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Outcome of D2 Gastrectomy with Curative Intent for Patients with Linitis Plastica: 10-Year Experience

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Abstract

Background: **Survival in patients with linitis plastica is poorer than that in patients with other macroscopic types of gastric carcinoma. No consensus has been reached regarding the therapeutic value of radical surgery for this condition. The aim of this study was to review and analyze the clinicopathological features and surgical outcome in patients with linitis plastica who underwent D2 gastrectomy with curative intent.**

Patients and Methods: **Medical records of 97 patients with gastric carcinoma who underwent D2 gastrectomy with curative intent during the 10-year period between October 1995 and September 2005 were retrospectively reviewed.**

Results: **Linitis plastica was diagnosed in 14 patients (14.4%). Significant differences were found with respect to tumor location, histology, angiolymphatic invasion, peritoneal washing cytology and TNM staging with other macroscopic type of gastric carcinoma. The survival outcome in patients with linitis plastica was worse than in patients with other macroscopic type of gastric carcinoma, with 5-year overall survival rate of 10% VS 68%, respectively.**

Conclusions: **D2 gastrectomy should be performed only in patients with linitis plastica with a chance of cure.**

Introduction

The classification of advanced gastric carcinoma into four gross morphological types by Borrmann in 1926[1] is presently accepted by many surgeons throughout the world.[2-6] Type I represents polypoid lesion without ulceration, type II encompasses fungating mass with superficial ulceration, type III represents ulcerated lesion with surrounding infiltration and type IV tumors are diffusely infiltrative lesion.

Borrmann type IV gastric carcinoma is often referred to as linitis plastica or scirrhous gastric carcinoma. In Korea, Borrmann type IV gastric carcinoma is not synonymous with linitis plastica, as is

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often the case in the West. Korean pathologists considered linitis plastica as part of Borrmann type IV gastric carcinoma when the entire stomach wall is involved with scirrhous gastric carcinoma.[7] Linitis plastica is an aggressive infiltrating tumor, consisting of poorly differentiated tumor cells accompanied by marked desmoplastic reaction, resulting in a rigid stomach resembling a leather bottle. Linitis plastica has special morphological characteristics of diffuse thickening and sclerosis of the gastric wall and giant mucosal fold.[2, 8-11]

In the early stage of tumor growth, cancer cells invade the lamina propria without ulceration. Tumor grows into the submucosa beneath an otherwise normal adjacent mucosa, and then invades the whole gastric wall with an indistinct border line. This results in an indistinct border between tumor and normal tissue.[1] Despite recent advances in the diagnosis and improved treatment of gastric carcinoma, most patients with linitis plastica are not detected at an early stage and the prognosis remains poor.[3,5]

No consensus has been reached regarding the therapeutic value of radical surgery for linitis plastica. Some surgeons have performed more radical operation such as en bloc total gastrectomy including pancreatic body and tail, spleen, gallbladder, transverse colon and left adrenal gland with survival improvement.[12] However, such more radical surgery may carry increased risk of morbidity and mortality. Moreover, other surgeons have reported failure to increase long-term survival with such operation and suggested that linitis plastica is not a surgical disease.[13]

The purpose of this study was to retrospectively review the clinicopathological features and surgical outcome in patients with linitis plastica who underwent D2 gastrectomy with curative intent. The results in patients with linitis plastica were compared with that of patients having other macroscopic type of gastric carcinoma.

Patients and Methods

Patients

Between October 1995 and September 2005, 79 patients with histologically confirmed adenocarcinoma of the stomach underwent D2 gastrectomy with curative intent by one surgeon (CE) in the Department of Surgery, Ramathibodi Hospital, Mahidol University. The medical records of these patients were retrospectively reviewed. Fourteen patients (14.4%) were classified as having linitis plastica.

Patients with linitis plastica (n = 14) were compared with those having other macroscopic type of gastric carcinoma (n = 83). For each patient, demographics information, clinical data, surgical notes, pathological reports and survival outcome were analyzed.

A combination of both the Japanese classification and the UICC/AJCC TNM staging system was used in this study. Pathological staging according to the TNM classification, 6th edition in 2002, was used.[14] Lymph node station and dissection were classified according to the Japanese classification, 2nd English edition in 1998.[15]

Surgical technique

All 14 patients underwent D2 gastrectomy with curative intent by one surgeon (CE). Pancreas-preserving total gastrectomy was performed according to the Maruyama techniques.[16] Lymph node dissection included lymph nodes group 1 to 11. Splenectomy was performed routinely in all cases to completely remove the splenic hilar node (group 10). Distal pancreatectomy was done only when necessary, ie. in case of direct tumor extension to the pancreas. When adjacent organs were involved in T4 tumor (transverse colon, pancreas, liver), they were always resected en bloc with the stomach when potentially curative resection was possible. Peritoneal washing cytology was routinely performed immediately after laparotomy.

