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Outcome of D2 Gastrectomy with Combined Resection of Invaded Adjacent Organs in Patients with T4 Gastric Carcinoma: 10-Year Experience

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Abstract

Background: **The surgical management of locally advanced gastric carcinoma with invasion to adjacent organs (T4) remains controversial and many still question the benefit of a combined resection with D2 gastrectomy.**

Objectives: **The aim of this study was to examine the morbidity and mortality associated with combined resection with D2 gastrectomy and also to determine the survival benefit.**

Patients and Methods: **Between October 1995 and September 2005, 11 patients had resection with curative intent for T4 gastric carcinoma invading adjacent organs. Clinicopathologic features, morbidity, mortality and survival outcome were reviewed. Independent prognostic factors for gastric carcinoma were evaluated by multivariate analysis.**

Results: **Undifferentiated tumor was reported in 72.7%. Angiolymphatic invasion was presented in 90.9%. Positive cytology was found in 72.7%. Nodal involvement was presented in all patients. Organs most commonly resected with the stomach were the pancreas, followed by transverse colon and left lobe of liver. Complications occurred in 45.4%. There was no operative mortality. The 5-year overall survival rate for T4 compared with T1-3 gastric carcinoma were 16% and 65%, respectively. One patient (9.1%) survives longer than 7 years after surgery.**

Conclusions: **Patients with locally advanced gastric carcinoma invading adjacent organs (T4) may benefit from aggressive en bloc combined resection with D2 gastrectomy if curative resection can be performed. This procedure can be performed with acceptable morbidity, no mortality, and long term survival could be achieved. But noncurative resection should be avoided in patients with T4 gastric carcinoma.**

Introduction

D2 gastrectomy for patients with gastric adenocarcinoma has become more widely accepted and has been shown to achieve good results. However, surgical management of locally advanced gastric carcinoma with invasion to adjacent organs (T4) remains controversial.[1] The prognosis of patients with T4 gastric carcinoma is usually poor.[2-4] Complete removal of all diseases, ie. R0 resection, is essential in gastric cancer treatment. Resection of invaded adjacent organs with gastrectomy is occasionally required in T4 gastric carcinoma to achieve complete tumor clearance. There were several studies in which the combined surgery was recommended.[2,4-7] However, the clinical efficacy of this radical combined surgery has remained unclear

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because it is difficult to resect the invading tumor completely, and postoperative complications can sometimes prove fatal.[2]

The purpose of this study was to retrospectively review the clinicopathological features and surgical outcome in patients with locally advanced gastric carcinoma with invasion to adjacent organs (T4) who underwent D2 gastrectomy and combined resection of the involved adjacent organs with curative intent. The results of patients with T4 gastric carcinoma were compared with that of patients having T1-3 gastric carcinoma.

Patients and Methods

Between October 1995 and September 2005, 97 patients with histologically confirmed adenocarcinoma of the stomach underwent D2 gastrectomy with curative intent at the Department of Surgery, Faculty of Medicine, Ramathibodi Hospital, Mahidol University. The medical records of these patients were retrospectively reviewed. Eleven patients (11.3%) were classified as T4 disease with macroscopic invasion to adjacent organs.

For each patient, demographic information, clinical data, surgical notes, pathologic reports and survival outcome were analysed.

We used a combination of both the Japanese classification and the UICC/AJCC TNM staging system in this study. Pathological staging according to the TNM classification, 6th edition in 2002[8], was used and lymph node station and dissection were classified according to the Japanese classification, 2nd English edition in 1998.[9]

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[8].

Surgical technique

All patients underwent D2 gastrectomy with curative intent by one surgeon (C.E.). D2 gastrectomy included total or subtotal gastrectomy with lymph node dissection of N1 and N2 level (tier). The extent of gastric resection was determined by tumor location. Generally, when the tumor was located in the lower third of the stomach, a subtotal gastrectomy was performed, providing that a distance of at least 5 cm between the tumor and proximal resection line was maintained. In other cases, a total gastrectomy was performed. Pancreas-preserving total gastrectomy was performed according to the Maruyama techniques.[10] Spleen was removed routinely in total gastrectomy to facilitate complete removal of the splenic hilar nodes (gr 10). Peritoneal washing cytology was performed routinely and immediately after laparotomy. Combined resection with curative intent was performed in patients with T4 gastric carcinoma who had no evidence of gross peritoneal dissemination or unresectable distant metastasis.

