102 (11.7)	104 (12)	
≥7	240	107 (44.6)	11 (4.6)	122 (50.8)	
Borrmann type					<0.001
I/II	299	243 (81.3)	23 (7.7)	33 (11)	
III/IV	810	527 (65)	90 (11.1)	193 (23.9)	
Resection type					<0.001
Subtotal	886	656 (74)	94 (10.6)	136 (15.4)	
Total	223	114 (48.3)	19 (8.5)	90 (43.2)	
Longitudinal location					<0.001
Other	875	658 (75.2)	100 (11.4)	117 (13.4)	
Entire	234	112 (47.9)	13 (5.6)	109 (46.5)	
Serum albumin, g/L					<0.001
≤3.5	286	29 (10.1)	78 (27.3)	179 (62.6)	
>3.5	823	741 (90)	35 (4.2)	47 (5.8)	
Histologic type					0.018
Differentiated	482	344 (71.4)	57 (11.8)	81 (16.8)	
Undifferentiated	627	426 (67.9)	56 (8.9)	145 (23.2)	
Lymphatic/venous invasion					<0.001
Negative	1003	739 (73.7)	110 (11)	154 (15.3)	
Positive	106	31 (29.2)	3 (2.9)	72 (67.9)	
Lymph node metastasis					<0.001
pN0	433	353 (81.5)	59 (13.6)	21 (4.9)	
pN1	190	138 (72.6)	22 (11.6)	30 (15.8)	
pN2	208	137 (65.9)	23 (11)	48 (23.1)	
pN3	278	142 (51)	9 (3.3)	127 (45.7)	

TABLE 5. Single Factor Analysis of Different Variables for 5-year Survival Rates of Patients With Advanced Gastric Cancer Who Underwent Curative Gastrectomy

Variable	n	5-year Survival Rate, %	Log-Rank Chi-Square	*P*
Age, years			1.648	0.199
<60	636	64.13		
≥60	473	60.06		
Sex			0.01	0.921
Male	800	62.61		
Female	309	63.41		
Tumor size, cm			52.070	<0.001
<7	869	67.72		
≥7	240	44.35		
Borrmann type			17.6	<0.001
I/II	299	71.89		
III/IV	810	59.49		
Resection type			2.196	0.138
Subtotal	886	64.70		
Total	223	60.65		
Longitudinal location			35.254	<0.001
Other	875	67.12		
Entire	234	46.99		
Serum albumin, g/L			4.243	0.039
≤3.5	286	58.03		
>3.5	823	64.51		
Histologic type			7.014	0.008
Differentiated	482	65.25		
Undifferentiated	627	57.04		
Lymphatic/venous invasion			81.682	<0.001
Negative	1,003	66.52		
Positive	106	31.02		
Width of serosa changes, cm			152.044	<0.001
≤3	883	70.43		
>3	226	33.13		
Depth of invasion			175.472	<0.001
T2	309	78.31		
T3	461	71.19		
T4a	339	40.36		
Lymph node metastasis			216.021	<0.001
pN0	433	80.82		
pN1	190	73.16		
pN2	208	54.28		
pN3	278	34.17		

Correlations Between Clinical Parameters and Peritoneal Recurrence

Peritoneal recurrence occurred in 222 of 1109 patients (20%). As shown in Table 2, peritoneal recurrence rates were correlated with tumor size, resection type, longitudinal location, serum albumin concentration, lymphatic/venous invasion, and lymph node metastasis status as well as the lesion size, but not with the histologically characterized type of tumor. Positive lymphatic/venous invasion and gastric lesion sizes >3 cm were strong indicators for the risk of recurrence. There was also a correlation between the recurrence rates, with Borrmann cancer types I and II being the most frequently detected cancers ($P < 0.001$).

When comparing predictive values of serosa changes >3 cm, lymph node metastasis, and serum albumin concentrations ≤3.5 g/L for peritoneal recurrence, the specificity of serosa changes >3 cm was highest (92.4%), and the sensitivity (71.6%) and accuracy (88.3%) were higher than the sensitivity (68.9%) and accuracy (81.8%) of serum albumin levels, but lower than the sensitivity values (95.5%) and accuracy levels (94%) of lymph node metastasis. Combination of all 3 parameters for peritoneal recurrence prediction led to an accuracy of 93.8%, a sensitivity of 77%, and a specificity of 98% (Table 3).

