

Clinicopathologic Characteristics of Gastric Cancer Patients according to the Timing of the Recurrence after Curative Surgery

Ji Yoon Choi, Tae Kyung Ha, and Sung Joon Kwon

Department of Surgery, Hanyang University College of Medicine, Seoul, Korea

Purpose: There are few studies that have focused on the predictors of recurrence after gastrectomy for gastric carcinoma. This study analyzed the patients who died of recurrent gastric carcinoma and we attempted to clarify the clinicopathologic factors that are associated with the timing of recurrence.

Materials and Methods: From June 1992 to March 2009, 1,795 patients underwent curative gastric resection at the Department of Surgery, Hanyang University College of Medicine. Among them, 428 patients died and 311 of these patients who died of recurrent gastric carcinoma were enrolled in this study. The clinicopathologic findings were compared between the 72 patients who died within one year after curative gastrectomy (the early recurrence group) and the 92 patients who died 3 years after curative gastrectomy (the late recurrence group).

Results: Compared with the late recurrence group, the early recurrence group showed an older age, a more advanced stage, a poorly differentiated type of cancer and a significantly higher tendency to have lymphatic invasion, vascular invasion and perineural invasion. Especially in the gastric cancer patients with a more advanced stage (stage III and IV), the early recurrence group was characterized by a significantly higher preoperative serum carcino embryonic antigen level, perineural invasion and a relatively small number of dissected lymph nodes.

Conclusions: The clinicopathologic characteristics of recurrent gastric cancer are significantly different according to the stage of disease, and even in the same stage. For the early detection of recurrence after curative surgery, it is important to recognize the clinicopathological factors that foretell a high risk of recurrence. It is mandatory to make an individualized surveillance schedule according to the clinicopathologic factors.

Key Words: Stomach neoplasms, Gastrectomy, Recurrence

Introduction

The incidence of gastric cancer has recently been gradually decreasing, and particularly the proportion of cases of early gastric cancer among all the cases of gastric cancer is rapidly on the rise. Yet the mortality rate due to gastric cancer is still high. (1,2) Surgical resection is currently the only radical treatment for gastric cancer, and the 5-year survival rate is continuously on

the increase because of performing radical resection, extended lymphadenectomy, postsurgical chemotherapy and adjuvant immunotherapy. Nevertheless, death is due to recurrence in 60~70% of the cases of gastric cancer.(3) In some cases, it can be resected again, which allows long term survival. Yet gastric cancer recurs as diverse patterns in several organs, and it is difficult to distinguish the recurrence patterns. Hence, this is treated by conservative treatments, and prognosis is poor.(4-6) The level of tumor infiltration and the presence or absence of lymph node metastasis are currently the important prognostic factors, but there are insufficient studies on the risk factors pertinent to the time of recurrence or the recurrence patterns. To understand the factors associated with recurrence and to help appropriately treat the at-risk group after surgery, we analyzed the clinicopathological

Correspondence to: Sung Joon Kwon
Department of Surgery, Hanyang University College of Medicine, 17, Haengdang-dong, Seongdong-gu, Seoul 133-792, Korea
Tel: +82-2-2290-8453, Fax: +82-2-2281-0224
E-mail: sjkwon@hanyang.ac.kr
Received September 24, 2010
Accepted November 25, 2010

characteristics of patients with the same disease stages according to the time of recurrence.

Materials and Methods

From June 1992 to March 2009, in the Department of Surgery at Hanyang University, 1,795 patients were diagnosed with gastric

Table 1. Patterns of recurrence after curative surgery in gastric cancer

Cause of death	No. of patients
Peritoneal seeding	170
Hematogenous recurrence	57
Liver	29
Lung	11
Bone	8
Brain	7
Abdominal wall	2
Locoregional recurrence	29
Remnant stomach	6
Gastric bed	6
Lymph node	17
Not defined recurrence site	55
Benign disease	39
Pneumonia	8
Myocardial infarction	7
Hepatic failure	7
Pulmonary embolism	4
Renal failure	3
Others	10
Other organ cancer	17
Cholangiocarcinoma	5
Lung cancer	3
Colorectal cancer	3
Leukemia	2
Hepatocellular carcinoma	1
Pancreatic cancer	1
Esophageal cancer	1
Multiple myeloma	1
Accident	11
Unknown origin	50
Total death	428
Stomach cancer	311
Others	67
Unknown	50

cancer and 428 of them died. Among them, we excluded the patients that the cause of death was not known (n=50), the patients who died due to accidents (n=11), the patients who died due to cancer in other organs (n=17) and the patients who died of other benign diseases (n=39). Finally, this study was conducted on 311 patients who died due to recurrent gastric cancer (Table 1). A radical resection was done for the patients without distant metastasis and without infiltration to the adjacent organs, the patients with infiltration and without macroscopic residual cancer and the patients who underwent lymphadenectomy higher than D2.

