CLINICAL MALIGNANCY RISK OF GIST ASSESSED BY ENDOSCOPIC ULTRASONOGRAPHY

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Background: The aim of the present study was to analyze clinico pathological findings in primary gastrointestinal stromal cell tumors (GIST) and to determine the clinical factors that indicate higher risk potential.

Methods: Forty-seven patients with primary GIST were enrolled, and their clinical, endsonographic ultrasonography (EUS), microscopic and immunohistochemical findings were evaluated. Risk categorization of GIST was made on histological tumor size and the mitotic rate.

Results: EUS features (a larger diameter, an irregular border, and cystic areas) were significantly correlated with higher risk and unfavorable prognosis. Pathological features (tumor size >50 mm, >10 mitoses per 50 high-power fields (HPF), necrosis, and high-risk category) were significant unfavorable prognostic factors. However, some high-risk GIST less than 50 mm in diameter did not have any cystic areas, an irregular border on EUS images. Among GIST that measured 50 mm or less on EUS, tumors with rapid growth and a change of internal echo (more inhomogeneity) were higher risk, while tumors that did not grow and showed no change of a homogeneous internal echo were lower risk.

Conclusions: EUS parameters (a larger diameter, an irregular border, and cystic areas) indicate high-risk potential. Tumor growth rate and change of internal echo pattern will be a helpful prognosticator, especially for asymptomatic and incidentally detected small GIST, where the classical EUS high-risk parameters come up against limiting factors.

Key words: clinical management, endoscopic ultrasonography, gastrointestinal stromal cell tumor (GIST), prognosis, risk.

INTRODUCTION

Gastrointestinal stromal cell tumors (GIST) has been used either as an umbrella term for all gastrointestinal stromal cell tumors or for stromal cell tumors without clear neural or smooth muscle origin. In 1998, Hirota et al.1 analyzed a series of 49 GIST and noted that most of these lesions expressed the proto-oncogene, KIT, which codes for a tyrosine kinase receptor involved in cell development. GIST can be differentiated from other spindle cell neoplasms of the gastrointestinal tract by using a battery of immunohistochemical stains. In fact, KIT expression may be the most specific diagnostic criterion for GIST.2–4

Previous studies2,3,5 have assessed various clinicopathological parameters for their association with survival in GIST patients. The presence of distant metastasis and/or direct invasion of adjacent structures, a large tumor size, and a high grade according to some histopathological grading systems have been identified as predictors of a poor prognosis. Histopathological grading has been based on assessment of the mitotic rate, nuclear atypia, necrosis, the amount of stroma, and vascularity. Among these factors, the mitotic rate is most closely correlated with a poor prognosis, as first described by Golden and Stout.5 These results were based on series containing many large GIST. Miettinen et al.7 studied 1765 cases with long-term follow-up GIST. They reported that the tumors varied from 0.5 to 44 cm (median, 6.0 cm) and most commonly presented with GI bleeding; 12% were incidentally detected. However, recent advances in diagnostic techniques, especially the widespread use of double-contrast radiography and endoscopy, have led to the detection of small and asymptomatic GIST. Especially in Japan, many gastric GIST have been detected incidentally as small tumors in asymptomatic patients, largely due to upper gastrointestinal mass or physical screening system. The natural history of small GIST has not been investigated adequately, because most patients are treated surgically soon after diagnosis by partial or radical gastrectomy in many countries. However, many GIST measuring <2 cm in greatest diameter rarely metastasize and have a slow growth rate. In fact, many small, incidentally discovered GIST may not be malignant or exhibit malignant behavior and thus may not be an immediate threat to the patient’s life. Because we still have little knowledge about the malignant potential of such small tumors, these lesions present a difficult management problem. With the aging populations and the increased use of imaging in developed countries, it is reasonable to assume that the issue of appropriate management of small GIST will become even more important.
Endoscopic ultrasonography (EUS) is the most appropriate technique for studying submucosal tumors of the gastrointestinal tract. Palazzo et al. reported that the combined presence of two out of three EUS features (irregular extraluminal margins, cystic spaces, and lymph nodes with a malignant pattern) had a positive predictive value of 100% for malignant or borderline GIST. In contrast, tumors less than 30 mm in diameter with regular margins and a homogeneous echo pattern are usually benign. However, their study was small, so the ability of EUS to distinguish between benign and malignant GIST needs to be confirmed.

