A Study of the Postoperative Course in Cases of GIST of the Stomach. The Efficacy of Imatinib in Cases of Recurrence

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Abstract. *Background: The postoperative course of cases of gastrointestinal stromal tumor (GIST) of the stomach was studied in patients who underwent surgery in this Department. In addition, treatment with the molecular-targeted drug imatinib was studied in cases of recurrence. Patients and Methods: We studied 40 cases with a diagnosis of GIST of the stomach where the patient subsequently underwent surgery in this Department between July 1985 (when this facility opened) and December 2007. Six of these cases involved patients with carcinoma or carcinoid tumors, which could have affected the procedure and prognosis, and 2 cases involved patients who developed cancer during the postoperative course of the GIST. Therefore these 8 patients were excluded, thus resulting in the study of a total of 32 patients. Results: The male:female ratio for the 32 patients was 17:15, the average tumor size was 4.7±3.4 cm (with a range of 1.3-16.0 cm), and the median follow-up was 92.2±73.7 months (with a range of 2-238 months). Recurrence occurred in 6 out of the 32 patients (18.8%) and was observed in the liver of 5 patients, in the lungs of 2 patients, in the peritoneum of 2 patients, locally in 1 patient, and in the bone of 1 patient (including patients with multiple sites). With respect to the tumor size, the incidence of recurrence of tumors smaller than 2 cm was 0%, 16.7% for patients with tumors 2 to 5 cm in size, and 27.3% for thesewith tumors larger than 5 cm. The incidence of recurrence was particularly marked in patients with tumors larger than 10 cm (66.7%). The treatment for recurrence was transcatheter arterial embolization for 1 patient and imatinib for 5 patients. In cases where imatinib was administered, 1 patient exhibited partial response, 1 patient exhibited stable disease, and 3 patients exhibited progressive disease, indicating a response rate of 20%. Postoperative recurrence of GIST of the stomach in this study occurred in 6 of 32 patients (18.8%). The incidence of recurrence of tumors larger than 10 cm was 2 out of 3 patients. Conclusion: In cases of recurrence, the response rate to imatinib was 20%. Imatinib was effective against GIST that were positive for KIT protein, but future study is needed to clarify the risk factors for recurrence and indications for adjuvant therapy in cases of GIST.*

The concept of and the therapies for gastrointestinal stromal tumors (GIST) have changed dramatically in recent years (1). These tumors most frequently occur in the stomach of the gastrointestinal tract (2, 3). Initial reports of GIST by Gold and Stout indicated that GIST were mesenchymal tumors arising from the gut wall; they also noted that these tumors were mostly of smooth muscle origin (4, 5). Research of this disease progressed with the heightened prevalence of immunohistochemical staining and electron microscopy in the 1980s (6, 7). Recently, the mesenchymal tumors occurring in the gastrointestinal tract that express KIT receptors have been defined as GIST (8, 9). Imatinib is a molecular-targeted drug that inhibits KIT protein synthesis and that effectively shrinks GIST, transforming treatment of recurrent GIST. The current study examined the postoperative course of cases of GIST of the stomach and examined the efficacy of imatinib in the cases of recurrence.

Patients and Methods

Since 1999, GIST have been diagnosed by this Department using immunostaining. Twenty-seven such cases of GIST were identified. In the years before 1998, we encountered 28 cases of mesenchymal tumors of the stomach. Specimens from these 28 cases were subjected to KIT immunostaining which indicated that 13 of these cases were positive for KIT protein thus leading to a diagnosis of GIST. Of these 40 total cases of GIST, 6 involved patients with other malignant neoplasms (carcinoma or a carcinoid tumor) which may have affected the surgical technique and prognosis and 2

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Table I. *Cases of recurrence*.

Recurrence rate		18.8% (6/32)	
Site of recurrence*			
Liver	5	Local	1
Lung	2	Bone**	1
Peritoneum	2		
Average of time from surgery to recurrence (months)		47.8±39.1 (12-112)	

*Including patients with multiple site; **the fourth lumber vertebra.

involved patients who developed other malignant neoplasms (breast carcinoma or maxillary carcinoma) during the postoperative course, therefore, these 8 patients were excluded. This resulted in a total of 32 patients in the current study.

Results

The male: female ratio for the 32 patients was 17:15, the mean age at surgery was 61.1±11.6 years (with a range of 36-79 years), the average tumor size was 4.7±3.4 cm (with a range of 1.3-16.0 cm), and the median follow-up was 92.2±73.7 months (with a range of 2-238 months). Recurrence occurred in 6 of the 32 patients (18.8%) (Table I) the most common site being in the liver. One patient had synchronous liver and peritoneal metastases. In the 5 patients who had metachronous recurrence, the average time from surgery to recurrence was 47.8±39.1 months (with a range of 12-112 months) (Table I). The treatment of recurrence involved transcatheter arterial embolization (TAE) in one patient with liver metastases. Before the appearance of imatinib, TAE was an effective treatment for liver metastases of GIST (10), and the patient survived 28 months following recurrence. One patient underwent a total gastrectomy for local recurrence following a wedge resection of the stomach. The patient again developed tumors in the liver, and imatinib was used to treat this patient. Imatinib was administered to five patients including this patient (Table II).