These 311 patients were divided to 1) 72 patients (23.2%) (the early recurrence group) whose recurrence time was within 1 year after surgery, 2) 92 patients (29.6%) (the late recurrence group) whose recurrence occurred 3 years after surgery and 3) 147 patients (47.2%) (the mid recurrence group) who had recurrent disease between 1 year to 3 years after surgery (Fig. 1), and the clinicopathological characteristics of the early recurrence group and the late recurrence group were compared and analyzed.

History taking, physical examination, general blood tests, biochemistry tests, tumor marker tests, chest X-rays, gastroscopic examination, abdominal ultrasonography, abdominal computed tomography and PET-CT were regularly performed at the postsurgical ambulatory follow-up.

The recurrence patterns were classified as local recurrence, peritoneal recurrence and hematogenous recurrence. The local recurrence group was defined as cases that according to the clinical findings or various test findings, the gastric cancer recurred in the remaining stomach, the anastomosis areas and the adjacent organs and lymph nodes. According to physical examination, abdominal plain radiography and abdominal computed tomography, peritoneal

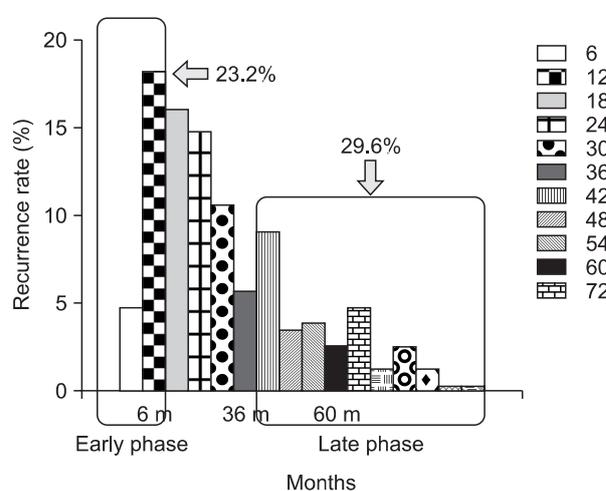


Fig. 1. Frequency of recurrence after curative operation.

recurrence was defined as the cases with tumors within the abdominal cavity, the cases with cancers detected by an ascites test, the cases in which diffuse metastasis was detected within the abdominal cavity during resurgery and the cases with tumor palpated on the rectal shelf by physical examination. Hematogenous recurrence was defined as the cases with hematogenous metastasis to distant organs such as the liver, bone, brain, abdominal wall etc., and this was detected by chest X-ray, abdominal sonography, a total bone scan, other radiologic tests and biopsy.

SPSS 13.0 was used for all the statistical analyses. Student's *t*-test was applied for comparing the various clinicopathological characteristics associated with recurrence. Logistic regression tests were applied for the multivariate analysis. *P*-values < 0.05 were considered to be statistically significant.

Results

1. The interval from surgery to recurrence

The interval of the 311 patients who died of recurred gastric cancer after radical treatment was from a minimum of 2 months to a maximum of 147 months, the average follow-up period was 30 months and the mean age was 56.2 years. Among them, the number of patients who recurred within 1 year was 72 patients, which was 23.2% of all the patients. The number of patients who recurred after 3 years was 92 patients, and they accounted for 29.6% of all the patients (Fig. 1). The cumulative recurrence rate up to 2 years after surgery was 39.2%, and the recurrence rate at the third year was 79.4% (Fig. 2).

2. The recurrence pattern

In regard to the recurrence pattern of all 311 patients, there were 170 patients with peritoneal recurrence, which was the most

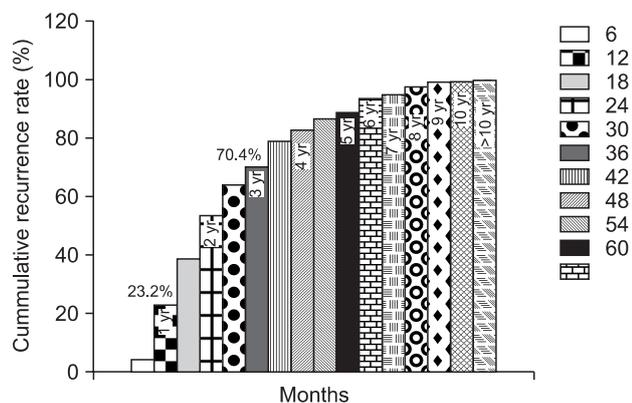


Fig. 2. Cummulativee rate of recurrence after curative resection.