TABLE 6. Multivariate Analysis of Different Variables for the 5-year Survival Rates of Patients with Advanced Gastric Cancer Who Underwent Curative Gastrectomy

Variables	Chi-Square	*P*	HR	95% CI
Tumor size, cm	1.006	0.316	1.185	0.851–1.651
Borrmann type	0.582	0.445	1.093	0.870–1.374
Longitudinal location	0.017	0.896	1.022	0.741–1.409
Serum albumin, g/L	9.320	0.002	1.382	1.123–1.701
Histologic type	1.466	0.226	0.875	0.706–1.086
Lymphatic/venous invasion	0.277	0.599	0.918	0.668–1.262
Width of serosa changes, cm	5.455	0.020	1.377	1.053–1.802
Depth of invasion	23.640	<0.001	1.529	1.288–1.814
Lymph node metastasis	94.972	<0.001	1.551	1.420–1.694

95% CI = 95% confidence interval, HR = hazard ratio.

Width of Serosal Changes and Clinicopathological Parameters

When the S0 with the Sw patients were compared, all analyzed clinicopathological parameters correlated with the width of the serosal changes, indicating that serosal changes reflect the severity of gastric cancers (Table 4).

Prognostic Factors for Patients With Advanced Stage gastric Cancers

Single factor analysis for 5-year survival rates revealed that tumor size, the Borrmann cancer type, longitudinal location, serum albumin concentrations, histology type, lymphatic/venous invasion, width of the serosa changes, T staging, and lymph node metastasis staging, but not the resection type, correlated with the 5-year survival rate (Table 5).

A further multivariate analysis revealed that only the serum albumin concentration, width of serosa changes, depth of tumor invasion, and lymph node metastasis correlated with the 5-year survival rate (Table 6).

TABLE 7. Single Factor Analysis of 5-year Survival Rate Factors for Patients With Advanced Gastric Cancer Who Underwent Curative gastrecTomy and Developed Peritoneal Recurrence

Variable	n	5-year Survival Rate, %	Log-Rank Chi-Square	*P*
Age, years			0.134	0.534
<60	112	40.1		
≥60	110	34.4		
Sex			1.343	0.174
Male	160	33.8		
Female	62	46.4		
Tumor size, cm			12.635	<0.001
<7	110	47.3		
≥7	112	27.5		
Borrmann type			12.810	<0.001
I/II	101	48.5		
III/IV	121	28.0		
Resection type			0.2880	0.592
Subtotal	100	33.9		
Total	122	40.1		
Longitudinal location			9.607	0.002
Other	128	45.3		
Entire	94	26.4		
Serum albumin, g/L			20.365	<0.001
≤3.5	153	20.1		
>3.5	69	45.1		
Histologic type			7.186	0.007
Differentiated	93	46.2		
Undifferentiated	129	30.9		
Lymphatic/venous invasion			14.810	<0.001
Negative	143	46.1		
Positive	79	21.4		
Width of serosa changes, cm)			14.8376	<0.001
≤3	63	58.6		
>3	159	28.9		
Depth of invasion			14.986	0.001
T2	42	61.9		
T3	31	32.7		
T4a	149	25.8		
Lymph node metastasis			29.940	<0.001
pN0	9	77.8		
pN1	53	58.5		
pN2	50	39.6		

Prognostic Factors for Patients With Peritoneal Recurrence

For peritoneal recurrence patients, single factor analyses for the 5-year survival rate revealed that the tumor size, Borrmann cancer type, longitudinal location, serum albumin concentrations, histology type, lymphatic/venous invasion, width of serosa changes, T staging, and lymph node metastasis staging, but not the resection type, correlated with the 5-year survival rate (Table 7). A multivariate analysis of the factors influencing the 5-year survival rate for patients with peritoneal recurrence showed that only the serum albumin concentration, lymph node metastasis, and width of the serosa changes correlated with 5-year survival (Table 8).

