·Gastric Cancer Column·

The relationship of prognosis to surgery and pathologic characteristics of stage IV (M0) gastric cancer patients

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[**Abstract**] **Background and Objective:** The proportion of stage IV gastric cancer in the whole gastric cancer population in China is still high. This study was to investigate the surgery and pathologic characteristic and prognostic factors of stage IV (M0) gastric cancer. **Methods:** Clinical data of 630 patients with pathologically confirmed stage IV (M0) gastric cancer treated at the affiliated Tumor Hospital of Harbin Medical University between January 1993 and August 2004 were analyzed using Cox proportional hazard model. Of the 630 patients, 338 received radical excision and 292 received palliative resection. **Results:** The overall 1-, 3-, 5-year survival rates were 63.8%, 31.4% and 14.3%, respectively. Univariate analysis showed that Borrmann type, lymphatic metastasis, organ involvement, tumor location, tumor size, pathologic type, radical excision and other organ excision were significant prognostic factors affecting 1-year survival rate ($P < 0.05$); Borrmann type, lymphatic metastasis, organ involvement, pathologic type and radical excision affected 3-year survival rate ($P < 0.05$); only organ involvement and pathologic type affected 5-year survival rate ($P < 0.05$). Multivariate analysis showed that pathologic type was independent prognostic factor for poor survival. **Conclusions:** Radical resection and combined organ resection could prolong the survival of stage IV (M0) gastric cancer patients. Chemotherapy, radiotherapy and targeted therapy should be considered for individual therapeutic regimen.

Key words: Gastric cancer, stage IV, surgery, survival

The clinical manifestations of gastric cancer are imperceptible. Most cases are diagnosed at advanced stage, with a relatively high proportion [1]. After decades of evolution, gastric cancer surgical techniques have been gradually improved, but the 5-year survival rate of gastric cancer patients after radical resection is still about 30% [2], and the 5-year survival rate of stage IV gastric cancer patients is even lower [3]. In order to investigate the prognostic factors of stage IV gastric cancer patients, we retrospectively analyzed 630 cases of stage IV gastric cancer without distant metastasis, explored the correlations of clinicopathologic features of stage IV gastric cancer to its prognosis.

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Materials and Methods

Selection of patients

Between January 1993 and August 2004, 630 patients with stage IV gastric cancer without distant metastasis (T1-3N3M0, T4N2M0) were treated at the Department of Gastrointestinal Surgery of Harbin Medical University Cancer Hospital. Inclusion criteria were as follows: (1) the primary tumor was removed, with $D2^+$ lymphadenectomy synchronously; (2) no distant metastasis (referring to extra-peritoneal cavity metastases according to the 13th Edition of definition by the Japanese Research Society for Gastric Cancer (JRSGC); (3) complete clinical data and follow-up information; (4) the causes of death were tumor metastasis and recurrence. Of the 630 patients, 480 were men and 150 were women with a ratio of 3.2:1. The median age of the patients was 54.5 years (range, 20–88 years). The median survival time was 12.5 months (range, 1–121 months). TNM staging was performed according to the definition by JRSGC (13th Edition).

Pathological data

Of the 630 patients, 92 (14.6%) had papillary adenocarcinoma and tubular adenocarcinoma, 360 (57.2%) had poorly differentiated adenocarcinoma, 174 (27.6%) had

signet-ring cell carcinoma and mucinous adenocarcinoma, and 4 (0.6%) had other types of gastric cancer (undifferentiated carcinoma and carcinoid); 372 (59.1%) had cancer located in the lower part of the stomach, 75 (11.9%) in the middle part, 92 (14.6%) in the upper part and 91 (14.4%) in whole stomach; 389 (61.7%) had tumor diameter of > 5 cm, and 241 (38.3%) had tumor diameter of ≤ 5 cm; 7 (1.1%) were at stage T1, 52 (8.3%) at stage T2, 251 (39.8%) at stage T3, and 320 (50.8%) at stage T4; 23 (3.6%) at stage N0, 49 (7.8%) at stage N1, 212 (33.7%) at stage N2, and 346 (54.9%) at stage N3; 87 had liver and gallbladder invasion, 95 had peritoneal metastasis, 205 had transverse colon and mesenteric invasion, 176 had pancreatic invasion, 48 had diaphragm invasion, and 19 had spleen metastasis.

