

Significance of Primary Malignant Tumors on the Outcome of Patients With Resected Gastrointestinal Stromal Tumors

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Abstract. *Aim: This study aimed to clarify the significance of primary malignant tumors for the outcome of resected gastrointestinal stromal tumors (GISTs). Patients and Methods: The medical history, pathological findings and prognosis of 66 patients with GISTs resected at our institute between January 2003 and December 2018 were investigated retrospectively and compared statistically. Results: Among 66 patients with GISTs, 24 (36%) had concomitant malignant tumors. In an average study period of 57 months, one patient died from GIST, seven from other malignant tumors, and one from another disease. Only coexistence of GIST and other malignant tumors was recognized as a prognostic factor. Increasing age was significantly correlated with other malignant tumor in combination with GIST. When comparing patients with GIST alone and GIST with other malignant tumors, the latter showed significantly poorer prognosis. Conclusion: Coexistence of other malignant tumors was commonly observed in patients with GIST, and was associated with poorer prognosis. This association should be carefully considered and monitored in patients with GISTs.*

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the digestive tract (1, 2). The prognosis of GISTs has improved due to the clarification of etiology and progress with specific treatments. A good prognosis has been observed for patients with low-risk GISTs (3, 4). Establishment of treatment has increased the rate of

resection of small-size GIST, and the number of operations for early GISTs has increased. The incidence of GISTs and other malignant tumors is considered high (5-10). The pathogenic relationship between GIST and other malignant tumors has been investigated, but is incompletely understood. The purpose of this study was to clarify the significance of primary malignant tumors for the outcome of resected GISTs

Patients and Methods

Retrospective analysis was performed on all 66 patients with GIST surgically treated at our hospital between January 2003 and December 2018. The diagnosis, treatment, and follow-up were evaluated based on contemporary standards and more, recently based on the latest guideline (11). The histological diagnosis of all GISTs had been confirmed by the Pathology Department of our hospital. All stromal tumors were diagnosed using immunohistochemistry. The tumors were classified according to the risk categories proposed by Miettinen *et al.* (12) and the TNM classification (13). All clinical records and pathological reports for each case were reviewed.

Statistical analysis was performed using SPSS statistics ver. 22.0 (IBM Japan, Ltd., Tokyo, Japan). Cox proportional hazards model was used for factor analysis for survival of patients with GIST. Comparisons between patients with GIST alone and GIST with other malignant tumor were performed using Fisher's exact test, unpaired *t*-tests, Mann-Whitney *U*-test and the chi-square test. In the survival analyses, the end-points were evaluated according to survival from first GIST resection. Survival curves were calculated using the Kaplan-Meier method (14). Between-group comparisons were performed using the log-rank test.

Results

The background data of all stud patients with resected GIST are shown Table I. The patients consisted of 35 men and 31 women, aged 33-87 (average=65.8) years. In the TNM risk classification, the majority of patients (40/66) were classified at risk level I, and only three at level IV. After a median follow-up of 57 months, 57 patients had survived without any recurrence, one died of recurrent GIST, seven died of other malignant diseases, and one died without GIST recurrence. Two patients underwent surgery several times for GIST

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Key Words: Gastrointestinal stromal tumor, second malignancy, prognostic factor, second cancer.

Table I. Background characteristics of the study patients (n=66).

Characteristic		Value
Age, years	Mean (range)	66 (33-87)
Gender, n (%)	Male	31 (47%)
	Female	35 (53%)
Size, mm	Mean±SD	51.4±37.6
Mitotic count, n/HPF	Mean±SD	4.4±8.7
WHO (UICC) classification, n (%)	IA, IB	40 (61%)
	II	11 (17%)
	IIIA, IIIB	12 (18%)
	IV	3 (5%)
Miettinen GIST classification	None	9
	Very low	22
	Low	13
	Moderate	8
Imatinib administration	Yes	14
	No	52
Other cancer type	Yes	24
	No	42

WHO (UICC): World Health Organization (Union for International Cancer Control).

Table II. Cox proportional hazards model for death.

