The prognostic significance of macroscopic serosal change in subserosal invasion (stage T3) gastric cancer

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ABSTRACT

BACKGROUND For patients with gastric cancer intraoperative macroscopic serosal change is not always consistent with pathological T stage. We investigated whether macroscopic serosal change is associated with unfavourable prognosis of patients with gastric cancer.

METHODS We reviewed 856 patients with stage T3 gastric cancer who underwent curative gastrectomy in our institution. All patients were classified as serosa negative and serosa positive according to the macroscopic serosal change during the operation. The prognostic difference between two groups was compared and clinicopathologic features were analysed.

RESULTS The percentage of macroscopic serosal change accounted for 55.7% of all patients. Compared with normal serosal surface, the patients with macroscopic serosal change had larger tumour size, more extensive stomach involvement and more advanced stage N. The prognosis of stage T3 with macroscopic serosal change was significantly poorer than that of those with normal serosal surface, especially for those with stages T3N0 and T3N1. Multivariate analysis identified macroscopic serosal change as an independent factor associated with unfavourable prognosis of stage T3 cancer.

CONCLUSION Although the depth of tumour invasion mainly depends on pathological evaluation after surgery, the prognostic significance of intraoperative macroscopic serosal change should not be ignored for those patients with subserosal invasion.

KEYWORDS

Gastric cancer – Macroscopic serosal change – T stage – Prognosis

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Introduction

Gastric cancer is one of the most common malignancies worldwide and remains the main cause of cancer-related death.¹ Curative resection, including adequate lymphadenectomy, is regarded as the optimum treatment modality for advanced gastric cancer.^{2,5} However, the prognosis for patients with gastric cancer is still unsatisfactory due to the high rate of recurrence and metastasis.⁴ The depth of tumour invasion (T stage) and the number of positive lymph nodes (N stage) are the two most important factors influencing the prognosis of patients with gastric cancer.^{5–7}

The TNM staging system of the American Joint Commission on Cancer (AJCC) is widely used to predict the prognosis of gastric cancer and to guide postoperative treatment. According to the 7th edition of TNM staging system, stage T1 is classified as T1a (mucosal invasion, M) and T1b (submucosal invasion, SM), T2 is defined as tumour invasion of muscularis propria, T3 is defined as subserosal invasion and T4 is further classified as T4a (serosal invasion, SE) and T4b (invasion of adjacent tissue and organ).⁸

In general, deeper tumour invasion could result in more apparent change of serosal surface. However, some studies have identified that intraoperative macroscopic serosal change is not always consistent with final pathological T stage.^{9–12} According to previously published reports, macroscopic serosal invasion during surgery may be overestimated in a high proportion of patients with stage T3, and serosal invasion is also underestimated in those with stage T4 cancer.^{9–11} When the serosal surface is invaded by the advanced tumour, there is a higher possibility of peritoneal metastasis and recurrence because of potential tumour cell exfoliation from the serosal surface.^{13,14} For patients without microscopic serosal invasion, however, whether macroscopic serosal change is associated with an unfavourable prognosis remains under investigation. There are few studies evaluating the prognostic significance of macroscopic serosal change in pathologically subserosal gastric cancer.^{9,11,12,15}

We reviewed patients with stage T3 gastric cancer who underwent curative gastrectomy in our research institution and compared the prognostic difference between serosa negative and serosa positive patients.

Materials and methods

Patients

The inclusion and exclusion criteria for this study were as follows:

- > Pathological diagnosis with primary gastric cancer via haematoxylin–eosin staining after surgery. Patients identified as having subserosal invasion (stage T3) were enrolled in the study.
- > Curative gastrectomy with lymph node dissection.
- > Patients with distant metastasis were excluded, including those with liver, peritoneal and extra-regional lymph node metastases. In patients with macroscopic serosal invasion, peritoneal washing was performed to detect free interperitoneal tumour cells. Those with cytology-positive results were excluded.
- > Patients who underwent neoadjuvant chemotherapy before curative surgery and had the history of other malignant tumours were excluded from the study.
- > Pathological information was complete, especially the depth of microscopic tumour invasion and macroscopic serosal change during the operation.