Surgery was considered potentially curative resection (UICC-R0) or resection with curative intent when there was no gross residual tumor after surgery and resection margins were free from cancer cells histologically.[14]

Statistical analysis

Clinicopathological features of linitis plastica were compared with those of other macroscopic types of gastric carcinoma. Student t-test and chi-square test were used for statistical analysis. The survival rates were estimated with the Kaplan-Meier method. Ninety-five percent Confidence Intervals were estimated using Greenwood's method. Univariable estimates of increased risk for each potential prognostic factors were done using Cox (proportional hazards) regression. Multivariable Cox regression was used to

obtain a final set of prognostic factors significantly associated with each outcome. Statistical significance was defined as a p-valve of 0.05 or less. All statistical analysis were performed using STATA version (Stata Corp, College station, Tx, USA).

Results

In 14 patients with linitis plastica, the median age was 60.5 years (ranged 41-74 years). Clinicopathological features of patients with linitis plastica are presented in Table 1.

Linitis plastica was identified in 14 patients (14.4%). All of them were poorly-differentiated carcinoma. Angiolymphatic invasion was reported in 11 patients (79%). Peritoneal washing cytology was positive in 8 patients (57.7%). All cases with linitis plastica had serosal invasion, with adjacent organs involvement in 4 patients (28.6%). Nodal involvement was identified in 13 patients (93%).

The mean number of examined nodes was 55.6 (range 32-126) and mean number of metastatic node was 30.2 (range 0-107). Distant metastasis was found in 2 patients (14.3%) with potentially curative resection (wedge liver resection in both patients). Twelve patients (86%) were classified as having stage IV disease.

Table 1 Clinicopathological features of patients with linitis plastica (n = 14)

Pts	Gender	Age	Histology	Angiolymphatic invasion	Cytology	pT	pN	M	Lymph node ratio	TNM staging
1	F	65	poorly differentiated	-ve	-ve	T3	N3	M0	18/53	IV
2	F	41	poorly differentiated	-ve	-ve	T3	N0	M0	0/52	II
3	M	71	poorly differentiated	-ve	-ve	T3	N2	M0	15/50	IIIB
4	M	51	poorly differentiated	+ve	-ve	T3	N3	M0	21/56	IV
5	M	56	poorly differentiated	+ve	+ve	T4	N3	M1(liver)	48/90	IV
6	M	67	poorly differentiated	+ve	+ve	T3	N3	M0	33/33	IV
7	M	54	poorly differentiated	+ve	+ve	T3	N3	M0	45/58	IV
8	M	57	poorly differentiated	+ve	-ve	T3	N2	M1(liver)	8/32	IV
9	M	74	poorly differentiated	+ve	+ve	T3	N3	M0	17/38	IV
10	M	41	poorly differentiated	+ve	+ve	T3	N3	M0	107/126	IV
11	F	66	poorly differentiated	+ve	+ve	T4	N3	M0	21/58	IV
12	F	58	poorly differentiated	+ve	+ve	T4	N3	M0	45/45	IV
13	F	63	poorly differentiated	+ve	-ve	T3	N3	M0	32/70	IV
14	F	66	poorly differentiated	+ve	+ve	T4	N3	M0	21/38	IV

Table 2 Treatment outcomes of patients with linitis plastica (n = 14)

Pts	Surgical treatment	Status	Follow-up (month)
1	Total gastrectomy	Alive	14
2	Total gastrectomy	Alive	84
3	Total gastrectomy	Alive	20
4	Total gastrectomy	Dead (P+L)	26
5	Total gastrectomy + wedge liver resection + distal pancreatectomy	Dead (P+L)	4
6	Total gastrectomy	Dead (P)	20
7	Total gastrectomy	Dead (P+D)	19
8	Total gastrectomy + wedge liver resection	Dead (P+D)	20
9	Total gastrectomy	Dead (P)	6
10	Total gastrectomy	Dead (P)	18
11	Total gastrectomy + distal pancreatectomy	Dead (P+D)	26
12	Total gastrectomy +distal pancreatectomy + transverse colectomy + wedge liver resection	Dead (P)	6
13	Total gastrectomy	Dead (P+L)	15
14	Total gastrectomy + distal pancreatectomy	Dead (P+L)	26

Note : P = peritoneal recurrence, L = locoregional recurrence, D= distant metastasis
Splenectomy was routinely performed.

Treatment outcomes of patients with linitis plastica are presented in Table 2. Total gastrectomy with splenectomy was performed in 9 patients. Extended resection was performed in 5 patients (T4 disease in 3 patients, T4 disease plus liver metastasis in 1 patient and liver metastasis in 1 patient). At the time of final follow-up, 11 patients (78.6%) died of recurrent disease with the median survival time of 16.4 months (range 4-26 months). Causes of death included peritoneal recurrence in 4 patients, peritoneal and locoregional recurrence in 4 patients, and peritoneal recurrence and distant metastasis in 3 patients.