Presented here is a case in which the patient responded to imatinib. The patient, a 76-year-old female, is denoted as Case 4 in Tables II and III. A computed tomography(CT) scan 2 years and 3 months after surgery showed discrete tumors in the anterior superior segment of the liver and the left upper quadrant, a discrete tumor in the hepatic portal region, and lobulated tumors around the intestinal tract in the left lower quadrant. In Japan, the recommended dose of imatinib is 400 mg, but a reduced dose of 200 mg was administered in the present study if the patient was smaller or elderly. A CT scan 2 months after the start of treatment indicated that the tumors in the anterior superior segment of the liver and the left upper quadrant had shrunk, and the tumor in the hepatic portal region and lobulated tumors around the intestinal tract in the left lower quadrant had developed cyst-like changes. These cyst-like changes were considered a characteristic change in response to imatinib therapy (11-13) (Figure 1).

Table II. *Treatment of recurrence*.

Case	Age/ gender (years)	Time from surgery to recurrence (months)	Site of recurrence	Treatment
1	77/M	12	Liver	TAE
2	42/M	112	Lung, liver	Imatinib
3	68/F	55	Local	Resection
		64	Liver	Imatinib
		77	Bone	BSC
4	76/F	27	Liver, peritoneum	Imatinib
5	57/M	33	Lung	Imatinib
6	53/F	Synchronous	Liver, peritoneum	Imatinib

TAE: Transcatheter arterial embolization; BSC: best supportive care.

Table III. *Outcome of treatment for recurrence*

Case	Site of recurrence	Treatment	Outcome
1	Liver	TAE	(died)
2	Lung, liver	Imatinib	PD (died)
3	Local	Resection	
	Liver	Imatinib	PD
	Bone	BSC	(died)
4	Liver, peritoneum	Imatinib	PR
5	Lung	Imatinib	SD
6	Liver, peritoneum	Imatinib	PD (died)

PD: Progress disease; PR: partial response; SD: stable disease.

Table IV. *Recurrence rate by tumor size*.

Tumor size (cm)	Number of cases	Number of recurrences
<2	3	0
≥2, <5	18	3
≥5	11	3
≥10	3	2

The treatment results for the other 4 patients were stable disease (SD) for 1 patient and progressive disease (PD) for 3 patients (all three died), thus indicating a response rate of 20% (Table III).

Discussion

A crucial clinical factor for the prognosis of GIST is tumor size (14, 15). The tumor size in the cases of recurrence in the present study indicated that the incidence of recurrence was 0% for tumors smaller than 2 cm, 16.7% for tumors 2 to 5 cm

