

Role of Metastasectomy on Overall Survival of Patients with Metastatic Gastric Cancer

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Purpose: The role of metastasectomy has been debatable and unclear in the treatment for patients with metastatic gastric cancer. Therefore, this study was designed to evaluate the role of metastasectomy on the overall survival of these patients.

Materials and Methods: In 2,406 patients who underwent gastrectomy for gastric cancer between 1998 and 2010, 188 (7.8%) patients had their first surgery for metastatic gastric cancer. To minimize the bias of systemic chemotherapy, 99 patients who received postoperative chemotherapy (fewer than 2 cycles) were excluded. The primary gastrectomy or metastasectomy had not been enforced in the following cases. Patients with far advanced peritoneal dissemination, multiple liver and lung metastasis (more than 2), and a poor general condition (Eastern Cooperative Oncology Group >2) were excluded. Based on the metastasectomy, the patients were classified into two groups, gastrectomy with metastasectomy and gastrectomy only group.

Results: There was no significant difference between both groups in clinicopathological characteristics except for the mean age ($P=0.047$). The univariate analysis for overall survival show statistical significances in metastasectomy ($P=0.026$), distal gastrectomy ($P=0.047$), and combined resection of another organ ($P=0.047$) group. With a multivariate analysis, metastasectomy was a significant factor in patient survival after surgery (odds ratio 1.679; $P=0.034$).

Conclusions: Based on our results, we assume that a detailed strategy for surgery is needed to improve the overall survival of patients with metastatic gastric cancer. Therefore, we suggest that a metastasectomy can help prolong overall survival in some patients with metastatic gastric cancer.

Key Words: Gastric cancer; Distant metastasis; Metastasectomy; Overall survival

Introduction

The overall prognosis of gastric cancer patients with distant metastasis remains very poor despite the decline in incidence and mortality rate of gastric cancer in most parts of the world.¹⁻⁴ Despite many investigators reporting that their surgical methods improve the overall survival of patients with gastric cancer and distant

metastasis, the proper surgical management remains controversial.

Recently, several investigators suggested that a primary debulking surgery or a primary gastrectomy with metastasectomy could help prolong the survival of patients with gastric cancer patients and distant metastasis.⁵⁻¹⁰ On the other hand, other studies suggested an unfavorable overall survival after resection of metastatic gastric cancer.¹¹⁻¹⁵ However, most studies were performed without consideration of the impact of systemic chemotherapy and the severity of the disease at time of treatment on the survival benefit.

Therefore, our study was designed to evaluate the impact of metastasectomy on survival of patients with gastric cancer patients and distant metastasis.

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Materials and Methods

1. Patients and methods

We reviewed the data on 188 patients with metastatic gastric cancer who underwent gastrectomy and who had postoperative systemic chemotherapy that was collected prospectively between 1992 and 2012 at Hanyang University Hospital. To minimize the bias of systemic chemotherapy, 99 patients who received postoperative systemic chemotherapy of less than two cycles were excluded from this study. Based on the metastasectomy, all patients were divided into two groups (gastrectomy with metastasectomy [GM] and gastrectomy only [GO]).

This study included 89 patients with an optimal Eastern Cooperative Oncology Group (ECOG) performance status (measured as an ECOG < 2). The purpose of the metastasectomy was to remove all metastatic lesions. In our approach to the metastasectomy, we did not attempt aggressive surgical procedures such as peritonectomy and hemihepatectomy, as these can increase the risk of postoperative morbidity and mortality. Therefore, the intent was to remove all visible metastatic lesions during the operation. The inclusion criteria for the metastasectomy group were a single metastasis in the liver or lung, no advanced peritoneal dissemination (P1 or P2, as per the Japanese Research Society for the Study of Gastric Cancer criteria). The inclusion criteria for the gastrectomy only were the presence of multiple liver metastasis, multiple lung metastasis, or advanced peritoneal dissemination (P3 as per the Japanese Research Society for the Study of Gastric Cancer criteria).

The exclusion criteria for this study were the rigid fixation of the pancreas head due to the primary gastric cancer, a palliative gastrectomy for uncontrolled bleeding, perforation or obstruction, and poor ECOG performance status (ECOG > 2).

2. Statistical analysis

The primary end-point for this study was survival; the overall survival rates were estimated by using the Kaplan–Meier method. Statistical analysis was performed by using PASW Statistics ver. 18.0 for Windows (IBM Co., Armonk, NY, USA). All values are expressed as mean with standard deviation. Categorical variables were analyzed by using the chi-square test and all continuous variables were analyzed by using Student's *t*-test, depending on the data. The long-rank test was used to compare significant differences between subgroups by using univariate analysis. Multivariate analysis was performed to identify prognostic factors

associated with overall survival. The Cox proportional hazards model was employed for multivariate regression analysis. The survival curve was calculated by using the Kaplan–Meier method. Hazard ratios with 95% confidence intervals were estimated for each variable in the multivariate analysis. A $P < 0.05$ was considered statistically significant.