Operation data

Of the 630 patients, 338 (53.7%) received radical resection and 292 (46.3%) received non-radical operation; 346 (54.9%) received distal gastrectomy, 54 (8.6%) received proximal gastrectomy, and 230 (36.5%) received total gastrectomy; 81 received combined organ resection, including 18 received partial hepatectomy, 14 received pancreatic body and tail resection, 19 received splenectomy, 26 received colon resection, and 4 received pancreatoduodenectomy.

Follow-up

The patients were followed-up by letter and telephone till August 2009. All living patients were followed up for over 5 years. All patients had complete follow-up data.

Statistical analysis

Categorical data were analyzed by the χ^2 test. Multivariate prognostic analysis was performed using Cox proportional hazards model. The level of significance was set at $P < 0.05$. Statistical analyses were performed with the SPSS13.0 software.

Results

Survival rate

The 1-, 3-, and 5-year overall survival (OS) rates were 63.8%, 31.4%, 14.3% in the whole group, respectively.

Relationship between pathologic features and prognosis of stage IV (M0) gastric cancer

Univariate analysis showed that lymphatic metastasis, organ invasion, tumor location, tumor size, Borrmann type, and pathologic type were significantly associated with 1-year survival rate ($P < 0.05$); Borrmann type, lymphatic metastasis, organ invasion and pathologic type were significantly associated with 3-year survival rate ($P < 0.05$); Borrmann type, organ invasion and pathologic type were significantly associated with 5-year survival rate ($P < 0.05$) (Table 1).

Relationship between operation patterns and prognosis of stage IV (M0) gastric cancer

The 1-, 3-, and 5-year OS rates were 69.8%, 39.1%, 18.3% in patients treated with radical resection, and 56.8%, 22.6%, 9.6% in patients treated with non-radical operation ($P < 0.05$). The 1-, 3-, and 5-year OS rates were 71.4%, 34.6%, 14.8% in patients treated with combined organ resection, and 58.8%, 30.0%, 14.2% in patients treated without combined organ resection, with significant difference in 1-year OS rates between the two groups ($P < 0.05$), but no significant difference in 3- and 5-year OS rates was found ($P > 0.05$). The scope of gastric resection had no relationship with prognosis ($P > 0.05$) (Table 2).

Prognostic factors

Cox multivariate prognostic analysis showed that lymphatic metastasis, organ invasion, Borrmann type, pathologic type, and radical resection were independent prognostic factors for 1-year survival; pathologic type, lymphatic metastasis and organ invasion were independent prognostic factors for 3-year survival; only pathologic type was an independent prognostic factor for 5-year survival (Tables 3–5).

Discussion

To date, the proportion of patients with stage IV gastric cancer in all gastric cancer patients is still high. With the carrying out of standard radical gastrectomy and extended radical gastrectomy, the prognosis of early gastric cancer and resectable advanced gastric cancer has been significantly improved. For stage IV gastric cancer, people try to improve the prognosis by expanding the scope of lymphadenectomy and combined organ resection, but have achieved no remarkable results. At present, most experts believe that treatment of gastric cancer should be based on a reasonable choice of operation pattern and treatment methods[4-6].