CD-117 (KIT) positivity is seen in benign, malignant, and all histological variants of GIST. Several investigations have identified a gain-of-function mutation in the juxtamembrane domain (exon 11) of c-kit in these tumors. Such gain-of-function mutations lead to constitutive activation of the tyrosine kinase receptor without binding of its ligand, stem cell factor. A number of clinical studies have indicated that such mutations are largely found in histologically and clinically malignant GIST. In contrast, there have been recent reports suggesting that the presence of a c-kit gain-of-function mutation in exon 11 does not always predict malignant behavior of GIST. A KIT tyrosine kinase inhibitor, STI-571, has recently shown promise in treatment of metastatic GIST. As a consequence, the treatment of GIST has evolved rapidly, with dramatic changes in clinical practice. The therapeutic relevance of KIT activation in GIST has generated a new requirement for reproducible diagnostic criteria for these tumors, both for selection of rational therapy and as a key criterion for eligibility to enter into trials of STI-571.

The aim of the present study was to analyze EUS findings and conventional pathological findings in primary GIST in order to determine the clinical risk; namely, risk factors that indicated aggressive behavior of GIST. We also investigated whether these factors had any prognostic significance.

### PATIENTS AND METHODS

During the period from 1987 to 2003, 47 patients with primary gastrointestinal stromal cell tumors (GIST), showing immunopositivity for KIT (CD-117), were enrolled in the present study. The diagnosis of GIST was based on previously published criteria. Forty-five patients underwent surgery, while histological specimens were obtained by fine-needle aspiration biopsy in two patients. There were 23 men and 24 women, with a mean age of 57.9 years (range: 28–80 years). The size (mm) of GIST ranged from 12 to 115 (mean ± SD; 47.2 ± 27.1) in diameter measured by EUS. The lesions included 44 gastric tumors, two duodenal tumors, and one esophageal tumor.

The following clinical features were reviewed for all tumors: age, gender (male or female), location (stomach, esophagus, or duodenum), and mucosal ulceration (present or none).

The following EUS features were recorded for all tumors: maximal diameter (mm), pattern of growth (extraluminal, intramural, or endoluminal), tumor border (irregular or regular), internal echo (inhomogeneous or homogeneous), and cystic areas (present or none). According to the method of Collins et al., the doubling time (DT) of the tumor was calculated. EUS examination was performed with 7.5 and 12 MHz radial transducers (Olympus GF-UM 3 or GF-UM 240; Olympus Optical Co., Tokyo, Japan) and was evaluated by four experienced gastroenterologists.

Microscopic features were evaluated as follows: the mitotic rate was determined by counting the mitotic figures in 50 consecutive high-power fields (HPF) from the most active areas of the tumor; nuclear atypia was classified as mild, moderate, or severe; cellularity was classified as sparse, moderate, or dense; and necrosis was classified as present or none. The tumors were immunohistochemically analyzed for c-kit (rabbit polyclonal antibody against human c-kit; DAKO, Hamburg, Germany), CD34 (Becton Dickinson Immunocytometry Systems, USA), muscle actin, and S-100 (DAKO).

Categorization of the GIST as high-risk, intermediate-risk, low-risk, and very low-risk tumors was based on histological tumor size and the mitotic rate. This was based on the National Institutes of Health GIST Workshop convened in April of 2001 in USA (Table 1).

The above features, clinical data, EUS findings, pathological findings and immunohistochemical data were evaluated without any information about the clinical outcome (Table 2). Then, the clinical charts for each patient were reviewed to determine their treatment, tumor recurrence, and survival. This study was performed according to our institutional guidelines, and informed consent was obtained from living patients or their family members.

### Statistical analysis

The Kruskal-Wallis test and chi-squared test were used for statistical comparisons. Multivariate logistic regression analysis, using the SPSS system, was used to study the relationship between high-risk GIST category and various EUS features. A P-value of less than 0.05 was considered statistically significant.