prevalent, 57 patients with hematogenous recurrence and 29 patients with local recurrence. There were 55 patients whose recurrence area

Table 2. Clinicopathological findings according to the timing of recurrence after curative surgery in gastric cancer

Factors	Early recurrence (≤1 year)		Late recurrence (>3 years)		P-value
	n=72	%	n=92	%	
Sex					
Male	46	63.89	57	61.96	NS
Female	26	36.11	35	38.04	
Age (yr)					
<59	32	44.44	57	61.96	0.025
≥59	40	55.56	35	38.04	
Operation					
Subtotal gastrectomy	38	52.78	58	63.04	NS
Total gastrectomy	34	47.22	34	36.96	
TNM stage (6th AJCC)					
I	1	1.39	12	13.03	<0.0001
II	3	4.17	17	18.48	
III	26	36.11	40	43.48	
IV	42	58.33	23	25.01	
Chemotherapy					
None	5	6.94	9	9.78	NS
Oral	10	13.89	20	21.74	
Systemic	57	79.17	63	68.48	
Lymph node dissection					
D2	48	66.67	61	66.31	NS
>D2	24	33.33	31	33.69	
Dissected lymph node (No)					
<45	45	62.50	48	52.17	NS
≥45	27	37.50	44	47.83	
Lymphatic invasion					
Positive	66	91.67	73	79.35	0.029
Negative	6	8.33	19	20.65	
Blood vessel invasion					
Positive	25	34.72	19	20.65	0.044
Negative	47	65.28	73	79.35	
Perineural invasion					
Positive	23	31.94	10	10.87	0.001
Negative	49	68.06	82	89.13	
Preoperative CEA (ng/ml)					
<5	52	73.61	73	79.35	NS
≥5	16	22.22	12	13.04	
Unknown	3	4.17	7	7.61	

was not clear, but they were confirmed to have recurrent gastric cancer (data from the Bureau of Statistics) (Table 1).

Table 2. Continued

Factors	Early recurrence (≤1 year)		Late recurrence (>3 years)		P-value
	n=72	%	n=92	%	
Preoperative CA19-9 (U/ml)					
<39	68	94.44	89	96.74	NS
≥39	3	4.17	3	3.26	
Unknown	1	1.39	0	0	
Site					
Lower third	38	52.78	41	44.57	NS
Middle third	20	27.78	38	41.3	
Upper third	10	13.89	10	10.86	
Entire stomach	4	5.55	3	3.27	
Tumor size(cm)					
<8	39	54.17	56	60.87	NS
≥8	33	45.83	36	39.13	
Histology					
Well differentiated	0	0	3	3.26	0.019
Moderate differentiated	16	22.22	27	29.35	
Poorly differentiated	36	50	27	29.35	
Signet ring cell	20	27.78	30	32.61	
Mucinous	0	0	5	5.43	
Type of recurrence					
Peritoneal seeding	37	51.39	42	45.65	NS
Hematogenous	18	25.00	13	14.13	
Locoregional	15	20.83	25	27.17	
Unknown origin	2	2.78	12	13.05	

NS = not significant; TNM = tumor node metastasis; CEA = carcino embryonic antigen.

3. Clinicopathological characteristics according to the recurrence time

The clinicocharacteristics of the early recurrence group and the late recurrence group were compared. Regarding the age distribution, the age of the early recurrence group was higher ($P=0.025$). Regarding the distribution according to the 6th AJCC staging system an advanced disease stage was more prevalent in the early recurrence group than in the late recurrence group ($P<0.001$). In addition, the cases with lymph node infiltration, vascular infiltration or perineural infiltration were significantly more prevalent in the early recurrence group than in the late recurrence group ($P=0.029$, $P=0.044$, $P=0.001$). Concerning the grade of histological differentiation, the cases with poorly differentiated histological types were significantly more abundant in the early recurrence group than in the late recurrence group ($P=0.019$) (Table 2).

Other than that, age, the surgical methods, additional adjuvant therapy, the range of lymphadenectomy, the number of resected lymph nodes and the presurgical serum CEA and CA19-9 values of the two groups were not significantly different.

Multivariate analysis was performed using logistic regression on age, the 6th AJCC staging system lymph node infiltration, vascular infiltration and perineural infiltration, which were all significant on the univariate analysis. It was observed that for the early recurrence cases, the statically significant factors were an advanced stage (stage III), perineural infiltration and age (Table 3).