Statistical analysis

Clinicopathologic features of T4 patients (adjacent organs involvement) were compared with those of T1-T3 patients (no adjacent organs involvement). Student t-test and chi-square test were used for statistical analysis. The survival rate was estimated with the Kaplan-Meier method. 95% Confidence Interval were estimated using Greenwood's method. Univariable estimates of increased risk for each potential prognostic factor were done using Cox (proportional hazards) regression. Multivariable Cox regression was used to obtain a final set of prognostic factors and a significant association was defined as a p-value of 0.05 or less. All statistical analyses were performed using STATA version (Stata Corp., College Station, Texas, USA)

Results

Of the 11 patients with T4 gastric carcinoma, the median age was 58 years (ranged 35-66 years). Clinicopathologic features of patients with T4 gastric carcinoma are presented in Table 1. Undifferentiated tumor was reported in 8 patients (72.7%). Nearly all patients revealed angiolymphatic invasion (91%). Four patients (36.4%) presented scirrhous macroscopic type. Positive peritoneal washing cytology, an incurable factor, was found in 8 patients (72.7%). Lymph node metastasis was observed in all of our T4 patients (100%). The median number of examined nodes was 54 (ranged 24-99) and metastatic nodes was 25 (ranged 5-72). Liver metastasis was found in one patient (9.1%) with potentially curative resection. All of the T4 gastric carcinoma was classified as stage IV disease.

Treatment outcome of patients with T4 gastric

Table 1 Clinicopathologic features of patients with T4 tumor (n = 11)

Pts	Gender	Age	Location	Macroscopic finding	Histology	Angio-lymphatic invasion	Cytology	pN	M	Lymph nodes ratio	TNM staging
1	M	35	Middle	Non-scirrhous	undifferentiated	-ve	-ve	N1	M0	5/63	IV
2	M	55	Lower	Non-scirrhous	undifferentiated	+ve	-ve	N1	M0	6/37	IV
3	M	64	Lower	Non-scirrhous	differentiated	+ve	-ve	N3	M0	16/63	IV
4	M	58	M+L	Non-scirrhous	differentiated	+ve	+ve	N1	M0	5/25	IV
5	M	56	Whole	Scirrhous	undifferentiated	+ve	+ve	N3	M1 (liver)	48/90	IV
6	M	59	M+L	Non-scirrhous	undifferentiated	+ve	+ve	N3	M0	24/24	IV
7	M	48	Middle	Non-scirrhous	differentiated	+ve	+ve	N1	M0	6/36	IV
8	F	66	Whole	Scirrhous	undifferentiated	+ve	+ve	N3	M0	21/38	IV
9	F	58	Whole	Scirrhous	undifferentiated	+ve	+ve	N3	M0	45/45	IV
10	F	66	Whole	Scirrhous	undifferentiated	+ve	+ve	N3	M0	21/58	IV
11	F	57	Middle	Non-scirrhous	undifferentiated	+ve	+ve	N3	M0	72/99	IV

Table 2 Treatment outcome of patients with T4 gastric carcinoma (n = 11)

Pts	Surgery	Complications	Final status	Follow-up (months)
1	Total gastrectomy+distal pancreatectomy	No	Alive	90
2	Subtotal gastrectomy+transverse colectomy	No	Alive with recurrence (P+L)	24
3	Subtotal gastrectomy+transverse colectomy	Wound infection	Alive with recurrence (P)	20
4	Total gastrectomy+distal pancreatectomy	No	Alive with recurrence (P+L)	20
5	Total gastrectomy+distal pancreatectomy + wedge liver resection	Subdiaphragmatic collection	Dead (P+L)	4
6	Total gastrectomy+distal pancreatectomy	No (P+D)	Dead	30
7	Total gastrectomy+transverse colectomy	No	Dead (P+D)	19
8	Total gastrectomy+distal pancreatectomy	Pancreatic fistula	Dead (P+L)	26
9	Total gastrectomy+distal pancreatectomy + transverse colectomy + wedge liver resection	Subdiaphragmatic collection (P+L+D)	Dead	6
10	Total gastrectomy+distal pancreatectomy	Pancreatic fistula	Dead (P+D)	26
11	Total gastrectomy+transverse colectomy	No	Dead (P)	8

Note: *P = peritoneal recurrence, L = locoregional recurrence, D = distant metastasis, Splenectomy was performed routinely in total gastrectomy group.*

carcinoma is presented in Table 2. Total gastrectomy with D2 lymph node dissection was performed in 81.8% and subtotal gastrectomy with D2 lymph node dissection in 18.2%.

Pancreas was the most frequently invaded organ, followed by transverse colon and liver. Multiple organs were invaded by the tumor in one patient. Details of combined resection procedures were shown in Table 2.

Postoperative complications were seen in 5 patients (45.4%). All of them recovered with conservative management. No hospital mortality was recorded in our series. At the final follow-up, 7 patients (63.6%) died of recurrence disease with an average survival

time of 15.5 months (ranged 4-30 months). Three patients (27.3%) were alive with recurrent disease with an average survival time of 21.3 months (ranged 20-24 months). Only one patient (9.1%) was still alive without disease with the follow-up time of 90 months. Ten patients (91%) developed recurrence. The most common pattern of recurrence was peritoneal, followed by locoregional and distant. Table 3 showed the comparison between the clinicopathological features of the 11 T4 patients and those of 86 T1-3 gastric carcinoma patients. Significant differences were noted for macroscopic type (0.028), angiolymphatic invasion (0.001), positive peritoneal washing cytology (0.002), TNM staging (0.001), and postoperative complication (0.02).