Results

1. Patient characteristics

The clinicopathological characteristics of the 89 gastric cancer patients with distant metastasis are presented in Table 1. There was no significant difference between both groups in most variable factors except for mean age (GM vs. GO group, 58.8 vs. 53.1, $P=0.047$).

2. Surgical outcomes

The median follow-up period was 14.9 months (range 1 to 157.6 months). The 3-year overall survival rates were 23.3 and 8.5% for the GM and GO groups, respectively (Fig. 1).

3. Analysis of prognostic factors for overall survival

In the univariate analysis for overall survival, there were significant differences in the 3-year survival rates for metastasectomy, distal gastrectomy, and combined resection of other organs was 23.3% vs. 8.5% ($P=0.026$), 17.8% vs. 9.1% ($P=0.047$) and 8.1% vs. 17.3% ($P=0.047$), respectively (Table 2). The multivariate analysis showed that a primary gastrectomy with metastasectomy (odds ratio=1.679, 95% confidence interval 1.040 to 2.711, $P=0.034$) was associated with survival (Table 3).

Discussion

Despite the extensive screening programs that have been operating under national health support for early detection of gastric cancer in Korea and Japan, many patients, at the time of diagnosis have very advanced gastric cancer with distant metastasis. A radical gastrectomy with a clear resection margin and D2 lymph node dissection has become a standard surgical method for advanced gastric cancer patients, but for patients with distant metastasis the role of surgery is still debatable.

Recently, the role of surgery in patients with metastatic gastric cancer is a matter of debate and controversy, as there is no current standard treatment for patients with metastatic gastric cancer.

Table 1. Clinicopathological characteristics of patients with metastatic gastric cancer

Variable	According to the metastasectomy		P-value
	GM group (n=30)	GO group (n=59)	
Gender			0.184
Male	23 (76.7)	37 (62.7)	
Female	7 (23.3)	22 (37.3)	
Age (yr)	58.8±12.9	53.1±12.2	0.047
Peritoneal dissemination			0.272
Yes	25 (83.3)	43 (72.9)	
No	5 (16.7)	16 (27.1)	
Liver metastasis			0.527
Yes	4 (13.3)	11 (18.6)	
No	26 (86.7)	48 (81.4)	
Number of metastatic organs			0.411
1	28 (93.3)	50 (84.7)	
≥2	2 (6.7)	9 (15.3)	
Type of surgery			0.331
Total gastrectomy	13 (43.3)	32 (54.2)	
Distal gastrectomy	17 (56.7)	27 (45.8)	
Lymph node dissection			0.197
< D2	0 (0.0)	2 (3.4)	
≥D2	30 (100.0)	57 (96.6)	
Number of cycles of chemotherapy	5.4±2.3	4.8±1.2	0.239
Regimen of first-line chemotherapy			0.263
5-fluorouracil/platinum	18 (60.0)	28 (47.5)	
Others	12 (40.0)	31 (52.5)	
Pathologic T staging*			0.800
T1			
T2	3 (10.0)	7 (11.9)	
T3	20 (66.7)	34 (57.6)	
T4	7 (23.3)	18 (30.5)	
Pathologic N staging*			0.740
N0	0 (0.0)	2 (3.4)	
N1	3 (10.0)	9 (15.3)	
N2	7 (23.3)	11 (18.6)	
N3	20 (66.7)	37 (62.7)	

Values are presented as number (%) or mean±standard deviation. GM group = gastrectomy with metastasectomy group; GO group = gastrectomy only group. *American Joint Committee on Cancer (AJCC) 6th edition on gastric cancer staging system.

According to the National Comprehensive Cancer Network clinical practice guidelines, palliative systemic chemotherapy and best supportive care are recommended in patients with metastatic gastric cancer.¹⁶ Recently, however, several investigators have suggested that cytoreductive surgery or a primary gastrectomy with

metastasectomy is associated with an increase in survival. The rationale for surgery is that the disease may respond to adjuvant treatment more effectively due to a reduction in tumor load. Theoretically, a reduction in the tumor burden can decrease the metabolic demands of the tumor. Also, because the tumor itself

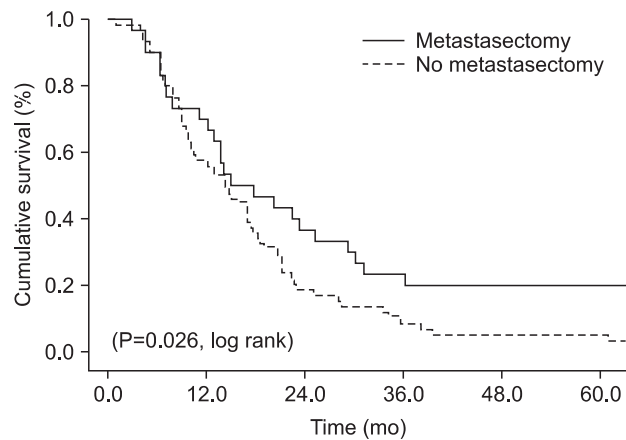


Fig. 1. Survival of patients with metastatic gastric cancer who underwent gastrectomy with and without metastasectomy.