4. Clinicopathological characteristics of the stage III and IV patients according to the recurrence time

Among the patients, for the stage III and stage IV patients whose incidence of recurrence was particularly high, we compared the clinicopathological characteristic according to the recurrence time for the patients with the same disease stage. In regard to the

Table 3. Multivariate analysis* (logistic regression test) of clinicopathologic factors according to early and late recurrence group

	P-value	Odds ratio	95% confidence interval
Age (≥58 years)	0.045	0.467	0.222~0.985
Perineural invasion	0.023	0.329	0.127~0.856
TNM stage			
Stage II	0.564	0.475	0.038~5.952
Stage III	0.066	0.120	0.013~1.147
Stage IV		0.042	0.004~0.433

TNM = tumor node metastasis. *Binary logistic regression with "enter" method.

number of resected lymph nodes (median value: 47), there were significantly fewer cases with more than 47 lymph nodes in the early recurrence group than in the late recurrence group ($P=0.020$), and perineural infiltration was significantly more abundant in the

Table 4. Clinicopathological findings according to the timing of recurrence in stage III and stage IV gastric cancer

Factor	Early recurrence (≤ 1 year)		Late recurrence (> 3 years)		P-value
	n=68	%	n=63	%	
Sex					
Male	42	61.76	37	58.73	NS
Female	26	38.24	26	41.27	
Age (yr)					
<57	30	44.12	36	57.14	NS
≥ 57	38	55.88	27	42.86	
Operation					
Subtotal gastrectomy	34	50	35	55.56	NS
Total gastrectomy	34	50	28	44.44	
Chemotherapy					
None	3	4.41	3	4.76	NS
Oral	10	14.7	11	17.46	
Systemic	55	80.89	49	77.78	
Dissected lymph node (No)					
<47	48	70.59	32	50.79	0.020
≥ 47	20	29.41	31	49.21	
Lymphatic invasion					
Positive	64	94.11	57	90.48	NS
Negative	4	5.89	6	9.52	
Blood vessel invasion					
Positive	23	33.82	14	22.22	NS
Negative	45	66.18	49	77.78	
Perineural invasion					
Positive	22	32.35	6	9.52	0.001
Negative	46	67.65	57	90.48	
Size (cm)					
<7	36	52.94	35	55.56	NS
≥ 7	32	47.06	28	44.44	NS

early recurrence group ($P=0.001$) (Table 4).

Multivariate analysis was performed by applying Logistic regression on the number of resected lymph nodes as well as perineural infiltration, which were significant on univariate analysis. It was observed that only perineural infiltration was significantly more prevalent in the early recurrence group ($P=0.006$) (Table 5).

Discussion

The incidence and mortality rate of gastric cancer are on the decrease, and due to the development of diagnostic methods, the rate of discovering early gastric cancer as well as the 5-year

Table 4. Continued

Factor	Early recurrence (≤ 1 year)		Late recurrence (> 3 years)		P-value
	n=68	%	n=63	%	
Site					
Lower third	36	52.94	27	42.86	NS
Middle third	18	26.47	23	36.51	
Upper third	10	14.7	10	15.87	
Entire stomach	4	5.89	3	4.76	
Histology					
Differentiated	15	22.06	16	25.4	NS
Undifferentiated	53	77.94	47	74.6	
Preoperative CEA (ng/ml)					
<5	49	72.06	51	80.95	NS
≥ 5	16	23.53	6	9.52	
Unknown	3	4.41	6	9.52	
Preoperative CA19-9 (U/ml)					
<39	65	95.59	60	95.24	NS
≥ 39	3	4.41	3	4.76	
Type of recurrence					
Peritoneal seeding	38	55.88	32	50.79	NS
Hematogenous	17	25	6	9.52	
Locoregional	6	8.82	5	7.94	
Unknown origin	7	10.3	20	31.75	

NS = not significant; CEA = carcino embryonic antigen.

Table 5. Multivariate analysis* (logistic regression test) of clinicopathologic factors according to early and late recurrence group in stage III and stage IV gastric cancer

	P-value	Odds ratio	95% confidence interval
Perineural invasion	0.006	0.250	0.092~0.678

*Binary logistic regression with "enter" method.

survival rate are gradually increasing.(1,2) Numerous studies on the clinicopathological characteristics that exert effects on the prognosis of gastric cancer have been conducted, and prognosis can be predicted by the level of the infiltration of tumors to the stomach wall and the presence of lymph node metastasis and distant metastasis, which are the basis of the classification of the disease stage of gastric cancer.(7) Nevertheless, despite the improved diagnostic methods and extended therapeutic resection, the percent of cases that recur within 2 years after surgery has been reported to be 60~70%(3-6) In such a manner, most cases of mortality are associated with recurrence. Studies on the factors associated with the recurrence of gastric cancer are ongoing, but the information on this is still not sufficient.