Table 3 Clinicopathologic features of T4 tumor versus T1-3 gastric carcinoma

Factors	Depth of tumor invasion		p-Value
	T1-3 (n = 86)	T4 (n = 11)	
Mean age (sd), yr	58.2 (12.8)	56.5 (8.9)	0.680
Gender			
Male	44 (51%)	7 (64%)	0.435
Female	42 (49%)	4 (36%)	
Tumor location			
Upper & Middle	46 (53%)	9 (82%)	0.074
Lower	40 (47%)	2 (18%)	
Macroscopic finding			
Scirrhous	10 (12%)	4 (36%)	0.028
Non scirrhous	76 (88%)	7 (64%)	
Histology			
Differentiated	23 (27%)	4 (36%)	0.503
Undifferentiated	63 (73%)	7 (64%)	
Angiolymphatic invasion			
Yes	32 (37%)	10 (91%)	0.001
No	54 (63%)	1 (9%)	
Peritoneal washing cytology			
Positive	14 (16.3%)	8 (72.7%)	0.002
Negative	72 (83.7%)	3 (27.3%)	
Nodal involvement			
No (pN0)	14 (16%)	0	0.148
Yes (pN1-3)	72 (84%)	11 (100%)	
Postoperative complication			
Yes	11 (12.8%)	5 (45.4%)	0.02
No	75 (87.2%)	6 (54.6%)	
TNM stage			
I A	2 (2%)	0	0.001
I B	7 (8%)	0	
II	12 (14%)	0	
III A	27 (32%)	0	
III B	13 (15%)	0	
IV	25 (29%)	11 (100%)	

Survival outcome for T4 patients compared with patients with T1-3 gastric carcinoma is presented in Table 4. The survival outcome of T4 patients was clearly worse than that of patient with T1-3 gastric carcinoma. The 5-year overall survival and disease free survival for patients with T4 gastric carcinoma was 16% and 9%, respectively. The 5-year overall survival and disease-free survival for patient with T1-3 gastric carcinoma was 65% and 52%, respectively.

Prognostic factors in 97 patients with gastric carcinoma are presented in Table 5 and 6. Univariate analysis revealed that T4 gastric carcinoma was one of the nine factors that influenced prognosis in potentially curative resected patients. However, multivariate analysis identified only three factors as significant independent prognostic factors for patients with gastric carcinoma, including TNM staging, presence of angiolymphatic invasion and positive peritoneal washing cytology.

Discussion

Surgery is the only possible curative treatment for gastric carcinoma. Approximately 10% to 20% of pattern were T4 disease with invasion to adjacent organs.[11,12] The best therapeutic surgical approach of locally advanced gastric carcinoma with invasion to adjacent organs (T4) remains controversial.[1,13] Combined resection of invaded adjacent organ with

Table 4 Survival outcome

Factors	5-yeas overall survival (95% CI)	5-year disease-free survival (95% CI)
Adjacent organs involvement (T4)		
Yes	16% (1% to 49%)	9% (1% to 33%)
No	65% (50% to 76%)	52% (39% to 63%)

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

Variable	Hazard ratio	95% CI	p-valve
Location of tumor			
Middle+Upper vs Lower	1.69	0.625 to 4.58	0.301
Macroscopic findings			
Scirrhous vs Non scirrhous	11.4	4.09 to 31.8	<0.001
Histology			
Undifferentiated vs Differentiated	1.73	1.01 to 2.97	0.047
Angiolymphatic invasion			
Yes vs No	17.4	5.87 to 51.8	<0.001
Adjacent organs invasion			
(T4) vs (T1-3)	4.10	1.71 to 9.80	0.002
Nodal involvement			
(N1-3) vs (N0)	5.25	2.95 to 9.45	<0.001
TNM stage grouping	4.33 (per higher category)	2.52 to 7.43	<0.001
Peritoneal washing cytology			
Positive vs Negative	12.3	5.36 to 51.8	<0.001
Surgical treatment			
Total vs Subtotal gastrectomy	2.26	0.869 to 5.89	0.095
Combined resection vs Gastrectomy alone	6.41	2.20 to 18.6	0.001
Adjuvant therapy			
Yes vs No	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	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

gastrectomy might be the only promising approach. However this procedure might induce more postoperative morbidity and mortality, which could offset any potential beneficial effect on survival. Some physicians still consider invasion of adjacent organs by T4 gastric carcinoma as a sign of incurable disease.[14] Nevertheless, several studies revealed that patients with T4 gastric carcinoma might benefit from aggressive en bloc combined resection with curative intent.[2,13,15-20]

Kodama et al in 1997[6] indicated that the best indication for an en bloc combined resection for T4 gastric carcinoma was invasion limited to only one organ, not more than N2, macroscopic finding not Borrmann type IV and no incurable factors.