Using to these eligibility criteria, the study included 856 patients with stage T3 gastric cancer who underwent curative gastrectomy in our institution between January 1995 and January 2010. This study was approved by the Ethics Committee of our research institution and all patients provided written informed consent prior to surgery.

Surgical procedures and postoperative treatment

Distal, proximal or total gastrectomy was mainly determined by tumour size, location and resection margins. The Billroth-I, Billroth-II, Roux-en-Y oesophagojejunostomy or other type of the anastomosis was performed to reconstruct the alimentary tract. The extent of lymph node dissection was based on the Japanese Classification of Gastric Cancer (JCGC).¹⁶ Data collected included sex, age, tumour location, tumour size, differentiation type, lymphovascular invasion, infiltration growth pattern, number of positive lymph nodes, depth of tumour invasion, macroscopic serosal change and adjuvant chemotherapy.

The depth of tumour invasion and metastatic status of retrieved lymph nodes were reviewed and assessed independently by two pathologists, and any disagreements were resolved by discussion with a third expert. All patients were staged according to the 7th edition of the AJCC TNM staging system.⁸ Patients with stage II–III were recommended to receive postoperative adjuvant chemotherapy. The administered regimens were fluorouracil or cisplatin/oxaliplatin-based systemic chemotherapy.

In our research institution, infiltration growth pattern was routinely evaluated by haematoxylin–eosin staining as a pathological feature of the resected specimen. According to the JCGC, the growth pattern of tumour cell infiltration into the surrounding tissue can be classified into three categories: INFa, INFb and INFg.¹⁷ The INFa pattern indicates that the tumour shows an expanding growth and a distinct border can be observed in the surrounding tissue. The INFg pattern is described as an infiltrating growth and indistinct

border with the surrounding tissue. The intermediate pattern between INFa and INFg is defined as the INFb pattern.¹⁷

Serosal change was defined as the macroscopic disruption of serosal continuity in the operative field. Compared with the normal serosal surface (serosa negative), the following features indicate a serosa-positive surface: protruding nodules in the serosal surface, diffuse and multiple colour changes or a reddish and oedematous appearance.¹⁸ Macroscopic serosal changes during surgery were determined by two surgeons and any disagreements were resolved by discussion with a third surgeon.

Follow-up

All patients who underwent curative resection in our institution were followed up every three months for the first two years, every six months for the second two years and annually thereafter until death or last follow-up date. During the follow-up period, all patients received endoscopy, abdominal computed tomography, ultrasound and tumour biomarkers to evaluate surgical outcome and to monitor postoperative recurrence. Tumour recurrences included local relapse (gastric remnant or anastomotic site), regional lymph nodes metastasis and distant metastasis (peritoneal seeding, hematogenous dissemination or extra-regional lymph nodes metastasis). All postoperative recurrences were diagnosed according to clinical and imaging findings and pathological results. In this study, the end-point event was defined as disease-free survival, which was the time span started from date of surgery to tumour recurrence or death from any cause. In our follow-up cohort, the median follow-up period was 27 months (range, 1–178 months).

Statistical analysis

The categorical variables were compared using Pearson's chi-square test or Fisher's exact test, and continuous variables were compared using Student's t test. Survival curves were constructed and plotted according to the Kaplan–Meier method and statistical differences between different patient groups were compared using the log-rank test. The survival data was presented as five-year disease-free survival for each group. The Cox proportional hazard model was used as the multivariate analysis to identify the independent prognostic factors; hazard ratios (HR) and 95% confidence intervals (CI) were calculated. All statistical analyses were performed using the SPSS19.0 statistical package. A *P*-value less than 0.05 was considered to be statistically significant.

Results

Clinicopathological characteristics of patients

The clinicopathological features of patients who underwent curative gastrectomy are summarised in Table 1. In the patient cohort, 28.4% were female and 71.6% were male, the median age was 61 years (range, 25–90 years). Among these patients, 82.6% underwent subtotal gastrectomy and the incidence of lymph node metastasis was 70.9% (607/856). The median of positive lymph nodes was

5 (range, 1–84). Of 607 patients who were identified with lymph node metastasis, the proportions of N1, N2 and N3 were 29.0%, 30.5% and 40.5%, respectively.