Three patients (21.4%) were still alive without disease with the median follow-up time of 39.3 months (range 14-84 months).

Table 3 Clinicopathologial features of linitis plastica versus other macroscopic types of gastric carcinoma

Factors	Linitis plastica		p-Value
	No (n = 83)	Yes (n = 14)	
Mean age (sd), yrs	57.7 (12.8)	59.7 (10.4)	0.582
Gender			
Male	44 (53%)	7 (50%)	0.835
Female	39 (47%)	7 (50%)	
Tumor location			
Upper & Middle	41(49%)	14 (100%)	<0.001
Lower	42 (51%)	0	
Histology			
Differentiated	27 (33%)	0	0.012
Poorly-differentiated	56 (67%)	14 (100%)	
Angiolymphatic invasion			
Yes	31 (37%)	11 (79%)	0.004
No	52 (63%)	3 (21%)	
Peritoneal lavage cytology			
Positive	16 (19.2%)	6 (42.9%)	0.02
Negative	67 (80.8%)	8 (57.1%)	
Depth of tumor invasion			
pT1-2	14 (17%)	0	0.097
pT3-4	69 (83%)	14 (100%)	
Nodal involvement			
No (pN0)	13 (16%)	1 (7%)	0.401
Yes (pN1-3)	70 (84%)	13 (93%)	
TNM stage			
I A	2 (2%)	0	0.004
I B	7 (9%)	0	
II	11 (13%)	1 (7%)	
III A	27 (33%)	0	
III B	12 (14%)	1 (7%)	
IV	24 (29%)	12 (86%)	

Table 4 Survival rates in patients with and without linitis plastica

Factors	5-year overall survival (95% CI)	5-year disease-free survival (95%CI)
Linitis plastica		
Yes	10% (1% to 35%)	10% (1% to 35%)
No	68% (54% to 79%)	52% (39% to 64%)

Table 3 compares the clinicopathological features of the 14 patients with linitis plastica to those 83 patients with other macroscopic types of gastric carcinoma. Significant differences were noted for tumor location ($p < 0.001$), histology ($p = 0.012$), angiolymphatic invasion ($p = 0.004$), peritoneal washing cytology ($p = 0.02$), and TNM staging ($p = 0.004$).

Survival outcome for patients with linitis plastica compared with patients with other macroscopic types of gastric carcinoma is presented in Table 4. The survival outcome of patients with linitis plastica was clearly worse than that of patients with other macroscopic types of gastric carcinoma. Cumulative 5-year overall survival rate for patients with linitis plastica was 10% compared with 68% for patients with other macroscopic types of gastric carcinoma.

Prognostic factors in 97 patients with gastric carcinoma are presented in Table 5 and 6. Univariate analysis revealed linitis plastica as one of the nine factors that influenced prognosis in potentially curative resection patients. However, multivariate analysis identified only three factors as significant independent prognostic factors for patients with gastric carcinoma, which include TNM staging, presence of angiolymphatic invasion and positive peritoneal washing cytology.

Discussion

Even though there have been substantial advances in the diagnosis of gastric carcinoma, most linitis plastica are not detected at an early stage.[17] Despite recent advances in the management of gastric carcinoma, the prognosis of linitis plastica remains poor.[3,5,9] Endoscopists often have difficulties recognizing these lesions, as only minor and non-specific changes can be seen on the mucosal surface. However, poor distensibility has been a frequent

Table 5 Significant prognostic variables related to overall survival, on univariable Cox regression.

Variables	Hazard ration	95% CI	p-value
Location of tumor			
Upper + Middle vs Lower	1.69	0.625 to 4.58	0.301
Macroscopic finding			
Linitis plastica vs Non Linitis	11.4	4.09 to 31.9	<0.001
Histology			
Poorly vs Differentiated	1.73	1.01 to 2.97	0.047
Angiolymphatic invasion			
Presence vs Absence	17.4	5.87 to 51.8	<0.001
T-category	3.66 (per higher category)	1.75 to 7.67	0.001
N-category	5.28 (per higher category)	2.95 to 9.45	<0.001
TNM staging grouping	4.33 (per higher category)	2.52 to 7.43	<0.001
Peritoneal washing cytology			
Positive vs cytology	12.3	5.36 to 51.8	<0.001
Surgical treatment			
Total vs Subtotal gastrectomy	2.26	0.869 to 5.89	0.015
Combined resection vs Gastrectomy alone	6.41	2.20 to 18.6	0.001
Adjuvant therapy	3.54	1.33 to 9.40	0.011

