Surgical Outcome of Serosa-negative Advanced Gastric Carcinoma

CHIKARA KUNISAKI, HIROSHI SHIMADA, MASATO NOMURA, GORO MATSUDA,
YUICHI OTSUKA, HIDETAKA ONO and HIROTOSHI AKIYAMA

Department of Gastroenterological Surgery, Yokohama City University,
Graduate School of Medicine, Yokohama, Japan

Abstract. *The purpose of the present study was to clarify prognostic factors and to investigate appropriate therapeutic strategies for T2 gastric carcinoma. A total of 297 consecutive patients with T2 gastric carcinoma (T2a; 130, T2b; 167) were enrolled in this study. The overall 5-year survival rate was 75.3%. There was a significant difference in survival between T2a and T2b tumor. Multivariate analysis showed that age, depth of invasion and lymph node metastasis independently influenced prognosis. Peritoneal recurrence was frequently observed in 37 patients. Multivariate analysis revealed that lymph node metastasis was an independent predictive factor for peritoneal recurrence. Furthermore, the quantity of the stroma was an independent prognostic factor for hematogenous metastasis, and lymph node metastasis for lymphatic metastasis. Prophylactic therapeutic strategy should be advised for patients with many metastatic lymph nodes, for peritoneal or lymphatic recurrence and in patients with "medullary" stroma for hematogenous recurrence .*

Irrespective of recent advances in diagnostic techniques and treatment for gastric cancer, the reported surgical results are disappointing in patients with tumor extending to the adjacent organs or spreading widely to the distant lymph nodes (1, 2). Even combined resection or super-extended lymph node dissection debatedly improve surgical outcome (3, 4). Particularly, peritoneal metastasis is the most frequent pattern of recurrence in patients with advanced gastric carcinoma (5, 6). More than half of the patients with serosa-invasive (T3) gastric carcinoma or tumor invading adjacent organs (T4) develop peritoneal metastasis even after curative resection. Most treatment modalities against

lethal peritoneal metastasis have so far failed (7, 8). To obtain good surgical results in advanced gastric cancer, an appropriate therapeutic strategy for peritoneal metastasis should be established. Furthermore, even serosa-negative advanced gastric carcinoma like T2 tumor (muscularis propria; T2a or subserosa invading tumor; T2b) sometimes recurs as peritoneal metastasis. Taking into consideration that peritoneal metastasis is mainly caused by exfoliated cancer cells from the serosal surface, it is very important to elucidate the mechanisms of peritoneal metastasis in T2 tumors. Assessment of the predictive factors for peritoneal metastasis and prognostic factors enables us to stratify patients and to design an appropriate therapeutic strategy for each patient with T2 tumor. The current study was conducted to evaluate prognostic factors in 297 advanced gastric cancer patients with T2 tumor.

Patients and Methods

Patients. A series of 297 patients underwent potentially curative resection for serosa-negative advanced gastric cancer, T2 tumor (muscularis propria; MP (T2a) or subserosal invasion; SS (T2b)) between April 1985 and March 1999 at the Second Department of Surgery, Yokohama City University School of Medicine, Japan. Preoperative and postoperative staging was based on the 2002 UICC/TNM classification (9). Histological evaluation followed the Japanese Classification of Gastric Cancer (10). The clinicopathological records of 297 patients (205 male and 92 female, with a mean age of 59.8±12.0 years) were analyzed.

Preoperative evaluation was performed with oral barium-meal examination, gastrofiberscopy with biopsy, and computed tomography (CT). Clinical T2 status was made based on the findings of barium-meal examination and endoscopy in all cases and endoscopic ultrasonography in some cases. Clinical lymph node metastasis was diagnosed by CT; irregular shape and lymph nodes more than 10 mm in diameter were strongly suspected as positive. One hundred and twenty-four tumors were located in the lower third of the stomach, 112 in the middle third, 54 in the upper third and 7 in the whole of the stomach. A macroscopically well-defined type was observed in 115 patients and an ill-defined type in 182 (including 11 scirrhous type). The mean tumor diameter was 47.5±26.0 mm (10-200 mm). Histologically, differentiated type was observed in 136