All patients with stage T3 disease were classified into serosa-negative -positive groups based on the macroscopic serosal changes in the operative field. Serosa-positive patients accounted for 55.7% (477/856) of all cases. Compared with the serosa-negative group, the patients with macroscopic serosal change were prone to larger tumour size (4.63 ± 1.83 cm vs 6.25 ± 2.58 cm, $P < 0.001$), more

extensive stomach involvement and more advanced N stage. However, there were no significant differences between the two groups in patient age, sex, tumour differentiation type, lymphovascular invasion, infiltration growth pattern and adjuvant chemotherapy (Table 1).

The impact of macroscopic serosal change on the prognosis of stage T3 disease

The Kaplan–Meier curves demonstrated that the prognosis of stage T3 disease with serosal change was significantly

Table 1 Clinicopathological characteristics of 856 patients with stage T3 gastric cancer according to macroscopic serosal change.

Factor	Patients		Macroscopic serosal change				P-value
	(n)	(%)	Negative		Positive		
			(n)	(%)	(n)	(%)	
Age (years):							0.684
≤ 60	420	49.1	183	48.3	237	49.7	
> 60	436	50.9	196	51.7	240	50.3	
Sex:							0.928
Female	243	28.4	107	28.2	136	28.5	
Male	613	71.6	272	71.8	341	71.5	
Tumour location:							< 0.001
Lower third	452	52.8	211	55.7	241	50.5	
Middle third	100	11.7	47	12.4	53	11.1	
Upper third	148	17.3	89	23.5	59	12.4	
≤Two-thirds stomach	156	18.2	32	8.4	124	26.0	
Tumour size:							< 0.001
≤ 5 cm	454	53.0	268	70.7	186	39.0	
> 5 cm	402	47.9	111	29.3	291	61.0	
Differentiation type:							0.150
Well/moderate	265	31.0	127	33.5	138	28.9	
Low/undifferentiated	591	69.0	252	66.5	339	71.1	
Lymphatic invasion:							0.257
No	662	77.3	300	79.2	362	75.9	
Yes	194	22.7	79	20.8	115	24.1	
Infiltration growth pattern:							0.488
a/b	436	50.9	188	49.6	248	52.0	
g	420	49.1	191	50.4	229	48.0	
N stage:							< 0.001
N0	249	29.1	139	36.7	110	23.1	
N1	176	20.6	91	24.0	85	17.8	
N2	185	21.6	69	18.2	116	24.3	
N3	246	28.7	80	21.1	166	34.8	
Chemotherapy:							0.160
No	575	67.2	245	64.6	330	69.2	
Yes	281	32.8	134	35.4	147	30.8

poorer than that of those without serosal change (five-year disease-free survival rate, 32.6% vs 47.5%, $P < 0.001$; Fig 1). The survival curves of the two patient groups, stratified by the TNM staging, were shown in Figures 2 and 3. For patients with stage II (T3N0 and T3N1) disease, the negative association between macroscopic serosal change and the prognosis of these patients was still significant, and the five-year disease-free survival rate of serosa-negative and serosa-positive groups were 61.7% and 46.5%, respectively ($P < 0.001$; Fig 1B). For the patients with stage III (T3N2 and T3N3) disease, however, there was no significant prognostic difference between the serosa-negative and serosa-positive groups (23.1% vs 23.4%, $P < 0.05$; Fig 1C).

Univariate and multivariate analysis of prognostic factors

In the univariate analysis (Table 2), the following eight factors were found to have statistically significant associations with prognosis: tumour location ($P = 0.001$), tumour size ($P = 0.011$), differentiation type ($P = 0.018$), lymphovascular invasion ($P < 0.001$), tumour infiltration pattern ($P = 0.004$), macroscopic serosal change ($P < 0.001$), N stage ($P < 0.001$) and adjuvant chemotherapy ($P = 0.002$). Subsequently, multivariate analysis was performed to determine the independent prognostic factors. According to the multivariate analysis, tumour location (upper third), tumour infiltration pattern (INFg), macroscopic serosal change, N stage and adjuvant chemotherapy were identified as the independent prognostic factors (Table 2).

