Upsala J Med Sci 107: 17–22, 2002

Early and Late Recurrences after Gastrectomy for Gastric Cancer: A Multiple Logistic Regression Analysis[1)]

Takashi Yokota, Toshihiro Saito, Shin Teshima, Yasuo Yamada, Kazutsugu Iwamoto, Michinori Takahashi, Shuichi Ishiyama, Katsuyuki Murata* and Hidemi Yamauchi

*Department of Gastroenterological Surgery, Sendai National Hospital, Sendai 983-8520, Japan and *Department of Hygiene, Akita University School of Medicine, Akita 010-8543, Japan*

ABSTRACT

Purpose: Although many studies have focused on clinical risk factors for prognosis of patients with surgically treated gastric cancer, little information is available regarding the timing of recurrent malignant disease. The purpose of this study was to determine the factors that are predictive of early and late recurrences after gastrectomy.

Patients and Methods: We reviewed the hospital records of patients with hisotological proof of gastric cancer who were admitted to Sendai National Hospital during the period from 1985 to 1995. A total of 923 records were examined, and 251 patients with recurrent disease were identified. The patients were divided into an "early recurrence group" consisting of 195 patients (died within one year after surgery) and a "late recurrence group" of 56 patients (died two years or more after surgery). Clinicopathological characteristics were examined, and independent risk factors influencing the timing of recurrence were determined by a multiple logistic regression analysis.

Results: The mean tumor size of early recurrence cases was larger than that of late recurrence cases (p=0.0294). Tumors penetrating the serosa with direct invasion to continuous structures were found more frequently in the early recurrence group than in the late recurrence group. The patients with early recurrence showed a higher tendency to have nodal involvement, lymphatic invasion and vascular invasion. The relative risks of early and late recurrences associated with different variables were estimated by a multiple logistic regression method. The following variables were found to be significant risk factors for early recurrence: male gender (p=0.0382), lymph node metastasis (p=0.0016), and vascular invasion (p=0.0006).

Conclusion: Male patients who have node-positive gastric cancer with vascular invasion have a high risk of early recurrence.

1) Received 25 March 2002
Revised manuscript accepted 3 May 2002

INTRODUCTION

In most patients with gastric cancer who experience recurrence after undergoing radical resection, the relapse occurs within a relatively short period after surgery (8). However, there are reports of relapse occurring a long time after surgery, and such reports have increased recently (2). The diagnosis and treatment of recurrent gastric cancer remains difficult. What, if any, are the factors that contribute to early recurrence and late recurrences? There are few papers which address prognostic factors in the distinction between early and late recurrences following resection for cure. It is not known whether prognostic factors can be applied to the timing of recurrence (8). In this study, we analyzed data from patients who died of recurrence after curative resection, and we examined the risk factors that influenced the timing of recurrence. In this report, we present a summary of the prognostic utility of clinical variables of early and late recurrence groups.

PATIENTS AND METHODS

Between January 1985 and November 1995, altogether 923 patients with gastric adenocarcinoma underwent surgery at the Department of Surgery, Sendai National Hospital. Patients were followed up to determine their malignancy-free intervals and periods of survival. Up until December 31, 2000, 622 patients had survived free of malignancy for 60 months or longer and 301 patients had died of recurrence. These 301 patients included 195 with early recurrence who died within one year after surgery and 56 with late recurrence who died two years or more after surgery. The macroscopic and histologic classifications of gastric cancer were based on the General Rules for Gastric Cancer Study in Japan (3). Microscopically, lymphatic invasion is defined as the degree of invasion within lymphatic capillaries whereas vascular invasion is defined as the degree of invasion within veins of the gastric wall. The type of operation performed depended on the location of the tumor. Patients with a tumor in the upper third including the whole stomach underwent a total gastrectomy. Survival was calculated from the date of operation to the date of the most recent follow-up examination or to the date of death. All data from both groups were analyzed by the chi-squared test, and independent risk factors influencing the timing of recurrence were determined by multiple logistic regression analysis.

RESULTS

Relevant clinicopathologic features of the 195 early recurrence patients and 56 late recurrence patients were compared, and the results are shown in Table 1. The gender

Table 1. Early vs. late recurrence after gastrectomy.