Correspondence to: Chikara Kunisaki, 3-46, Fukuura Kanazawa-ku, Yokohama 236-0004, Japan. Tel: +81-45-787-2650, Fax: +81-45-782-9161, e-mail: s0714@med.yokohama-cu.ac.jp

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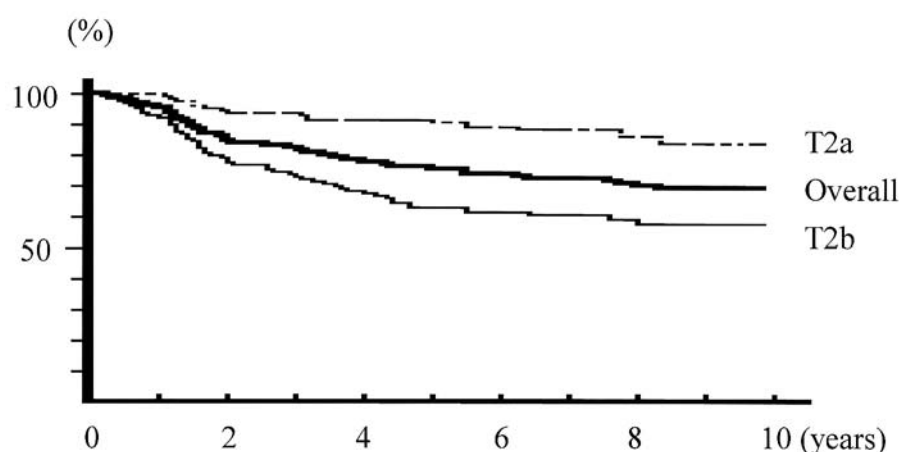
Figure 1. *Survival in patients with T2 gastric cancer.*

patients and undifferentiated in 161. The classification of depth of invasion comprised 130 T2a and 167 T2b. In all patients, at least 15 lymph nodes were dissected for pathological evaluation. Lymph node involvement was detected in 152 patients; pN1 in 92, pN2 in 45 and pN3 in 15 according to Japanese classification and, furthermore, pN1 in 113, pN2 in 28 and pN3 in 11 according to UICC/TNM classification. Lymph node dissection was performed in the Japanese manner. The D1 group (29 patients) was submitted to a gastrectomy with N1 level lymph node dissection, the D2 group (195 patients) to a gastrectomy with N2 level lymph node dissection, and the D3 group (73 patients) with N3 level lymph node dissection.

All patients were followed-up according to our standard protocol (every 4-8 weeks, at least 5 years) including tumor marker studies, gastrofiberscopy, abdominal ultrasonograpy, computed tomography and chest radiography. A diagnosis of peritoneal dissemination was confirmed by aspiration biopsy for patients in whom peritoneal dissemination was suspected by physical examination or imaging modalities. Mean follow-up duration was 69.8 ± 43.9 months.

As concerns adjuvant chemotherapy, 152 patients with lymph node metastasis were treated with postoperative chemotherapy within 8 weeks after surgery. Principally, oral fluoropyrimidine was administered to patients. An intravenous dose of 30 mg/m^2 of methotrexate (MTX) plus 250 mg/m^2 of 5-fluorouracil (5-FU) plus 15 mg/m^2 of cisplatin (CDDP) (n=15) and an intravenous dose of 30 mg/m^2 of MTX plus 250 mg/m^2 of 5-FU (n=10) were additionally administered to patients who gave informed consent.

Statistical analysis. Data were collected and analyzed by SPSS for Windows (SPSS Inc, Chicago, IL, USA). Survival curves were calculated according to the Kaplan-Meier method, including all causes of death and the log-rank test was used for comparisons. Prognostic factors were evaluated with univariate and Cox proportional hazards regression model. An automated forward stepwise procedure was used to clarify the combination of clinicopathological factors which affected survival. Predictive factors for recurrence were evaluated with univariate and multiple logistic regression analysis. All probabilities were two-tailed, with a *p* value less than 0.05 regarded as statistically significant.