Discussion

The depth of tumour invasion (T stage) was regarded as an important factor associated with prognosis.^{5,7} With the increased depth of tumour invasion, macroscopic disruption of serosal continuity could be observed. However, the discordance between pathological T stage and intraoperative macroscopic serosal change may still exist according to previous studies.^{9–12} Yoo *et al* reported that macroscopic serosal change could occur in 49% of T1–T2 stage disease, but normal serosal surface could be observed in only 14% of T3–T4 stage disease.¹² In other words, a proportion of T1–T3 stage disease may be overestimated as serosal invasion during the operation, and T4 stage disease may be underestimated due to a normal serosal surface. Kang *et al* reviewed and collected analytical data of 2835 patients with gastric cancer who underwent curative gastrectomy, and their results indicated that 18.9% of the patients without pathological serosal invasion were identified as having macroscopic serosal change.⁹ Among these patients, the proportion with stages T1, T2 and T3 disease were 3.5%, 24.5% and 75.5%, respectively.⁹ These results suggested that the discordant result between macroscopic and microscopic serosal invasion could be observed in a higher proportion of patients with stage T3 disease. In our study, the percentage of macroscopic serosal change accounted for 55.7% of all patients with stage T3 disease and the result was similar to previous studies.^{11,15} In addition, we evaluated the impact of macroscopic serosal change on the

Table 2 The univariate and multivariate analysis of prognostic factors in 856 patients with stage T3 gastric cancer who underwent gastrectomy.

Factor	Univariate		HR	Multivariate	
	5-year DFS (%)	(P-value)		(95% CI)	(P-value)
Age (years):		0.401			–
≤ 60	39.8		–	–	
> 60	37.4		–	–	
Sex:		0.523		–	–
Female	41.6		–	–	
Male	37.5		–	–	
Tumour location:		0.001			
Lower third	40.3			1	
Middle third	48.3	0.461		0.895	0.658–1.217
Upper third	34.4	0.011		1.534	1.201–1.958
≤Two-thirds stomach	30.2	0.002		1.187	0.937–1.505
Tumour size:		0.011			0.420
≤ 5 cm	40.8		1		
> 5 cm	36.2		0.929	0.754–1.145	
Differentiation type:		0.018			0.560
Well/moderate	43.4		1		
Low/undifferentiated	36.5		1.058	0.850–1.317	
Lymphovascular invasion:		< 0.001			0.082
No	41.9		1		
Yes	27.1		1.198	0.969–1.482	
Macroscopic serosal change:		< 0.001			0.014
Negative	47.5		1		
Positive	32.6		1.280	1.048–1.562	
Infiltration growth pattern:		0.004			< 0.001
a/b	44.1		1		
g	33.3		1.237	1.032–1.482	
N stage:		< 0.001			
N0	63.5			1.792	1
N1	40.9	< 0.001		2.063	1.340–2.396
N2	34.1	< 0.001		2.063	1.551–2.744
N3	14.0	< 0.001		4.159	3.192–5.419
Chemotherapy:		0.002			< 0.001
No	36.4		1		
Yes	45.0		0.680	0.545–0.848	

prognosis for stage T3 disease. Our results indicate that macroscopic serosal change has an adverse impact on the prognosis of these patients, especially in stage T3N0 and T3N1 (stage II) disease. When other clinicopathological factors are included in the multivariate analysis,

macroscopic serosal change remains a significant and independent prognostic factor.

Similarly, the prognostic significance of macroscopic serosal change is validated in other studies.^{9,11,12} Kang *et al* found that patients with stage T3-T4a disease with

macroscopic serosal changes had a poorer prognosis than those with normal serosal surface when stage-by-stage comparisons were made.⁹ Kim *et al* reported that the prognosis for patients with stage T3 disease with macroscopic serosal invasion was not significantly different from that of those with stage T4a disease.¹⁵ Accurate staging is an important tool to guide treatment, and several studies have emphasised the prognostic value of surgical staging in advanced disease.^{19,20} Macroscopic serosal change can help to determine the surgical T stage. In view of its prognostic significance, the integration of surgical and pathological tumour staging may provide more accurate prognostic information for gastric cancer.