Table 6 Final set of significant prognostic variables related to overall survival, on multivariable Cox regression (adjusted for age and sex)

Variable	Hazard ratio	95% CI	p-value
TNM stage grouping	256 (per higher category)	1.29 to 5.08	0.007
Presence of angiolymphatic invasion	6.51	1.79 to 23.7	0.004
Positive peritoneal washing cytology	3.73	1.50 to 9.24	0.004

finding. Up to 30% of linitis plastica, particularly those without mucosal lesion, an endoscopic tissue biopsy can be negative.[18]

The incidence of linitis plastica was 10-20% from many reports.[2,3,19-21] In this series from potentially curative resection patients, the incidence was 14.4%. Yoshikawa, et al. in 2001[21] reported that more than two thirds of linitis plastica were either unresectable or were resected for palliation. Accordingly, the prognosis for linitis plastica has been poor.

Several poor prognostic indicators of linitis plastica patients were identified in this study. All of them were poorly-differentiated tumors. Other authors reported that 60.3-77.4% of linitis plastica were classified as poorly-differentiated carcinoma.[2,17] And also, all of them had serosal invasion. This finding was similar to other studies.[2,6] Lymph node involvement was observed in almost all patients (93%). Other reports also observed a very high incidence of nodal involvement.[6,10,22] Angiolymphatic invasion was reported in most of linitis plastica patients (79%). Most of linitis plastica (86%) were classified as type IV disease at the initial diagnosis. Only one patient (7%) was in stage II disease. Others reported 6.7-19.1% of linitis plastica belonged to stage II disease.[2,23] More than half of the linitis plastica (57.7%) revealed positive peritoneal washing cytology. Kodera, et al. in 2004[16] reported that the incidence of positive cytology was 43%. The survival rates of linitis plastica with positive cytology were not different from linitis plastica without gastrectomy. Surgery may not

have survival benefit for linitis plastica with positive cytology.[24-28]

Five clinicopathological features were significantly different between the linitis plastica and those with other macroscopic types of gastric carcinoma. (Table 3)

All of these findings explained the poor results of linitis plastica even after curative resection in this study. The cumulative 5-year overall and disease-free survival rates of patients with linitis plastica were 10% and 10%, respectively, while 5-year overall and disease-free survival rate for patients with other macroscopic types of gastric carcinoma was 68% and 52%, respectively. Others reported 5-year survival rate after gastric resection ranging from 10% to 33.4%.[2,3,5,6,9,10] Early detection may increase the survival rate as linitis plastica was detected at stage III (1/14) and IV (12/14) disease in 92.9% of patients in this study.

All patients with linitis plastica in this study died from peritoneal recurrences as at least one part of recurrent pattern (Table 2). This finding was similar to other reports.[6,17,29]

From multivariate analysis in this study, linitis plastica was not a significant independent prognostic factor for patients with gastric carcinoma (Table 4). However, it is one of the significant prognostic factors for patients with gastric cancer reported by Otsuji et al in 2004.[10]

Whether linitis plastica is a surgical disease still remains rather problematic. The survival outcome after D2 gastrectomy with curative intent was clearly lower in linitis plastica than those patients with other macroscopic types of gastric carcinoma in this study. Most of the patients died within 2 years after surgery. However, 3/14 patients (21.4%) were still alive without disease with median follow-up time of 39.3 months and with the longest survival of 84 months. The author suggests that D2 gastrectomy is justified if curative resection is possible. Several authors also supported curative resection for linitis plastica. Liu, et al in 2003[3] and Kunisaki, et al in 2005[20] reported that the number of metastatic nodes in curatively resected linitis plastica was an independent prognostic factor. They concluded that D2 gastrectomy is justified in linitis plastica without extensive lymph node metastasis. Kodera, et al in 2001[5] reported that long-term survivors were observed only among the linitis plastica treated with curative R0 resection. Many Japanese surgeons reported that curative extended lymphadenectomy was one of the significant prognostic factors. They suggested that D2 gastrectomy is rational if possible.[8,10,19-21,25,30]

There was no significant difference in survival between linitis plastica undergoing and those not undergoing palliative surgery, so palliative gastrectomy should not be performed.

Conclusions

Since linitis plastica often involves the entire stomach, total gastrectomy is usually performed. Significant differences were found with respect to tumor location, histology, angiolymphatic invasion, peritoneal washing cytology and TNM staging compared with other macroscopic type of gastric carcinoma. Postoperative survival in patients with linitis plastica was worse than in patients with other macroscopic types of gastric carcinoma, with 5-year overall survival rate of 10% VS 68%, respectively. Indications for radical resection should be carefully weighed against potential complications of surgery. Ideally, D2 gastrectomy should be performed only in patients with linitis plastica with a chance of cure.

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