Variable		Early recurrence	Late recurrence	P value
Age		61.2Å}0.9	60.1Å}1.9	Ns**
Gender				
Male		121 (62)*	32 (57)	ns
Female		74 (38)	24 (43)	
Tumor size (cm)		8.4Å}0.3	7.1Å}0.5	0.0294
Depth of invasion			<0.0001	
mucosa		1 (1)	3 (6)	
submucosa		4 (2)	2 (4)	
proper muscle		3 (2)	5 (8)	
subserosa		23 (15)	20 (38)	
serosa exposed		75 (48)	19 (38)	
invading other organs		50 (32)	3 (6)	
Histological type			ns	
diffuse		85 (54)	24 (51)	
intestinal		73 (46)	23 (49)	
Lymph node metastasis	positive	151 (96)	38 (75)	<0.0001
	negative	7 (4)	13 (25)	
Lymphatic invasion	positive	123 (90)	39 (78)	0.0248
	negative	13 (10)	11 (22)	
Vascular invasion	positive	55 (40)	8 (17)	0.0028
	negative	81 (60)	40 (83)	
Tumor site			0.0285	
upper		38 (21)	17 (31)	
middle		30 (17)	16 (30)	
lower		57 (32)	11 (20)	
whole		53 (30)	10 (19)	

* (%)

** ns: not significant.

rates were 1.6 and 1.3 for early recurrence and late recurrence groups, respectively. The mean tumor size of the early recurrence cases was larger than that of the late recurrence cases (p=0.0294). Tumors penetrating the serosa with direct invasion to continuous structures were found more frequently in the early recurrence group than in the late recurrence group. The patients with early recurrence showed a higher tendency to have nodal involvement, lymphatic invasion and vascular invasion. The both groups tumors were most often located in the antrum and body of the stomach. Tumors occupying the entire stomach were found in 30% of patients in the early recurrence group and in 19% of patients in the late recurrence group. A multiple logistic regression model showed male gender (OR 2.524; 95%CI 1.052-6.057), lymph node metastasis (OR 18.658; 95%CI 3.004-114.353) and vascular invasion (OR 7.228; 95%CI 2.351-22.218) to be significantly correlated with early recurrence (Table 2). The longest interval between surgical treatment and recurrence observed in this series of patients was 78 months. This was a case of peritoneal recurrence of gastric cancer, the invasion of which was limited to the proper muscle layer histologically.

Table 2. Significant risk factors for early recurrence in patients with gastric cancer determined by using a multiple logistic regression model.

Variable	Odds ratio	95%CI	p value
Age	1.005	0.974-1.036	ns*
Gender (male/female)	2.524	1.052-6.057	0.0382
Tumor size	1.002	0.990-1.014	ns
Lymph node metastasis	18.658	3.004-114.353	0.0016
Lymphatic invasion	0.276	0.062-1.222	ns
Vascular invasion	7.228	2.351-22.218	0.0006
Depth of invasion**		ns	
submucosa	0.378	0.012-12.069	
proper muscle	4.360	0.185-102.681	
subserosa	4.033	0.193-84.274	
serasa exposed	0.916	0.045-18.628	
invading other organs	0.083	0.002-2.913	
Tumor location***		ns	
upper	1.801	0.572-5.675	
middle	1.332	0.439-4.038	
whole	1.034	0.267-4.010	

* ns: not significant,

** The risk factor of early recurrence in patients with gastric cancer invading the mucosal layer was calculated against that in patients with gastric cancer invading other layers. ***The risk factor of early recurrence in patients with gastric cancer located in the antrum against that in patients with gastric cancer located in other regions of the stomach was analyzed.

DISCUSSION

In the literature there has been little information regarding the timing of recurrent malignant disease in patients with surgically treated gastric cancer. However, in the present study we were able to determine factors that would enable discrimination of early recurrence from late recurrence. Female patients with node-negative and vascular invasion-negative tumors have advantage over male patients with node-positive and vascular invasive tumors in terms of early recurrence.

No differences in recurrence rates were found for different histologic types. Initially, it was thought that diffuse type of gastric adenocarcinoma tended to recur soon after the operation, but the present series showed that recurrence rates of this type of adenocarcinoma were comparable with those for intestinal type. Extended lymph node involvement has been found to be related to an increased risk for early recurrence in several previous studies (1, 8, 11). However, in our study it could not be demonstrated that lymphangio-invasive growth is a certain factor for early recurrence. Thus, there was no statistically significance when a multiple logistic regression analysis was performed between cases with and without lymphatic invasion (odds ratio, 0.267; 95%CI 0.062-1.222). In some studies, the number of positive nodes at the time of surgery was found to be a predictive factor of early recurrence and poor prognosis. The 5th edition of TNM classification grades lymph node involvement in

gastric cancer by the number of metastatic lymph node. Kodera et al. reported that the number of metastatic nodes after D2 lymphadenectomy reflected prognosis well and was shown by multivariate analysis to be a strong independent prognostic factor according to this international stage classification (4). This is confirmed by Omejc et al. (9) and Lee et al. (6). The information about the number of lymph nodes seems to be of importance in evaluating the impact of lymph node metastasis, though the variables are not considered in the present study. A very interesting finding in this study is that gender was one of the most significant predictive factors of timing of recurrence. In our study it was also confirmed that large size of the primary tumor of the stomach is a predictive factor for early recurrence (1, 12).