Kitamura et al in 2000[18] and Saito et al in 2001[12] reported that resection of the invaded organ in combination with gastrectomy should be performed when lymph node metastasis is not evident.

On the contrary, Kobayashi et al in 2004[1] showed good survival even in node-positive patients, except for those with a lymph node ratio greater than 0.2, when D2 gastrectomy with combined resection was performed. Therefore, they concluded that node-positive patients were also candidates for combined resection with curative intent.

Kunisaki et al in 2006[13] reported that for T4 gastric carcinoma with relatively few (<6) metastatic nodes, good results can be obtained with curative resection. However, it is difficult to diagnose pre-

operative lymph node metastasis with the currently available imaging tools.

Isozaki et al in 2000[2] reported that for patients with T4 gastric carcinoma located in the middle or lower-third of the stomach, aggressive surgical resection of invaded adjacent organs with extended lymph node dissection should be performed to improve long-term outcome. The strongest prognostic factor identified in T4 gastric carcinoma was curative resection.[1,13]

This study revealed that the tumor frequently invaded the pancreas, followed by the transverse colon or mesocolon and left lobe of liver. Several reports also revealed these findings.[2,13,16,17] Only two reports showed that organs most commonly resected with the stomach were the transverse colon, followed by the pancreas and liver.[7,14]

For patients with T4 gastric carcinoma with invasion of the pancreatic head or duodenum, pancreaticoduodenectomy is required.[21] However, this procedure has been rarely performed because of substantial morbidity and mortality. Fortunately, no patient in this series required pancreaticoduodenectomy. Recently, some favorable results of patients undergoing this procedure have been reported from Japan.[22-24] Report from the National Cancer Center Hospital in Tokyo in 2005[21] concluded that if curative resection can be achieved by pancreaticoduodenectomy, this procedure should be performed in patients with tumor invading the pancreatic head or duodenum. However, patients with incurable factors should not be considered for pancreaticoduodenectomy.

The survival rate in the curative resection (R0) group was significantly higher than that of patients undergoing noncurative resection.[1,2,5-7,13] In this series, the surgical outcome of T4 gastric carcinoma was clearly worse than that of T1-3 gastric carcinoma. The 5-year overall survival rate for patients with T4 and T1-3 gastric carcinoma was 16% and 65%, respectively. In previous reports, the 5-year survival rate ranged from 15% to 41%.[1,2,13,15] T4 gastric carcinoma usually has associated incurable factors. Positive cytology was found in 72.7% with no long term survival. Cytologic examination did not influence the decision to perform D2 gastrectomy with extended resection because the results were reported about one week after surgery. Its benefit was for the purpose of prognosis. Other poor prognostic factors were also frequently found in this study. Nodal involvement was reported in all patients, with N3 disease in 63.6%. Angiolymphatic invasion was presented in 90.9%. Undifferentiated tumor type was reported in 72.7%. Other reports indicated that the incidence of curative resection in T4 gastric carcinoma was 25% to 36%.[16,17]

Although the survival rate of patients who underwent a D2 gastrectomy with combined resection of the invaded adjacent organs was poor, one patient (9.1%) survives longer than 7 years after surgery. In addition, according to the UICC/AJCC TNM staging classification, stage IV gastric carcinoma contains T4, N3 or M1 disease.[8] The 5-year survival rate in patients with stage IV gastric carcinoma is expected to be 0-9%.[25] T4 tumor in this study obtained a slightly better survival rate (16%).

In this series, postoperative morbidity was 45.4%. All of them recovered with conservative management. No hospital mortality was recorded. Previous studies reported postoperative morbidity rate ranged between 10% to 31.2% and mortality rate between 2.6% and 15%.[1,13-15,19,26]

In this series, the most common pattern of recurrence was peritoneal, followed by locoregional and distant. These findings were also reported in other previous studies. T4 gastric carcinoma invading adjacent organs was not a significant independent prognostic factor for patients with gastric carcinoma.

Conclusions

Present study demonstrated that D2 gastrectomy with combined resection of invaded adjacent organs for T4 gastric carcinoma can be performed with acceptable morbidity, no mortality, and with long term survival. We recommend the use of aggressive D2 gastrectomy with combined resection of invaded adjacent organs in patients with T4 gastric carcinoma in whom curative resection can be performed, that is those with negative cytology. However, noncurative resection should be avoided in patients with T4 gastric carcinoma.

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