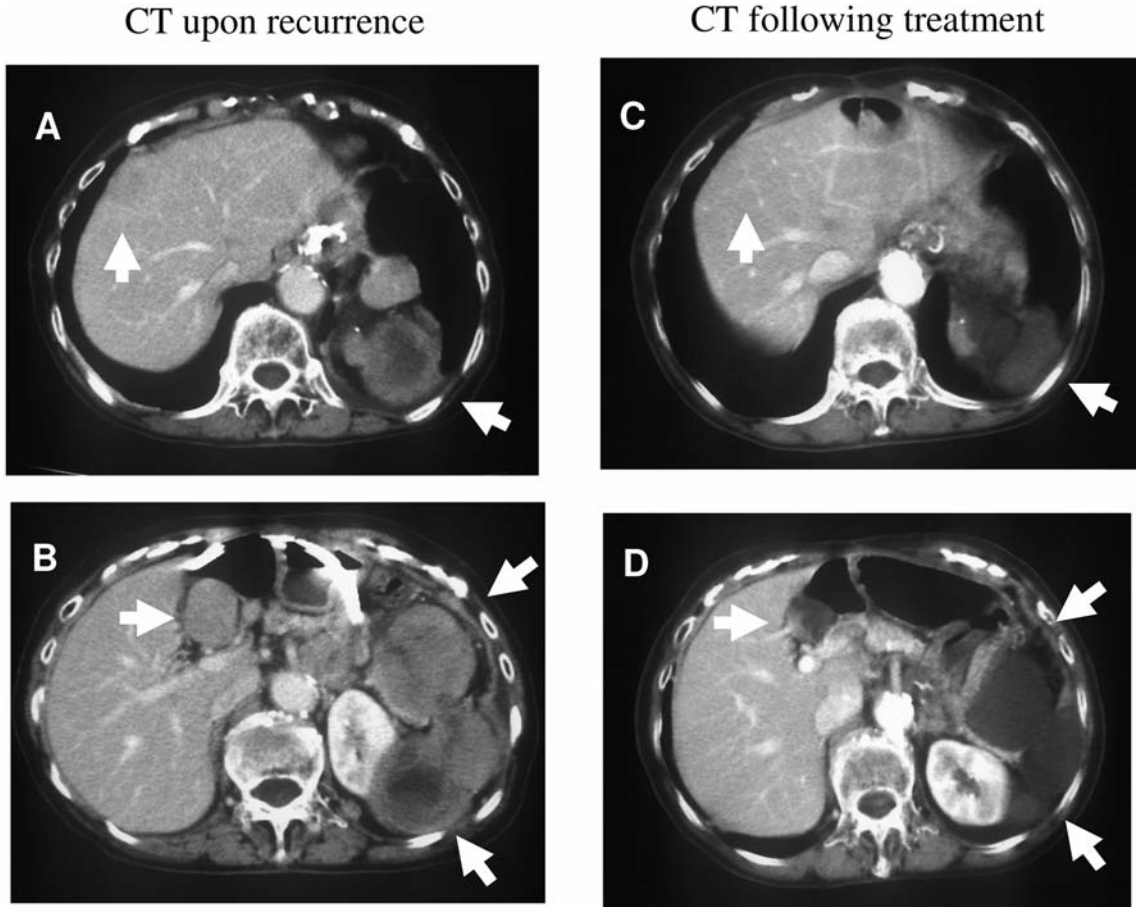

Figure 1. *CT upon recurrence: A, Discrete tumors were found in the anterior superior segment of the liver and the left upper quadrant. B, A discrete tumor was found in the hepatic portal region and lobulated tumors were found around the intestinal tract in the left lower quadrant. CT following treatment: C, The tumors in the anterior superior segment of the liver and the left upper quadrant shrank; D, the tumor in the hepatic portal region and the lobulated tumors in the left lower quadrant exhibited cyst-like changes.*

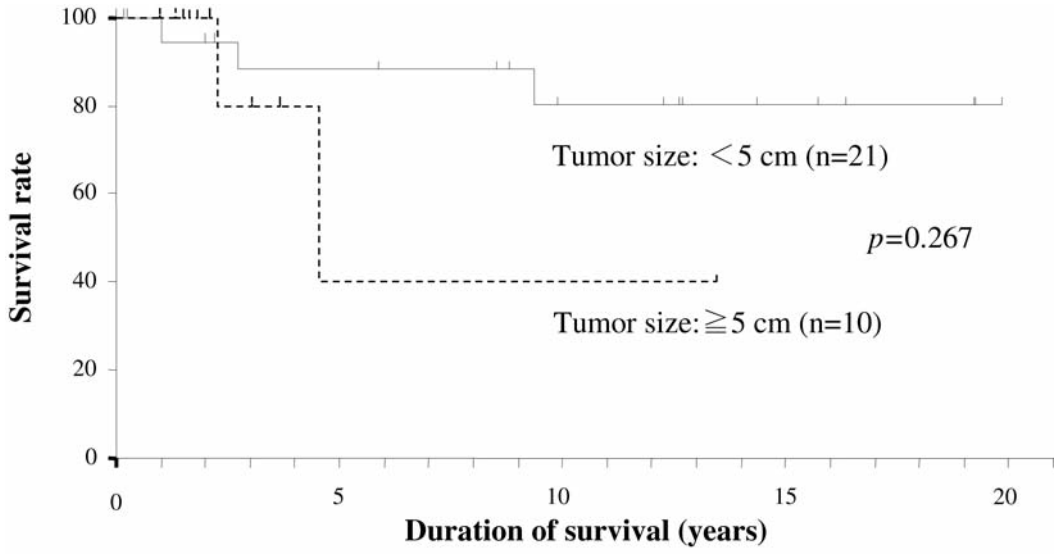

Figure 2. *The Kaplan-Meier curve for postoperative recurrence-free survival for 31 patients.*

in size and 27.3% for tumors larger than 5 cm. In cases where the tumor was larger than 10 cm, the incidence of recurrence was particularly marked at 2 out 3 patients (Table IV).

A significant difference in recurrence for patients with tumors larger than 5 cm has been reported (14). An examination of postoperative recurrence-free survival in the remaining 31 cases in the present study (one patient was excluded because diagnosis of a GIST coincided with metastasis in the liver and peritoneum) using the Kaplan-Meier method showed no significant difference, but recurrence did tend to occur more readily for tumors larger than 5 cm (Figure 2).

Imatinib is currently considered the drug of first choice in cases where tumor resection is not permitted or in cases of metastasis and recurrence (15). With respect to its efficacy, the drug is reported to have a high response rate (partial response (PR) of 53-69%) (16-18). Nevertheless, the response rate of imatinib therapy following GIST recurrence in this Department was not satisfactory. In recent years, attempts have been made to use imatinib as a neoadjuvant or adjuvant therapy (19). Adjuvant therapy in particular is reported to help improve the recurrence-free survival rate, and it should improve prognosis for GIST patients with a high risk of recurrence (20, 21). However, at present, there are no established rules for application of adjuvant therapy. In the future, adjuvant therapy should be explored and the risk factors for GIST recurrence should be ascertained by focusing on the extent of tumor size, one of the simplest and most definitive factors for surgeons.

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