TABLE 8. Multivariate Analysis of Factors for 5-year Survival Rates in Patients With Advanced Gastric Cancer That Underwent Curative Gastrectomy and Developed Peritoneal Recurrence

Variables	Chi-Square	*P*	HR	95% CI
Tumor size, cm	0.125	0.724	1.207	0.425–3.423
Borrmann type	0.003	0.960	0.980	0.441–2.147
Longitudinal location	1.501	0.220	1.289	0.859–1.936
Serum albumin, g/L	16.103	<0.001	2.000	1.425–2.805
Histologic type	0.137	0.711	0.877	0.439–1.754
Lymphatic/venous invasion	2.801	0.094	1.350	0.950–1.920
Width of serosa changes, cm	9.235	0.002	1.867	1.248–2.793
Depth of invasion	3.698	0.054	1.236	0.996–1.533
Lymph node metastasis	17.373	<0.001	1.521	1.249–1.852

95% CI = 95% confidence interval, HR = hazard ratio.

Taken together, the recurrence rate was higher in patients with serosal changes >3 cm (70.4%) than in patients with serosal changes ≤3 cm (7.1%) (Table 2), and the degree of the serosal changes indicated the severity of the gastric cancer (Table 4). In addition, our statistical evaluation of factors influencing the 5-year survival rate of patients with advanced stage gastric cancer showed that the width of the serosa changes correlated with the survival of all patients (Table 6), as well as recurrence patients (Table 7), which was revealed by the Kaplan–Meier curves of all patients (Fig. 1) and recurrence patients (Fig. 2).

DISCUSSION

Although the therapy of patients with locally advanced gastric cancer is continually improving, peritoneal recurrence remains a frequent occurrence in relapsed patients.[10,11] When patients develop overt peritoneal metastasis after curative resection, the only therapeutic options are palliative surgery or adjuvant chemotherapy, but these treatments are difficult, demanding, and often unrewarding. Several authors have reported that normothermic intraperitoneal chemotherapy and hyperthermic intraperitoneal chemotherapy (HIPC) have some benefit in the prevention of peritoneal recurrence. One randomized trial of postoperative adjuvant intraperitoneal chemotherapy revealed a significant reduction in local and peritoneal recurrences in patients with advanced tumors who underwent normothermic intraperitoneal chemotherapy.[12] Another randomized prospective study demonstrated that HIPC was capable of improving survival times in patients with more advanced stages of the disease.[13] Other authors obtained similar results in favor of HIPC.[14–17] A proposed strategy to diagnose

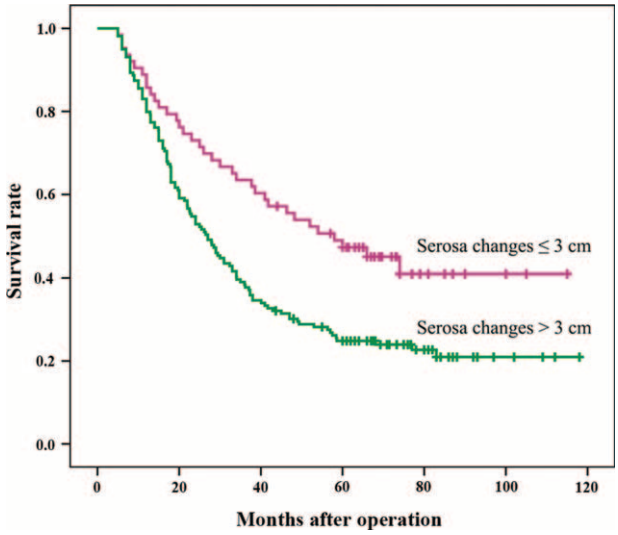

FIGURE 1. Kaplan–Meier curves of gastric cancer postintervention survival with indicated serosa changes at surgery. Horizontal marks (I) indicate censored values.

peritoneal carcinomatosis after gastric cancer surgery is preoperative PLC to identify patients at very high risk before surgery.[18] Fukagawa et al (2010)[19] reported that if intraoperative lavage cytology is positive in type 4 gastric cancer patients the prognosis becomes so poor that multimodality therapy, including perioperative chemotherapy, is essential. Bonenkamp et al (1996)[20] reported that cytological examination of abdominal washings increased the accuracy of staging and improved the selection of patients suitable for curative or palliative resection. In contrast, other studies noted that PLC is insensitive in predicting the development of peritoneal recurrence.[5] In 2010, PLC was incorporated into the 7th edition of the Union for International Cancer Control/American Joint Committee on Cancer staging system as a specific index of peritoneal