Generally, recurrence refers to the growth of cancer lesions pertinent to the primary cancer after radical resection is performed according to the objective decision of surgeons.(8) The aim of radical resection of gastric cancer is first to completely remove the primary lesions with appropriate margins and second to prevent metastasis of cancer by the complete resection of the lymph nodes in the vicinity of the stomach.(9) In regard to distant metastasis that develops after such radical resection, the possibility is high that cancer has already formed beyond the range of surgery and at the time of surgery. Regarding local metastasis, the possibility of the presence of microscopical residual cancer cells is high. When reviewing the characteristics of recurrence according to the advanced level of cancer, in patients with progressive stomach cancer, the progression routes are diverse such as lymphoid, hematogenous and direct infiltration, peritoneal dissemination, etc. In most cases, the cancer progresses by several routes and not by a single route. On the other hand, in patients with early gastric cancer, progression is caused by overlooking multiple lesions, incomplete resection without securing sufficient margins after radical resection and insufficient lymphadenectomy in most cases.(9,10)

In most studies, recurrence has been classified as the early recurrence group and the late recurrence group based on 2 years and 3 years, respectively, and the risk factors associated with recurrence or the survival period after recurrence were analyzed. (6,11-16) This is based on the observation that for approximately 70% of recurred patients, the cancer recurs within 2 years after surgery, and cases that recur after 5 years are rare.(15)

Shiraishi et al.(11) classified 138 patients who died of recurrence after radical stomach resection as 104 cases (75.36%) of the early recurrence group (recurred within 2 years after surgery) and 34 cases (24.64%) of the late recurrence group (recurred after 2 years),

and they compared the clinicopathological characteristics. It was observed that in the early recurrence group, the average size of tumors was significantly larger ($P < 0.01$) and the cases with lymph node metastasis ($P = 0.01$), lymph duct infiltration ($P < 0.01$) and advanced disease stages ($P = 0.01$) were significantly more abundant.

In addition, Yokota et al.(14) classified 251 patients who died of recurrence after radical stomach resection as the group that recurred within 2 years and the group that recurred after 2 years. In regard to the incidence of recurrence and the timing, there were 195 patients (77.69%) and 56 patients (22.31%) in each group, respectively, and the early recurrence group was larger. In the early recurrence group, the size of tumor was significantly larger ($P = 0.029$). In addition, serous infiltration ($P = 0.038$), lymph node metastasis ($P = 0.001$), and the incidence of vascular infiltration ($P < 0.001$) were significantly higher in the early recurrence group.

Efforts have recently been made to apply immunohistochemical staining to find predictive factors for recurrence after radical resection of gastric cancer, in addition to the previously determined clinicopathological factors. Kim et al.(17) compared the expressions of c-erbB2, EGFR, MLH1, MSH2 and aquaporins of the recurred group with early gastric cancer after therapeutic radical resection with those of the non-recurrence group with early gastric cancer. They reported that the expression of c-erb B2 was significantly higher in the recurrence group ($P = 0.024$).

In this current study, based on 72 patients (23.2%) whose recurrence time was within 1 year and 92 patients (29.6%) whose recurrence time was longer than 3 years, the patients who died of recurred gastric cancer after radical resection were divided to the early recurrence group, the mid recurrence group and the late recurrence group. Different from most studies(6,9,11-13) that classified patients based on 2 years after surgery.

In this study we defined the early recurrence group based on the approximately early 25% cases of all recurrence cases and the late recurrence group based on the approximately late 25% cases of all recurrence cases.

Thus, if recurrence could be detected early based on our study's data, this could be an important for more aggressive therapies for recurrent lesions rather than just performing radical resection. In the early recurrence group, as compared with the late recurrence group, an advanced disease stage was more prevalent, the mean age was higher, the incidence of vascular, lymph duct and perineural infiltration was higher and the histological types with poor differentiation were more abundant. Particularly, for the patients with a highly advanced gastric cancer (stage III, stage IV),

perineural infiltration was abundant in the early recurrence group, and there were significantly more cases with a relatively small number of dissected lymph nodes. In such a manner, although the recurrence time was different according to the disease stages, within a same disease stage, some clinicopathological factors showed significant differences according to the recurrence time.