Stage IV gastric cancer has its own clinicopathologic features. Our study showed that only pathologic type was an independent prognostic factor for 5-year survival rate: the prognosis of papillary adenocarcinoma, tubular adenocarcinoma and poorly differentiated adenocarcinoma was better than that of signet-ring cell carcinoma and mucinous adenocarcinoma. Papillary adenocarcinoma and tubular adenocarcinoma are usually well differentiated, with low malignancy and slow disease progression. Although poorly differentiated adenocarcinoma has high malignancy, it is sensitive to radiotherapy and chemotherapy which could prolong survival in a certain period. Signet-ring cell carcinoma and mucinous adenocarcinoma are insensitive to radiotherapy and chemotherapy, progress rapidly, have poor prognosis. Lymphatic metastasis, organ invasion and radical gastrectomy were not prognostic factors for 5-year survival rate, indicating that even using radical gastrectomy, expanding the scope of lymphadenectomy, and combining organ resection could prolong survival in a period, of time, and can hardly achieve truly radical resection, because exfoliated cells and occult distant metastasis are difficult to be found and eliminated. In this study, patients with Borrmann type 4 gastric cancer had shorter survival, with a 5-year survival rate of 0. This may be related to that Borrmann type 4 gastric cancer is concealed and is difficult to be detected at early stage, and shows infiltrative growth, often has micrometastasis in the gastric wall. Seven patients with T1 gastric cancer had extensive metastasis, 6 of them died within 1 year after operation, suggesting that the scope of lymphadenectomy for early gastric cancer could not be blindly reduced. When level III lymph node metastasis is found,

Table 1 Relationship between clinicopathologic characteristics and prognosis of stage IV (M0) gastric cancer

Parameter	Patient No.	1-year(patient No.)		χ^2	*P*	3-year(patient No.)		χ^2	*P*	5-year(patient No.)		χ^2	*P*
		Survival	Death			Survival	Death			Survival	Death		
Gender				1.059	0.304			0.407	0.524			0.840	0.359
Men	480	301	179			124	356			72	408		
Women	150	101	49			74	76			18	132		
Age (years)				5.225	0.073			2.142	0.343			3.342	0.188
< 40	48	32	16			19	29			11	37		
40–60	348	234	114			103	245			49	299		
> 60	234	136	98			76	158			30	204		
Tumor location				32.439	< 0.001			3.159	0.368			7.794	0.050
Antrum	372	258	114			124	248			49	323		
Middle	75	52	23			25	50			18	57		
Cardia	92	57	35			27	65			16	76		
Total	91	35	56			22	69			7	84		
Tumor diameter (cm)				8.628	0.003			1.221	0.269			2.370	0.124
⩽ 5	241	171	70			82	159			41	200		
> 5	389	231	158			116	273			49	340		
Pathologic type				10.541	0.005			20.702	0.000			18.187	0.000
Polypoid and tubular	92	68	24			47	45			26	66		
Poorly differentiated	360	244	116			107	253			39	321		
Mucinous, signet-ring and others	178	110	88			44	134			25	153		
Borrmann type				99.174	< 0.001			30.464	0.000			11.418	0.022
0	7	3	4			3	4			2	5		
1	57	39	18			27	30			10	47		
2	39	29	10			12	27			6	33		
3	471	329	142			155	316			72	399		
4	56	2	54			1	55			0	56		
T stage				5.177	0.159			4.147	0.246			3.152	0.369
T1	7	3	4			3	4			2	5		
T2	52	31	21			18	34			7	45		
T3	251	171	80			88	163			38	213		
T4	320	199	121			89	231			43	277		
N stage				37.760	< 0.001			18.513	< 0.001			24.788	< 0.001
N0	23	14	9			11	12			9	14		
N1	49	34	15			23	26			14	35		
N2	212	168	44			79	133			32	180		
N3	346	186	160			85	261			35	311		
Organ invasion				95.994	< 0.001			37.572	< 0.001			8.195	0.004
Yes	312	140	172			82	230			32	280		
No	318	282	56			116	202			58	260		

Table 2 Relationship between Operation pattern and prognosis of stage IV (M0)