Characteristic		HR	95% CI	p-Value
Age	Per 1-year increase	1.025	0.964-1.090	0.432
Gender	Male	0.944	0.253-3.527	0.932
	Female	1.000	Ref	
Size	Per 1 mm increase	0.992	0.971-1.014	0.486
Mitotic count	<5/HPF	1.000	Ref	
	≥5/HPF	1.530	0.410-5.718	0.527
WHO (UICC) classification	IA, IB	1.000	Ref	
	II	0.642	0.075-5.518	0.686
	IIIA, IIIB	1.248	0.242-6.441	0.792
	IV	2.684	0.311-23.168	0.369
Miettinen GIST risk classification	Per increase	1.240	0.646-2.381	0.519
	None, very low, low	1.000	Ref	
	Moderate	n.c.	–	
	High	1.590	0.397-6.370	0.513
Imatinib administration	Moderate/high	1.036	0.258-4.162	0.960
	Yes	1.000	Ref	
Other cancer	No	1.693	0.450-6.373	0.436
	No	1.000	Ref	
	Yes	4.880	1.008-23.626	0.049

GIST: Gastrointestinal stromal tumor; WHO (UICC): World Health Organization (Union for International Cancer Control).

recurrence, one of whom underwent resection of recurrent intra-abdominal tumors twice, administered imatinib mesylate, and survived for 13 years without GIST recurrence. Another patient underwent a hepatectomy for liver metastases at 3 years and 6 months after gastrectomy and died of GIST 3 months

Table III. Characteristics of patients with only gastrointestinal stromal tumor (GIST) and those with other coexisting malignant tumor types.

Characteristic		Other malignant tumor		p-Value
		Yes (n=24)	No (n=42)	
Age, years	Mean±SD	70.88±9.52	62.90±12.09	0.007 ^a
Gender, n	Male	13	22	>0.999 ^b
	Female	11	20	
Diameter (mm)	Mean±SD	40.50±32.35	57.60±39.72	0.078 ^a
WHO (UICC) classification	IA, IB	14 (21%)	26 (39%)	0.765 ^b
	II	3 (5%)	8 (12%)	
	IIIA, IIIB	6 (9%)	6 (9%)	
	IV	1 (2%)	2 (3%)	
Mitotic count, n (%)	<5/HPF	9 (14%)	12 (18%)	0.584 ^b
	≥5/HPF	15 (23%)	30 (45%)	
Miettinen GIST classification, n (%)	None	7 (11%)	2 (3%)	0.329 ^c
	Very low	5 (8%)	17 (26%)	
	Low	5 (8%)	8 (12%)	
	Moderate	1 (2%)	7 (11%)	
	High	6 (9%)	8 (12%)	0.787 ^b
	None/low	17 (26%)	27 (41%)	
	Moderate/high	7 (11%)	15 (23%)	

WHO (UICC): World Health Organization (Union for International Cancer Control); SD: standard deviation. ^aUnpaired *t*-test; ^bFisher's exact test; ^cMann-Whitney *U*-test.

after the hepatectomy. The GISTs were located in the stomach in 88%, intestine in 8%, peritoneum in 2%, rectum in 2% and duodenum in 2%. The tumor sizes ranged from 5 to 165 (average=51.4) mm. Among the 66 patients, 24 (36%) were diagnosed as having 29 other malignant tumors, including three patients with two other malignant tumors and one patient with three other malignant tumors. The incidence rates of other malignant tumors were 17% for those located in the stomach, 11% for the colorectum and anus, 5% for the liver (cholangiocellular carcinoma, 3%; hepatocellular carcinoma, 2%), 3% for the bladder, and 2% each for the esophagus, larynx, breast, prostate, ureter, ovary, and lung. Among the patients with both GISTs and other malignant tumor, eight cases had already been detected before the GIST treatment, 11 had been detected simultaneously, and nine had been detected after the GIST treatment. Among the 11 patients with simultaneous detection of GISTs and other malignant tumors, six had gastric cancer and one had esophageal cancer. Among the seven resected GISTs with gastric or esophageal cancer at the same time, three were not diagnosed preoperatively, and the average tumor diameter was small (16 mm). For the seven patients who died of malignant tumor other than GISTs, four died of stomach cancer and three of liver cancer. For the patients with GIST without other malignancies, one died of their disease at 3 years and 9 months postoperatively.