Lymph node metastasis is a well known prognostic factor that exerts effects on the recurrence rate as well as the overall survival rate. Tumor cells released from primary lesions penetrate the basement membrane, they transverse the interstitial tissues and penetrate the vascular basement membrane, they enter the circulation system and then they form tumor cell embolism. They, in turn, are released again through the basement membrane and form distant metastatic lesions. In addition, it has been reported that perineural infiltration, which has already been recognized as a major factor that mediates effects on tumor recurrence after surgery in patients with pancreas, biliary tract, esophagus and colorectal cancer, is associated with the recurrence of gastric cancer.(18–20) Bilici et al.(18) analyzed the perineural infiltration of 238 patients who underwent radical gastrectomy, and it was observed that 180 patients (75.6%) showed perineural infiltration. When their clinicopathological characteristics were analyzed and compared with those of the group without perineural infiltration, the average size of tumor was significantly larger ($P<0.001$), the

differentiation grade was worse ($P=0.009$) and an advanced disease stage ($P<0.001$), lymph node metastasis ($P<0.001$) and vascular infiltration ($P<0.001$) were significantly more abundant. In addition, the average survival period of the group with perineural infiltration was 28.1 months, and it was significantly shorter than 64.9 months of the group without perineural infiltration ($P=0.001$). Perineural infiltration is a process of tumor infiltration due to the neurotropic properties of tumor cells and it refers to the process of the denaturation of nerve fibers due to tumor cells infiltrating nerve bundles or nerve sheaths in the vicinity of tumors. Examined under an electronic microscope, nerve sheaths, lymph ducts and blood vessels are connected to each other anatomically, and through this, tumor cells infiltrate to adjacent tissues through the nerve sheaths and then they disseminated into the lymphoid system and toward the peritoneal membrane. Therefore, for cases with lymph node metastasis or perineural infiltration, even if radical resection is performed, the possibility of recurrence is high. It has been suggested that the follow-ups should be regularly performed and this may be of help to detect recurrence early.

For making the diagnosis of recurrence, not only imaging tests, but also tumor markers, hepatic function tests, general blood tests and other hematological tests are applied. Currently at our hospital, after radical gastrectomy and depending on the disease stage, different categories of tests and test intervals are applied. In

Table 6. Post-operative surveillance schedule according to stage

	3M	6M	9M	12M	15M	18M	21M	24M	27M	30M	33M	36M	42M	48M	54M	60M
Stage I/II																
CBC/LFT	O	O		O		O		O		O		O	O	O	O	O
CXR				O				O				O		O		O
CT/US		O		O		O				O			O	O	O	
PET-CT								O				O		O		O
EGD		O				O				O			O		O	
TM		O		O		O		O		O		O	O	O	O	O
Stage III/IV																
CBC/LFT	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O
CXR		O		O		O		O		O		O	O	O	O	O
CT/US	O		O		O		O		O		O			O	O	
PET-CT		O				O				O			O			O
EGD		O				O				O			O			O
TM	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O

CBC = complete blood count; LFT = liver function test; CXR = chest X-ray; CT = abdomen computed tomography; US = abdomen ultrasonography; EGD = esophagogastroduodenoscopy; TM = tumor marker.

other words, for stage I and stage II patients, general blood tests, hepatic function tests and tumor marker tests are performed at 6 month intervals. Abdominal computed tomography is performed at 6 month intervals up to 18 months after surgery, and at 12 month intervals after 18 months. In addition, gastroscopy is performed for the first time 6 months after surgery and at 12 month intervals afterward. PET-CT is performed 24 months after surgery for the first time. For the highly advanced cancer stage III and stage IV patients, since the risk of recurrence is high, general blood tests, liver function tests and tumor marker tests are performed at 3 month intervals, and abdominal computed tomography is performed 3 months after surgery for the first time and then at 6 month intervals afterward. PET-CT as well as gastroscopy are performed 6 months after surgery for the first time, and at 12 month intervals afterward (Table 6). In such a manner, the follow-up observation is performed differently according to the disease stage in order to detect recurrence after surgery early and to facilitate establishing treatment plans accordingly.

It is clear that an early diagnosis and radical resection during the initial surgery are the most important factors to increase the survival rate and to lower the recurrence rate. It is also true that with the development of chemotherapy, immunotherapy and other diverse therapies, the survival rate and treatment outcomes are improving.(21-23) Nonetheless, gastric cancer recurs after surgery in many patients, and once cancer recurs, the prognosis is very poor because definite treatments have not been established. (24-26) Gastric cancer is different from other cancers, it recurs as asynchronous multicentric cancer rather than locally, and so radical resection is difficult in many cases, and the cancer's responsiveness to systemic treatments such as chemotherapy is poor(25-27) Gastric cancer shows complex patterns of recurring at diverse times and the studies on factors that can predict the recurrence time are not still sufficient.