Parameter	Patient No.	1-year(patient No.)		χ^2	*P*	3-year(patient No.)		χ^2	*P*	5-year(patient No.)		χ^2	*P*
		Survival	Death			Survival	Death			Survival	Death		
Radical resection				11.418	0.001			19.672	< 0.001			9.805	0.002
Yes	338	236	102			132	206			62	276		
No	292	166	126			66	226			28	264		
Operation scope				2.142	0.343			1.518	0.468			0.843	0.656
Distal	346	212	134			106	240			48	298		
Proximal	54	36	18			14	40			6	48		
Entire	230	154	76			78	152			36	194		
Other organ resection				4.241	0.039			0.425	0.514			0.021	0.884
Yes	81	60	21			28	53			12	69		
No	549	323	226			170	379			78	471		

Table 3 Multivariate analyses of 1-year survival of stage IV (M0) gastric cancer patients

Variate	B	SE	Wald	*P*
Lymphadenectomy	0.534	0.072	6.381	0.021
Organ invasion	0.639	0.091	10.013	0.000
Pathologic type	0.734	0.103	13.198	0.000
Borrmann type	0.587	0.073	7.348	0.027
Tumor location	0.242	0.041	3.477	0.311
Radical resection	0.779	0.097	8.491	0.011

Table 4 Multivariate survival analyses of 3 year survival

Variate	B	SE	Wald	*P*
Lymphadenectomy	0.512	0.069	5.937	0.043
Organ invasion	0.763	0.074	6.177	0.024
Pathologic type	0.798	0.089	10.042	0.000
Borrmann type	0.641	0.076	8.371	0.013
Radical resection	0.430	0.053	4.193	0.054

Table 5 Multivariate survival analyses of 5 year survival

Variate	B	SE	Wald	*P*
Organ invasion	0.392	0.061	3.462	0.102
Pathologic type	0.643	0.074	7.187	0.001
Borrmann type	0.489	0.058	4.295	0.071
Radical cure	0.406	0.059	3.736	0.098

expanding the scope of lymphadenectomy could not significantly increase 5-year survival rate[7]. In fact, that extensive lymph node dissection (ELND) increases the survival rate is due to the so-called 'stage-shifting phenomenon', which increases staging by ELND, improves stage-specific survival rate, but could not improve overall survival rate [8]. Extended lymphadenectomy significantly increases postoperative complications [9]. Therefore, the scope of lymphadenectomy should be decided based on an accurate preoperative and intraoperative assessment rather than blindly expanded.

In this study, the 5-year OS rate was significantly higher in radical resection group than in non-radical resection group, the 1-year OS rate was significantly higher in patients treated with combined organ resection than in those without combined organ resection. Therefore, we advocate that the scope of resection should be expanded as long as patients could tolerate to create chances for subsequent non-surgical treatment and improve the efficacy. Recently, we treated some gastric cancer patients with surrounding organ invasion and retroperitoneal lymph node metastasis by 2–3 courses of neoadjuvant chemotherapy, and achieved down-staging effect. Meanwhile, we observed that some patients treated with standard postoperative chemotherapy achieved complete remission, and short-term efficacy was significantly improved.

Gockel *et al.*[10] found that there was no significant difference in 5-year survival rate between the patients with gastric cardia carcinoma treated by proximal gastric resection and total gastrectomy, while perioperative mortality of total gastrectomy group was increased significantly. Under these circumstances, we consider to prolong patients' survival by improving the quality of life. In view of this problem, we carried out proximal gastrectomy with single loop jejunal interposition for cardia cancer and cardia-reserved proximal gastrectomy for gastric cancer with a distance of more than 5 cm from the cardia, and achieved certain effect on improving the nutritional status and reducing reflux, but the effect on prolonging survival should be further observed[11].

To sum up, for stage IV gastric cancer, the selection of operation pattern, lymphadenectomy scope and combined organs resection should be based on lesion location, size, depth of invasion, organs invasion and lymph node metastasis to improve 5-year survival rate. At the same time , to select reasonable methods of digestive tract reconstruction based on the patient's age and physical condition may help to improve the quality of life.

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