To investigate the prognoses of patients with GIST, patient age, gender, tumor diameter, mitotic rate, Miettinen risk

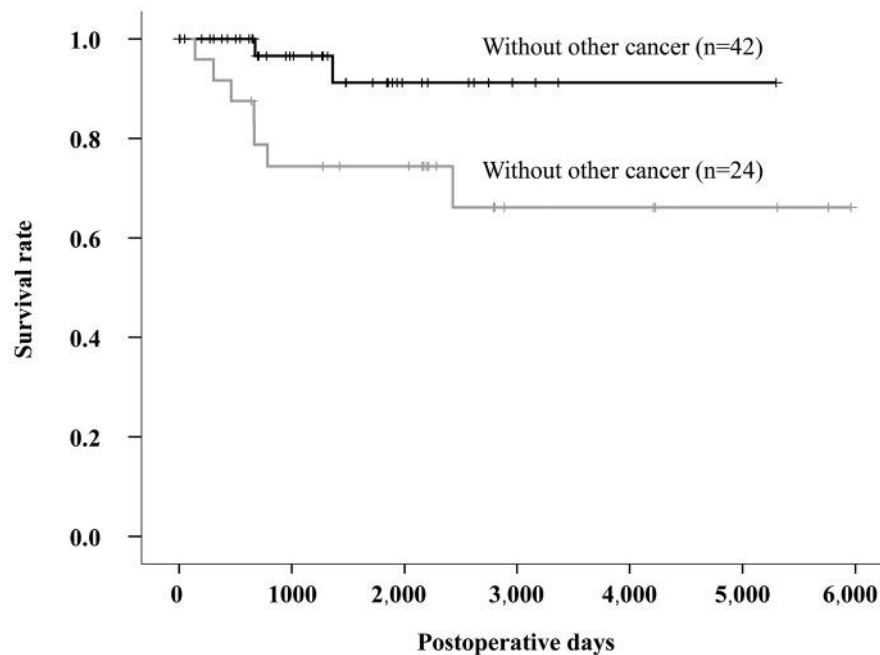


Figure 1. Kaplan-Meier analysis of disease-specific survival for patients with gastrointestinal stromal tumor (GIST) alone and those with other coexisting malignant tumors ($p=0.029$). The average disease-specific survival observation period for those with GIST was 4,926.6 days (95% confidence interval=4,429.5-5,423.7) for patients with GIST alone and 4,270.6 days for patients with additional malignancies.

classification, TNM classification, and coexistence of other malignant tumors were investigated (Table II). In the prognostic evaluation based on survival analysis using prognostic factors for GIST, no significant difference was observed in age, gender, tumor diameter, mitotic rate, and risk classification; only the coexistence of other malignant tumor showed a statistically significant association with poorer survival.

Differences between patients with GISTs with and without other malignant tumors are shown in Table III. The average age was significantly higher for the patients with other malignant tumors than those without. The tumor diameter, gender ratio and Miettinen GIST classification did not differ between the groups.

Twenty patients treated with imatinib mesylate after GIST resection had been followed up for an average of 1,425 days, and 46 patients not treated with imatinib mesylate had been followed up for an average of 1,855 days. The average age, gender, and GIST classification stages of both groups did not significantly differ (data not shown). The incidence of other malignant tumors after GIST resection also did not significantly differ between those receiving imatinib mesylate (2/20) and those not (7/46) ($p=0.576$).

A comparison between survival curves of patients with GIST alone and those with other malignant tumors is shown in Figure 1. Patients with GIST alone appeared to have a significantly superior disease-free survival.