Results

Survival. The five-year survival rate was 75.3% in patients with T2 tumor. There was a significant difference in survival between patients with T2a tumor and patients with T2b tumor (Figure 1).

Prognostic factors. Univariate analysis revealed that the location of the tumor, tumor diameter, depth of invasion, lymph node metastasis, lymphatic invasion and venous invasion significantly affected prognosis whereas age, gender, macroscopic appearance and histological type did not. Multivariate analysis showed that age, depth of invasion and lymph node metastasis independently influenced prognosis (Table I). The 5-year survival rate was 93.7% in patients with T2a and node-negative tumor and was 52.6% in patients with T2b and node-positive tumor. There was a significant difference between the two groups (Figure 2).

First site of recurrence. Periodic evaluation after surgery revealed cancer recurrence in 71 patients. Peritoneal metastasis was observed in 37, followed by hematogenous recurrence and, thirdly, lymphatic recurrence (Table II).

Predictive factors for peritoneal recurrence. Univariate analysis revealed that there were significant differences in the location of the tumor, macroscopic appearance, tumor diameter, depth of invasion, lymph node metastasis, lymphatic invasion and venous invasion. In patients with peritoneal metastasis, tumor occupying the whole of the stomach, macroscopically ill-defined tumor, larger tumor, deeper tumor, tumor with more metastatic lymph nodes, and tumor with high lymphatic and venous invasion were frequently observed (Table III).
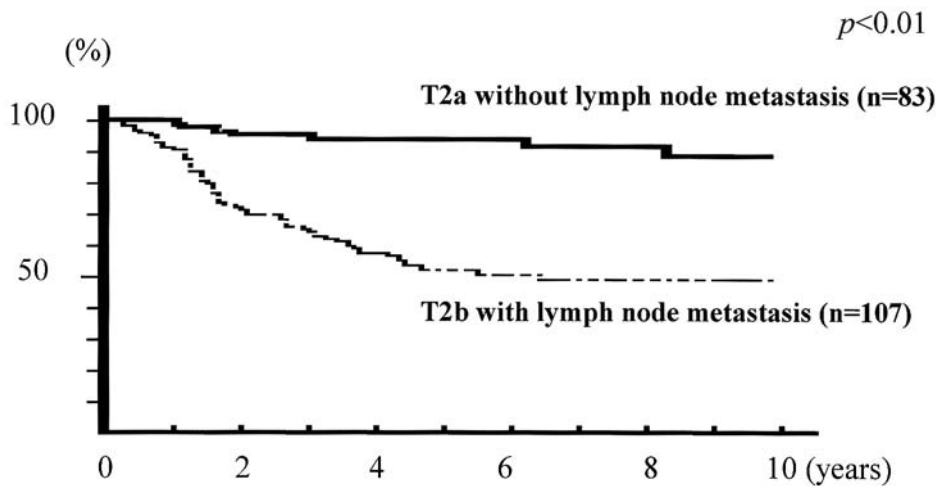
Figure 2. *Survival in patients with and without prognostic factors.*