However, it has been reported that after radical resection, the survival rate can be increased through efforts to detect recurrence early by regular examination as well as by determining the appropriate range of surgery and performing radical treatments after the definite diagnosis.(28-30) From July 1988 to December 1995, Kim et al.(28) examined the clinicopathological characteristic of patients who developed local metastasis in the remaining stomach after radical gastrectomy, and the gastric cancer was primarily diagnosed by gastroscopy and an upper gastrointestinal series. The CEA level was elevated in 4 cases, and N2 and N3 group lymph node infiltration was abundant. It has been reported

that in such local recurrence cases caused by residual cancer, at the time of detection, the progression level of the lesion was severe and so the prognosis was poor. Nonetheless, in regard to clinically significant factors, it is thought that more comprehensive follow-up observation should be performed if the above findings are detected by presurgical tests as well as postsurgical tests. Moreover, it has been suggested that studies on methods that could be of help to improve the survival rate after recurrence are required.

Therefore, not only improving the quality of life according to radical treatments, but also the prevention of recurrence as well as the early detection of recurrence are important as study subjects. It has been shown that the clinicopathological characteristics of primary cancer are associated with the recurrence patterns and the recurrence time, and so if appropriate follow-up observation is performed on the factors that were significant in this study, recurrence could be detected early and then properly treated, and the mortality rate of gastric cancer itself could be decreased. For this, among various clinicopathological factors, efforts should be made to find new predictive factors that are clearly correlated with the recurrence of gastric cancer. In addition, studies on surgery, chemotherapy and other optimal treatment methods according to such correlation are also required.

In gastric cancer patients who recurred after radical resection, according to the disease stages and even in the same disease stage, the characteristics and time of recurrence vary according to diverse clinicopathological factors. Therefore, by considering this, if the interval of postsurgical follow-up observation and the types of tests are individualized, this would be useful to detect recurrence early and it would be of great help to improve the prognosis through appropriate treatments at early times.

References

1. Huh H, Hyung WJ, Chen J, Choi SH, Noh SH. Implication of lymphatic or blood vessel invasion in early gastric cancer. *J Korean Surg Soc* 2003;64:134-139.
2. Liu C, Zhang R, Lu Y, Li H, Lu P, Yao F, et al. Prognostic role of lymphatic vessel invasion in early gastric cancer: a retrospective study of 188 cases. *Surg Oncol* 2010;19:4-10.
3. Kim CD, Chang MC, Roh HR, Chae GB, Yang DH, Choi WJ. Factors influencing recurrence after curative resection for advanced gastric cancer. *J Korean Surg Soc* 2003;65:301-308.
4. Kim HI, Kim CS, Kim SJ, Mok YJ, Park SS. Risk factors of the recurrence after a curative resection of gastric carcinoma invad-