Recurrence of cancer may develop after surgery because of an incomplete primary operations but early relapse also seems to indicate aggressive biologic behavior of the tumor. If risk factors for early recurrence can be identified at the time of surgery, they could be of importance in clinical decision-making. Patients with a high risk for early recurrence may benefit from additional systemic treatment after the operation. Gastric cancer is a common disease in Japan, and a number of adjuvant studies using postoperative chemotherapy following surgical resection have been carried out. It has been reported that postoperative chemotherapy prolongs the mean survival time not only for patients who have undergone a curative operation but also for those who have undergone a non-curative operation (10). Although various methods of adjuvant chemotherapy in the treatment of gastric cancer have been attempted in Japan, very few trials have shown any significant improvement in patient survival in randomized control trials (5). Recently, a new adjuvant therapy for gastric cancer using regimens that include TS-1, a novel oral fluoropyrimidine anticancer agent, has been developed, and this therapy has led to a remarkable reduction in metastatic lesions as well as in primary tumors in some patients with gastric cancer. Whether chemotherapy using TS-1 could be effective in the prevention of recurrence due to distant metastasis is now evaluated in a randomized controlled study started in our hospital by two of us (T. S. and S. T.).

REFERENCES

1. Adachi Y, Oshiro T, Mori M, Maehara Y, Sugimachi K. Prediction of early and late recurrence after curative resection for gastric carcinoma. Cancer 77: 2445-2448, 1996.
2. Iwanaga T, Koyama H, Furukawa H, Taniguchi H, Wada A, Tateishi R. Mechanisms of late recurrence after radical surgery for gastric carcinoma. Am J Surg 135: 637-640, 1978.
3. Japanese Research Society of Gastric Cancer: General rules for gastric cancer study in surgery and pathology. Jpn J Surg 11: 129-145, 1977.
4. Kodera Y, Yamamura Y, Shimizu Y, Torii A, Hirai T, Yasui K. The number of metastatic lymph nodes: a promising prognostic determinant for gastric carcinoma in the latest edition of the TNM classification. J Am Coll Surg 187: 597-603, 1998.
5. Lamberti C, Bordiga S, Zecchina A, Artioli G, Marra G, Spano G. Ti location in the MFI framework of Ti-Silicalite-1: a neutron powder diffraction study. J Am Chem Sco 123: 2204-2212, 2001.
6. Lee WJ, Lee PH, Yue SC, Chang KC, Wei TC, Chen KM. Lymph node metastases in gastric cancer: significance of positive number. Oncology 52: 45-50, 1995.
7. Nakajima T, Ochiai T, Ogawa M, Maruyama M, Kurihara M, Kaminishi M, Kubota T, Yoshida S, Kato Y, Konishi T. Meeting report of the 71st Japanese gastric cancer congress. Gastric Cancer 2: 145-150, 1999.
8. Shiraishi N, Inomata M, Osawa N, Yasuda K, Adachi Y, Kitano S. Early and late recurrence after gastectomy for gastric carcinoma. Univariate and multivariate analyses. Cancer 89: 255-261, 2000.
9. Omejc M, Juvan R, Jelenc F, Repes S. Lymph node metastases in gastric cancer: correlation between new and old UICC TNM classification. Int Surg 86: 14-19, 2001
10. Sawai K, Takahashi T, Suzuki H. New trends in surgery for gastric cancer in Japan. J Surg Oncol 56: 221-226, 1994.
11. Yokota T, Kunii Y, Teshima S, Yamada Y, Saito T, Takahashi M, Kikuchi S, Yamauchi H. Significant prognostic factors in patients with node-negative gastric cancer. Int Surg 84: 331-336, 1999.
12. Yokota T, Kunii Y, Saito T, Teshima S, Yamada Y, Iwamoto K, Takahashi H, Takahashi M, Kikuchi S, Yamauchi H. Prognostic factors of gastric cancer tumors of less than 2 cm in diameter: Rationale for limited surgery. Eur J Surg Oncol 28: 209-213, 2002.

Address correspondence to: Takashi Yokota, M.D.
Department of Gastroenterological Surgery, Sendai National Hospital, Miyagino-ku, Sendai 983-8520, Japan.
Tel: 022-293-1111
Fax: 022-291-8114
E-mail address: yokota-t@snh.go.jp