Table I. *Prognostic factors in uni-and multivariate analysis.*

	Univariate analysis		Multivariate analysis	
	Hazard ratio (95%CI)	*p*-value	Hazard ratio (95%)	*p*-value
Age	1.0187 (0.9996-1.0382)	0.0555	1.0265 (1.0081-1.0451)	0.0046
Gender				
Male/Female	1.4586 (0.7721-2.7556)	0.2448	-	
Location of tumor		0.0060	-	
Middle third/Lower third	0.8505 (0.5047-1.4333)	0.5431		
Upper third/Lower third	1.1470 (0.5763-2.2827)	0.6962		
UE+*/Lower third	2.7310 (1.1326-6.5849)	0.0253		
Whole/Lower third	4.5319 (1.5854-12.9546)	0.0048		
Macroscopic appearance		0.1104	-	
Ill-defined/Well-defined	1.0518 (0.6548-1.6897)	0.8344		
Scirrhous/Well-defined	2.5086 (1.0375-6.0657)	0.0412		
Tumor diameter (mm)		0.0181	-	
>50 <100/<50	1.3838 (0.8637-2.2172)	0.1768		
>100/<50	3.0959 (1.3827-6.9270)	0.0060		
Depth of invasion				
T2b/T2a	3.5512 (2.0486-6.1560)	0.0000	2.2105 (1.2249-3.9892)	0.0085
Histological type				
Undifferentiated/Differentiated	0.9330 (0.5974-1.4571)	0.7604	-	
Lymph node metastasis (UICC/AJCC)		0.0000		0.0000
pN1/pN0	1.7930 (1.0247-3.1373)	0.0408	1.5364 (0.8721-2.7069)	0.1372
pN2/pN0	7.7182 (4.1101-14.4938)	0.0000	5.8686 (3.0164-11.4180)	0.0000
pN3/pN0	18.2331 (8.3549-39.7908)	0.0000	15.5996 (6.7939-35.8004)	0.0000
Lymphatic invasion				
Presence/Absence	2.4014 (1.4443-3.9927)	0.0007	-	
Venous invasion				
Presence/Absence	2.7907 (1.7595-4.4264)	0.0000	-	

*UE+: Upper third with esophageal invasion

Multivariate analysis with the same clinicopathological variables revealed that lymph node metastasis was only selected as an independent predictive factor for peritoneal metastasis (Table IV).

Predictive factors for hematogenous recurrence. Location of the tumor, lymph node metastasis, quantity of stroma and venous invasion predicted hematogenous recurrence in univariate analysis (Table V). Furthermore, the quantity

Table II. *First site of recurrence.*

		(n=71)
	n	(%)
Peritoneal metastasis	37	52.1
Hematogenous	24	33.8
Lymphatic	10	14.1

Table IV. *Predictive factors for peritoneal metastasis in multivariate analysis.*

Variable	Coefficient	SE	Odds ratio (95%CI)	*p*-value
Lymph node metastasis				0.0000
pN1/pN0	0.3799	0.5365	1.2991 (0.7190-2.3470)	0.4789
pN2/pN0	2.2264	0.5906	9.2666 (5.1336-16.7266)	0.0002
pN3/pN0	4.1235	0.7951	61.777 (27.8937-136.8109)	0.0000

Table III. *Predictive factors for peritoneal metastasis in univariate analysis.*

	Peritoneal metastasis		
	Presence (n=37)	Absence (n=226)	*p*-value
Location of the tumor			0.0203
Lower third	16	94	
Middle third	11	90	
Upper third	5	33	
UE+*	1	6	
Whole	4	3	
Macroscopic appearance			0.0018
Well-defined	9	89	
Ill-defined (excluding scirrhous)	23	132	
Scirrhous	5	5	
Tumor diameter (mm)			0.0000
<50	13	143	
≥50, <100	18	76	
≥100	9	7	
Depth of invasion			0.0000
T2a	3	118	
T2b	34	108	
Histological type			0.2358
Differentiated	13	103	
Undifferentiated	24	123	
Lymph node metastasis (UICC/AJCC)			0.0000
pN0	7	128	
pN1	10	87	
pN2	12	10	
pN3	8	1	
Quantity of stroma			0.0117
Medullary	4	23	
Intermediate	13	135	
Scirrhous	20	68	
Lymphatic invasion			0.0000
Presence	32	116	
Absence	5	110	
Venous invasion			0.0000
Presence	26	83	
Absence	11	143	

UE+*: Upper third with esophageal invasion

Table V. *Predictive factors for hematogenous metastasis in univariate analysis.*