Discussion

This study enrolled 66 patients with GIST who were treated surgically. A high incidence (36%) of coexistence of GISTs with other malignant tumors was observed. On comparing patients with GISTs with and without other malignant tumors, the former were found to be older and have significantly worse prognoses but no differences in GIST staging were observed between the groups.

Many cases of GIST with other malignant tumors have been reported. The incidence rate of additional malignancies ranges from 4.5 to 43% (5-10,15-17). In a recent large-scale study, the occurrence of secondary tumors was reported to be increasing because older patients were expected to develop malignancies; indeed, 25.2% of older adults (aged ≥ 65 years) newly diagnosed with cancer had a history of prior cancer (18). In the current study, the mean age at the time of GIST surgery was 65.8 years. The frequency of GIST with other malignant tumors (36%) was considered high, although the frequency was different from the evaluation method in the previous study. Moreover, the number of GIST cases coexisting with other malignant tumors was considered to be increased due to the extended follow-up period.

Others have investigated the type and chronology of other malignant tumors in relation to GIST (6, 7, 9). No clear trends have been established but many GIST cases coexisted with gastric cancer. A report demonstrated that GISTs were

present with high frequency (35%) in the resected stomach of patients with gastric cancer (19). The size of GIST malignancies simultaneously resected with other malignancies tended to be small and the grade low (20). Therefore, pathological examination of surgical specimens from gastric cancer surgery may find GIST and increase the number of patients with GIST. Reports on GISTs simultaneous with other gastrointestinal cancer types have revealed worse prognosis than that of GIST alone (21, 22).

GISTs commonly activate the mutations of the gene encoding KIT proto-oncogene, receptor tyrosine kinase (KIT). Although hereditary GIST syndrome has been reported (23, 24), the frequency of occurrence is low. Some reports also revealed that specific genetic abnormalities occurred when neurofibromatosis type 1 or neuroendocrine tumor merged with GIST (25, 26). No mutational correlation was reported between GISTs and the coexistence of tumors of different histogenesis regarding *KIT* and platelet-derived growth factor receptor alpha genes (27). Thus, further genetic research is expected.

In the current study, the mortality rate of patients with GIST was very low. GIST prognosis is determined by metastasis, tumor size, number of mitoses, and degree of risk (12). According to the therapeutic guidelines, the ratio of low-risk patients increases with the increasing resection of smaller and less malignant GISTs. A good prognosis is observed after surgery for those with low-risk GISTs (28). In the current study, three patients were classified as risk class IV according to the TNM classification, of whom only one died. The other two patients survived for a long period due to multidisciplinary treatment. The proportion of patients in the high-risk group was extremely low; therefore, we consider that the prognostic outcome of GIST itself was not reflected in the prognostic determination and instead was influenced by other factors. In the current study, the prognosis of GIST tended to be determined by the other malignant tumors that coexisted with GIST.

The prognosis of GIST is improved by tumor resection and adjuvant drug therapy (imatinib mesylate administration) (29, 30). Improvement of the prognosis in the high-risk patients is likely to have been due to treatment with imatinib mesylate. Giuliani *et al.* showed an increase in secondary malignancies after treatment of GISTs with imatinib mesylate, which suggested that the prognosis was extended because of imatinib mesylate administration (31). The low occurrence of secondary malignancies after imatinib mesylate administration in the current study may be due to the short follow-up period.

Based on the above considerations, we believe that the coexistence of other malignant tumors negatively influences the prognosis of patients with GIST. Therefore, a stricter follow-up for other malignancies should be conducted in patients with GIST because of their long-term survival and the fact that prognosis seems to be adversely affected by the coexistence of other malignant tumors.

Conclusion

Co-existence of GIST and other malignant tumors is often observed and seems to adversely affect the outcome of GIST.

Conflicts of Interest

The Authors have no conflicts of interest to declare regarding this study.

Authors' Contributions

Shuzo Kohno designed the study and wrote the article. Shuzo Kohno and Hiroaki Aoki evaluated clinical data. Shuzo Kohno, Hiroaki Aoki, Masaichi Ogawa, Kazuhiko Yoshida and Katsuhiko Yanaga interpreted the results.

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