can produce an immunosuppressive cytokine, reducing the tumor burden may also have an immunologic benefit.^{3,13,17-19}

In practice, however, the procedure is difficult to perform for many reasons. Many experts on gastric cancer treatment suggested that patients with metastatic gastric cancer who had surgery did not experience an increase in overall survival. Also, many patients have a high associated mortality and morbidity. Based on these results, these experts suggested that the majority of patients with metastatic disease did not require surgery.

Based on our results of the overall survival of patients with gastric cancer, those patients with metastases show a poor overall 5-year survival rate (12.9%). We saw the need to reconsider the surgical strategy on the basis of the differences in the characteristics of these patients. Unlike most gastric cancer patients without metastasis, patients with metastases show a wide range of physiological presentations based on their specific medical condition and the stage of their disease. Therefore, an appropriate surgical strategy for improving the overall survival should be considered according to the specific condition of the individual patient.

Our institution, as previously mentioned, had implemented a strict method for patient selection for surgery in patients with metastatic gastric cancer. To the exclusion of palliative surgery for obstruction or bleeding, the primary gastrectomy with or without metastasectomy is rigorously enforced in patients < 70 years of age, those with a good performance status (ECOG < 2), patients with a resectable primary tumor (excluding fixed gastric cancers in the pancreas head), and in patients with a less aggressive cancer (< P2, solitary liver metastasis, etc.). Our most important policy in selecting patients for the procedure is the presence of the possibility for systemic chemotherapy after gastrectomy. The results of this

Table 2. One- and three-year survival rates of patients with M1* gastric cancer after surgery

Variable	1-year survival rate (%)	3-year survival rate (%)	P-value
Gender			0.361
Male	70.0	15.0	
Female	44.8	10.3	
Elderly patient (yr)			0.248
≤65	66.0	15.4	
>65	50.0	8.3	
ECOG performance status			0.146
0	53.8	7.7	
1	65.1	15.9	
T stage*			0.730
≤T3	60.9	15.6	
T4	64.0	8.0	
N stage*			0.221
≤N2	68.8	15.6	
N3	57.9	12.3	
Extent of gastrectomy			0.047
Distal	73.3	17.8	
Total	50.0	9.1	
Metastasectomy			0.026
Yes	70.0	23.3	
No	57.6	8.5	
Combined resection of other organs			0.047
Yes	54.1	8.1	
No	67.3	17.3	
Tumor size (cm)			0.078
≤10	67.2	16.4	
>10	50.0	7.1	
Histology			0.794
Well-defined	84.4	9.4	
Undefined	49.1	15.8	
Bormann type			0.151
B1,2	50.0	25.0	
B3,4	63.0	12.3	

ECOG = Eastern Cooperative Oncology Group. *American Joint Committee on Cancer (AJCC) 6th edition on gastric cancer staging system.

study are to achieve better surgical results in improving the overall survival of patients with metastatic gastric cancer. In particular in this study we assumed that metastasectomy could be useful in improving the overall survival in a strictly selected patient group.

Table 3. Multivariate analysis of prognostic factors associated with overall survival

Variable	Relative risk	95% CI	P-value
Metastasectomy	1.679	1.040~2.711	0.034
Combined resection of other organ (no vs. yes)	1.485	0.965~2.283	0.072
Tumor size (≤ 10 cm vs. > 10 cm)	1.482	0.933~2.355	0.096
Extent of gastrectomy (subtotal vs. total)	1.181	0.726~1.923	0.502

CI = confidence interval.

There are several limitations inherent in our retrospective study. Although the baseline characteristics of the patients between two groups were similar, there was a clear difference in the progression of disease (P1, P2 vs. P3, solitary liver metastasis vs. multiple liver metastasis). This difference may be a confounding factor in the evaluation of the impact of metastasectomy on overall survival. Unfortunately, we could not analyze the impact of surgery on overall survival according to the specific organ because of our low case number, therefore further studies are needed to evaluate the impact of surgery on overall survival according to the specific organ. Although our study is limited in its ability to evaluate surgical outcomes, our findings regarding the survival benefit of metastasectomy strongly support the hypothesis that metastasectomy can play a vital role in improving overall survival of patients with metastatic gastric cancer.

In our study we are not proposing that primary gastrectomy with metastasectomy is the gold standard in improving the overall survival for all patients with metastatic gastric cancer. Unlike those without metastasis, patients with metastases have a wide variation in their general health because of the range in disease progression. Therefore, we suggest that primary gastrectomy with metastasectomy can help improve overall survival in some patients with metastatic gastric cancer.

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