	Hematogenous metastasis		
	Presence (n=24)	Absence (n=226)	*p*-value
Location of the tumor			0.0200
Lower third	10	94	
Middle third	7	90	
Upper third	3	33	
UE+*	4	6	
Whole	0	3	
Macroscopic appearance			0.1744
Well-defined	14	89	
Ill-defined (excluding scirrhous)	10	132	
Scirrhous	0	5	
Tumor diameter (mm)			0.6760
<50	16	143	
≥50, <100	8	76	
≥100	0	7	
Depth of invasion			0.0786
T2a	8	118	
T2b	16	108	
Histological type			0.4223
Differentiated	13	103	
Undifferentiated	11	123	
Lymph node metastasis (UICC/AJCC)			0.0073
pN0	8	128	
pN1	11	87	
pN2	4	10	
pN3	1	1	
Quantity of stroma			0.0000
Medullary	13	23	
Intermediate	11	135	
Scirrhous	0	68	
Lymphatic invasion			0.2974
Presence	15	116	
Absence	10	110	
Venous invasion			0.0389
Presence	14	83	
Absence	10	143	

UE+*: Upper third with esophageal invasion

Table VI. *Predictive factors for hematogenous metastasis in multivariate analysis.*

Variable	Coefficient	SE	Odds ratio (95%CI)	*p*-value
Quantity of stroma				0.0010
Intermediate/ Medullary	-2.0223	0.6130	0.1324 (0.0398-0.4401)	0.0010
Scirrhous/ Medullary	-3.1781	1.1365	0.0417 (0.0045-0.3865)	0.0052

Table VIII. *Predictive factors for lymphatic metastasis in multivariate analysis.*

Variable	Coefficient	SE	Odds ratio (95%CI)	*p*-value
Lymph node metastasis				0.0000
pN1/pN0	1.3024	0.8481	3.6781 (0.6978-19.3885)	0.1246
pN2/pN0	2.5494	1.0525	12.799 (1.6267-100.7201)	0.0154
pN3/pN0	4.1589	1.5836	63.794 (2.8722-1426.0790)	0.0086

Table VII. *Predictive factors for lymphatic metastasis in univariate analysis.*

| | Lymphatic metastasis | | |
	Presence (n=10)	Absence (n=226)	*p*-value
Location of the tumor			0.7318
Lower third	4	94	
Middle third	4	90	
Upper third	1	33	
UE+*	1	6	
Whole	0	3	
Macroscopic appearance			0.2858
Well-defined	3	89	
Ill-defined (excluding scirrhous)	4	132	
Scirrhous	1	5	
Tumor diameter (mm)			0.4211
<50	5	143	
≥50, <100	4	76	
≥100	1	7	
Depth of invasion			0.0090
T2a	1	118	
T2b	9	108	
Histological type			0.1297
Differentiated	7	103	
Undifferentiated	3	123	
Lymph node metastasis (UICC/AJCC)			0.0005
pN0	2	128	
pN1	5	87	
pN2	2	10	
pN3	1	1	
Quantity of stroma			0.3732
Medullary	1	23	
Intermediate	8	135	
Scirrhous	1	68	
Lymphatic invasion			0.0756
Presence	8	116	
Absence	2	110	
Venous invasion			0.1373
Presence	6	83	
Absence	4	143	

UE+*: Upper third with esophageal invasion

of the stroma independently predicted hematogenous recurrence (Table VI).

Predictive factors for lymphatic recurrence. Depth of invasion, lymph node metastasis and lymphatic invasion predicted lymphatic recurrence (Table VII). Lymph node metastasis independently predicted lymphatic recurrence in multivariate analysis (Table VIII).

Discussion

From the current results, long-term results in patients with T2 gastric carcinoma depend on subclassification of the depth of invasion (T2a *versus* T2b) and pN status (number of metastatic lymph nodes) after curative resection. The predictive factors for peritoneal, hematogenous and lymphatic recurrence in patients with T2 gastric carcinoma were lymph node metastasis (number of metastatic lymph nodes), quantity of stroma and lymph node metastasis, respectively. Few reports have discussed the appropriate prophylactic or therapeutic strategies for each recurrence in T2 gastric carcinoma (11, 12).