- ing the muscularis propria. *J Korean Surg Soc* 2006;70:98-101.
5. Shin DW, Hyung WJ, Noh SH, Min JS. Risk factors for recurrence after curative surgery for early gastric cancer. *J Korean Gastric Cancer Assoc* 2001;1:106-112.
 6. Sakar B, Karagol H, Gumus M, Basaran M, Kaytan E, Argon A, et al. Timing of death from tumor recurrence after curative gastrectomy for gastric cancer. *Am J Clin Oncol* 2004;27:205-209.
 7. Kim W, Park CH, Park SM, Park WB, Lim KW, Kim SN. Prognostic significance of lymphatic and perineural invasions in patients with gastric cancer who have no lymph node and serosal involvement. *J Korean Gastric Cancer Assoc* 2001;1:77-82.
 8. Baik SH, Yang SI, Shin YM. Clinicopathological analysis of recurrence in stage 1 gastric cancer. *J Korean Surg Soc* 2010;79:35-42.
 9. Park KJ, Park JG, Kim JP. Clinical analysis on recurrence pattern of gastric cancer. *J Korean Cancer Assoc* 1990;22:556-566.
 10. Lai JF, Kim S, Kim K, Li C, Oh SJ, Hyung WJ, et al. Prediction of recurrence of early gastric cancer after curative resection. *Ann Surg Oncol* 2009;16:1896-1902.
 11. Shiraishi N, Inomata M, Osawa N, Yasuda K, Adachi Y, Kitano S. Early and late recurrence after gastrectomy for gastric carcinoma. Univariate and multivariate analyses. *Cancer* 2000;89:255-261.
 12. Sun Z, Li DM, Wang ZN, Huang BJ, Xu Y, Li K, et al. Prognostic significance of microscopic positive margins for gastric cancer patients with potentially curative resection. *Ann Surg Oncol* 2009;16:3028-3037.
 13. Ogata K, Mochiki E, Yanai M, Toyomasu Y, Ando H, Ohno T, et al. Factors correlated with early and late recurrence after curative gastrectomy for gastric cancer. *Hepatogastroenterology* 2009;56:1760-1764.
 14. Yokota T, Saito T, Teshima S, Yamada Y, Iwamoto K, Takahashi M, et al. Early and late recurrences after gastrectomy for gastric cancer: a multiple logistic regression analysis. *Ups J Med Sci* 2002;107:17-22.
 15. Choi HS, Park SH, Kim JH. Factors predicting timing of recurrence after radical gastrectomy for gastric carcinoma. *J Korean Surg Soc* 2003;65:515-521.
 16. Cho JN, Kim YH. Clinicopathologic evaluation of patients with recurrence of gastric cancer within 6 months after curative resection. *J Korean Surg Soc* 2009;77:385-390.
 17. Kim JW, Hwang I, Kim MJ, Jang SJ. Clinicopathological characteristics and predictive markers of early gastric cancer with recurrence. *J Korean Med Sci* 2009;24:1158-1164.
 18. Bilici A, Seker M, Ustaalioglu BB, Kefeli U, Yildirim E, Yavuzer D, et al. Prognostic significance of perineural invasion in patients with gastric cancer who underwent curative resection. *Ann Surg Oncol* 2010;17:2037-2044.
 19. Tanaka A, Watanabe T, Okuno K, Yasutomi M. Perineural invasion as a predictor of recurrence of gastric cancer. *Cancer* 1994;73:550-555.
 20. Kim W, Park CH, Park SM, Park WB, Lim KW, Kim SN. Prognostic significance of lymphatic and perineural invasions in patients with gastric cancer who have no lymph node and serosal involvement. *J Korean Gastric Cancer Assoc* 2001;1:77-82.
 21. Villarreal-Garza C, Rojas-Flores M, Castro-Sánchez A, Villa AR, García-Aceituno L, León-Rodríguez E. Improved outcome in asymptomatic recurrence following curative surgery for gastric cancer. *Med Oncol* 2010. [Epub ahead of print]
 22. Dikken JL, Jansen EP, Cats A, Bakker B, Hartgrink HH, Kranenburg EM, et al. Impact of the extent of surgery and postoperative chemoradiotherapy on recurrence patterns in gastric cancer. *J Clin Oncol* 2010;28:2430-2436.
 23. Buzzoni R, Bajetta E, Di Bartolomeo M, Miceli R, Beretta E, Ferrario E, et al. Pathological features as predictors of recurrence after radical resection of gastric cancer. *Br J Surg* 2006;93:205-209.
 24. de Manzoni G, Pedrazzani C, Pasini F, Durante E, Gabbani M, Grandinetti A, et al. Pattern of recurrence after surgery in adenocarcinoma of the gastro-oesophageal junction. *Eur J Surg Oncol* 2003;29:506-510.
 25. Lee HJ, Kim YH, Kim WH, Lee KU, Choe KJ, Kim JP, et al. Clinicopathological analysis for recurrence of early gastric cancer. *Jpn J Clin Oncol* 2003;33:209-214.
 26. Ha TK, Kwon SJ. Clinicopathologic characteristics according to the type of recurrence in curatively-resected gastric cancer patients. *J Korean Gastric Cancer Assoc* 2007;7:23-30.
 27. Mikami K, Maekawa T, Shinohara T, Hoshino S, Yamauchi Y, Noritomi T, et al. Predictive factors of early recurrent death after a curative resection of gastric cancer. *Int Surg* 2009;94:144-148.
 28. Kim JM, Kwon OJ, Kwon SJ, Shin DI, Park CD, Lee KS, et al. Remnant gastric cancer. *J Korean Surg Soc* 1997;52:520-528.
 29. Baik SH, Yang SI, Shin YM. Clinicopathological analysis of recurrence in stage 1 gastric cancer. *J Korean Surg Soc* 2010;79:35-42.
 30. Nashimoto A, Yabusaki H, Nakagawa S. Proper follow-up schedule after curative gastric surgery. *Gan To Kagaku Ryoho* 2009;36:1402-1407.