At present, there is no consensus on macroscopic serosal change and its assessment mainly depends on the arbitrary judgement of the surgeon. In the study by Jeong *et al*, however, the accuracy, sensitivity and specificity of macroscopic judgement of serosal change were 88%, 82% and 89%, respectively, which was consistently better than pre-operative computed tomography.¹⁰ Even when patients with early disease were excluded, the accuracy, sensitivity and specificity of macroscopic judgement of serosal change still reached 71.5%, 81.8% and 65.3%, respectively.¹⁰ Visual examination and careful palpation during surgery remains the most important method for diagnosing macroscopic serosal invasion. In addition to the depth of tumour invasion, the horizontal area of tumour invasion may have an adverse impact on the prognosis for advanced disease. Soga *et al* demonstrated that the width of subserosal invasion is an independent prognostic factor for the stage T3 disease.²¹ In their study, a width of subserosal invasion of 2 cm or greater had more frequent peritoneal recurrence and a poorer prognosis than narrow subserosal invasion.²¹ Similarly, Nakamura *et al* showed that the prognosis for stage T3N0 with wider subserosal invasion (≥ 1.5 cm) was no different from that of T4N0.²² These results suggest that the width of subserosal invasion may be an indicator of latent serosal exposure.

We found that patients with macroscopic serosal change had a larger tumour size, more extensive stomach involvement and more advanced N stage than those without serosal change. These findings were in accordance with previous studies.^{10,11} Macroscopic serosal change may reflect a larger tumour burden and more aggressive biological features. In addition, serosal change may increase the risk of peritoneal metastasis and recurrence due to the tumour cell exfoliation from the serosal surface,^{13,14} which may result in an unfavourable prognosis.

Increased evidence has shown that patients with serosal invasion could benefit from hyperthermic intraperitoneal chemotherapy during surgery.^{23–25} In this study, postoperative adjuvant chemotherapy also proved to be a significant factor influencing the prognosis of patients with stage T3 disease. In addition to curative resection and close postoperative monitoring, these treatment modalities may be necessary for the patients with macroscopic serosal change. On the other hand, some scholars have considered that

macroscopic serosal change may be not fully attributed to the direct invasion of advanced tumour but could be partly induced by a tumour-related inflammatory response.^{11,26} Tumour invasion and tissue necrosis may result in the inflammatory response around the growing tumour, and the noncancerous stromal reaction may mimic the macroscopic serosal invasion of the tumour.¹² Moreover, the systemic inflammatory response may release cytotoxic mediators such as tumour necrosis factor alpha, interleukin 1 and interleukin 6 and promote the migration and metastasis of cancer cells.²⁶ The systemic inflammatory response could play an important role in tumour recurrence and metastasis. Some studies have reported that intra-abdominal infection is a significant risk factor associated with tumour recurrence and an unfavourable prognosis.^{27,28} The exact mechanism behind noncancerous serosal change needs to be further investigated and validated.

Some limitations should be emphasised in our study. First, in view of the retrospective nature of our study, all results could have been influenced by some confounding factors or unknown factors. Second, the assessment of macroscopic serosal change may be subjectively influenced by the surgeons, which may result in potential bias. However, macroscopic serosal change is properly evaluated by experienced surgeons during the gastrectomy. In our research institution, the evaluation criteria on macroscopic serosal change were agreed among experienced surgeons. Third, although microscopically serosal invasion can be assessed by routine pathological examination, it is not always easy to distinguish it from the subserosal invasion. Therefore, the possibility of a missed lesion in the serosal layer is not completely excluded, even after carefully pathological examination. In future, serial and multiple sections may provide a more reliable method for the detection of microscopically serosal invasion.²⁹

Conclusion

Our results indicate that macroscopic serosal change can occur in a high proportion of patients with stage T3 disease. The macroscopic serosal change had a negative impact on the prognosis for these patients, especially for those with T3N0 and T3N1 disease. Although the depth of tumour invasion is mainly judged by pathological evaluation, the prognostic significance of macroscopic serosal change should not be ignored. The integration of pathological T stage and macroscopic serosal change during surgery may provide more accurate prognostic information for patients with gastric cancer.

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