Among various prognostic factors, depth of invasion has a strong influence on survival. Serosa-positive gastric carcinoma predominantly develops peritoneal metastasis resulting in death. However, there are few comparative analyses restricted to patients with serosa-negative advanced gastric carcinoma. In both Japanese (10) and UICC/TNM Classification (11), tumor invading muscularis propria or subserosa is defined as the same entity. Nevertheless, there was a significant difference in surgical results in patients with T2a and T2b in the present study. In T2 gastric carcinoma, the depth of invasion was an independent prognostic factor. Therefore, it is necessary to re-examine this classification.

Peritoneal metastasis is the most common pattern of recurrence in patients with gastric carcinoma. Particularly, peritoneal metastasis is frequently observed in patients with serosa-positive tumor. However, even early gastric carcinoma rarely proceeds to peritoneal metastasis after curative gastrectomy (13). Furthermore, serosa-negative advanced gastric carcinoma (T2 tumor) often recurrs as peritoneal

metastasis even after curative gastrectomy (14, 15) as the present study suggests. Some reports suggested the possibility of injury of the lymphatics during the operative procedure in patients with highly extending metastatic lymph nodes resulting in spreading viable cancer cells into the peritoneal cavity (16). In another report, an ultra-rapid quantitative RT-PCR method detected cancer cells in peritoneal lavage samples obtained immediately after lymph node dissection in patients with serosa-negative gastric carcinoma (17). They also concluded that lymph node metastasis was the independent predictor of the existence of intraperitoneal free cancer cells. These reports justify the results of the present study showing that the number of metastatic lymph nodes can predict peritoneal metastasis in serosa-negative gastric carcinoma.

In other reports, detection of carcinoembryonic antigen messenger RNA by real time quantitative reverse transcription polymerase chain reaction and of inositol 1,4,5-triphosphate receptor type3 (IP3R3) in peritoneal lavage samples are useful to predict peritoneal recurrence (18, 19). Therefore, these tests would be useful in patients with T2 gastric cancer. Furthermore, there have been the reports suggesting the diagnostic and prognostic value of the serum concentrations of tumor markers (CEA, CA 19-9 and CA 72-4) in patients with gastric cancer (20, 21). Moreover, some clinicians have focused on the clinical significance of serum level of soluble cell adhesion molecules (E-selectin, ICAM-1 and VCAM-1) in gastric cancer patients (22). Periodical evaluation of the serum concentrations of tumor markers would also provide important information as to diagnosis and prognosis in patients with T2 gastric cancer.

To overcome peritoneal metastasis, various treatments have been tried (23, 24). In our previous treatments, continuous hyperthermic peritoneal perfusion did not offer any survival benefits in patients with T2b gastric carcinoma without peritoneal metastasis (prophylactic CHPP) (25) or advanced gastric carcinoma with peritoneal metastasis (therapeutic CHPP) (data not shown). To improve the therapeutic outcome, chemotherapeutic agents should be selected for high-risk patients according to the results of chemo-sensitivity testing or assessment of the activity of rate-limiting enzymes in the catabolism of 5-fluorouracil.

The quantity of the stroma independently predicted hematogenous recurrence in T2 gastric carcinoma in the present study. In general, scant quantity of the stroma, "medullary type", is related to hematogenous metastasis as in liver metastasis (26). This finding is also applicable to early gastric cancer with liver metastasis (27).

Lymphatic recurrence was frequently detected in patients with a high number of metastatic lymph nodes. Even meticulous extended lymphadenectomy had a limitation (28), because it was practically impossible to eliminate all metastatic lymph nodes in a regional area. Therefore, it should be important to develop new useful systemic treatments such as immunotherapy or chemotherapy after curative resection in patients with T2 gastric carcinoma showing numerous metastatic lymph nodes as risk factors for recurrence.

Therefore, for improvement of the therapeutic outcome in patients with T2b gastric carcinoma, prophylactic treatment should target each recurrent pattern.

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