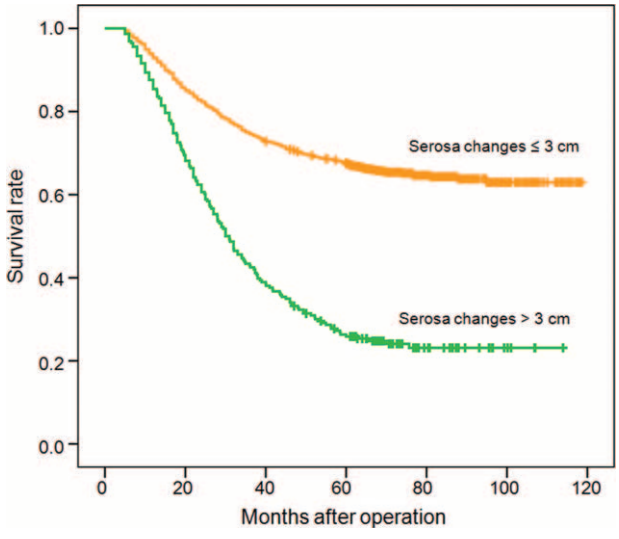

FIGURE 2. Kaplan–Meier curves of postinterventional survival with indicated serosa changes at surgery and peritoneal recurrence after gastric cancer treatments. Horizontal marks (I) indicate censored values.

dissemination. Patients with positive peritoneal cytology without peritoneal metastases are classified as M1, but the sensitivity of positive peritoneal cytology is low, owing to a considerable false negative rate, with the incidence of peritoneal recurrence ranging from 18% to 35%. It is widely accepted that a correlation exists between peritoneal recurrence and serosal invasion in patients with gastric cancer. Malignant cells exfoliated from the serosal lesions are the main reason for the development of peritoneal metastasis. Jeong et al[21] reported that the overall accuracy of macroscopic diagnosis of serosal invasion was 88%, and its sensitivity and specificity was 82% and 89%, respectively, while the extent of macroscopic serosal invasion was proposed to be helpful in planning adjuvant chemotherapy.[22] A few reports have shown that the width of serosal changes is a useful indicator for the prediction of peritoneal recurrence. Several authors have used 2.0, 2.5, or 3.0 cm as the cutoff points and reported that the prognosis of patients with extended serosal changes was significantly poorer than those with narrow serosal changes.[23–25] Our study revealed that the width of serosal changes in gastric cancer patients is significantly correlated with the recurrence rate ($P < 0.001$) and the 5-year survival rate ($P < 0.001$) of surgically treated gastric cancer, as well as the 5-year survival rate of peritoneal recurrence patients ($P < 0.001$). Other significant correlations between the 5-year survival rate of postoperative gastric cancer patients were the serum albumin concentration $\leq$3.5 g/L, depth of invasion, and lymph node metastasis, findings in agreement with previously reported 5-year survival rates correlated with smaller serosal invasion and fewer metastatic nodes in stage IIIA gastric cancer patients.[1] When data predicting peritoneal recurrence were combined (serosa lesion size >3 cm, lymph node metastasis, and serum albumin concentrations $\leq$3.5 g/L), the specificity became 98%, the sensitivity 77%, and accuracy 93.8%. Therefore, we suggest, in agreement with a previous study, that serosal changes might serve as a powerful additional indicator for prophylactic adjuvant chemotherapy for gastric cancer patients.[26]

In conclusion, based on our findings of correlations between the extent of gastric serosal changes and recurrence, as well as the 5-year survival rates in gastric cancer patients, we propose that the width of gastric serosal changes should be used as an additional indicator for prophylactic postoperative measures to prevent peritoneal recurrence, using adjuvant chemotherapies such as HIPC.

ACKNOWLEDGEMENTS

The authors thank the support from Postdoctoral Science Foundation of Heilongjiang Province (No. LBH-Z14136).

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