### RESULTS

#### Clinical diagnostic factors and risk groups of GIST

The clinical diagnostic factors and risk groups of the tumors are shown in Table 3. In two out of 47 patients, follow-up with EUS-fine-needle aspiration biopsy was continued without surgery. So, risk category couldn’t be calculated exactly. Therefore, these two patients were excluded from this risk category analysis.
The 45 tumors were divided into four categories: high-risk tumors (n = 14), intermediate-risk tumors (n = 6), low-risk tumors (n = 24), and very low-risk tumor (n = 1).

Clinical features
There were no significant differences of age, gender, and mucosal ulceration among the four tumor groups.

EUS features
The maximal diameters (mm) of very low-risk GIST, low-risk GIST, intermediate-risk GIST, and high-risk GIST (mean ± SD) were 12, 31.8 ± 6.7, 48.5 ± 18.7, and 80.3 ± 26.6, respectively. Among the EUS features of GIST, a larger diameter (50 mm ≤), an irregular border, and cystic areas were significantly correlated with higher risk. There was no significant difference of the tumor growth pattern and the internal echo pattern among the four tumor groups. Multivariate analysis using the logistic regression model demonstrated that a larger diameter (50 mm ≤) was a significant determinant (odds ratio, 61.96) for the high-risk GIST category (Table 4).

Prognostic factors and clinical outcome
The potential prognostic factors and the clinical outcome are shown in Table 5. Postoperative recurrence occurred in seven patients, including five with liver metastasis and two with peritoneal dissemination. Thirty-seven patients remained alive at final follow-up, while six had died of GIST and three had died of other causes. One of the 47 patients dropped out of follow-up study. So, this patient was excluded from Table 2.
this prognostic assessment study. The follow-up period (mean ± SD) was 64.5 ± 42.7 months.

**Clinical features**

Gender and mucosal ulceration were not found to be significant indicators of a poor prognosis.

**EUS features**

A tumor diameter greater than 50 mm, an irregular border, and cystic areas were significantly associated with a worse prognosis. In contrast, the tumor growth pattern and internal echo were not significant prognostic indicators.

**Pathological features**

Among the pathological features, a tumor size greater than 50 mm, >10 mitoses per 50 HPF, necrosis, and high-risk category were significant unfavorable prognostic factors, while nuclear atypia and cellularity were not.

**Clinical course of relatively small GIST without treatment or with treatment after 6 months or longer follow up**

In 12 out of 47 patients, every GIST had been detected incidentally as small tumors in asymptomatic patients, largely due to mass screening or at the annual health check-up. After informed consent was obtained from these patients, and monitoring was performed every 6 months. The follow-up study of EUS appearance of GIST without treatment (n = 2) or with surgery after 6 months or longer follow up (n = 10) is summarized in Table 6. At initial EUS examination, the tumor size (mean ± SD) was 23.1 ± 8.5 mm. An irregular border was found in one patient and a regular border in 10 patients. None of the tumors showed cystic areas. Six tumors showed extraluminal growth, three tumors showed intraluminal growth, and two tumors showed endoluminal growth. As for the internal echo, six tumors were inhomogeneous and five tumors were homogeneous. At the final examination, tumor size (mean ± SD) was 29.6 ± 10.5 mm. An irregular border was found in one patient and a regular border in 11 patients. None of the tumors exhibited cystic changes. Six tumors showed extraluminal growth, three tumors showed intraluminal growth, and two tumors showed endoluminal growth. For the internal echo, six tumors were inhomogeneous and five tumors were homogeneous. At the final examination, tumor size (mean ± SD) was 23.1 ± 8.5 mm. An irregular border was found in one patient and a regular border in 11 patients. None of the tumors showed cystic areas. Six tumors showed extraluminal growth, three tumors showed intraluminal growth, and two tumors showed endoluminal growth. Regarding the internal echo, nine tumors were inhomogeneous and three tumors were homogeneous. During this follow-up study, there were no changes in cystic areas, tumor border, and the pattern of tumor growth. On the other hand, there was a difference in the rate of tumor growth and a change of the internal echo was seen in some patients.

Surgical resection was eventually performed in 10 patients with GIST, which increased in size, and follow-up without surgery was continued in two patients. Among the patients with DT of 16 months or less, one tumor was in the high-risk category.
group, two tumors were in the intermediate-risk group, and two tumors were in the low-risk group. On the other hand, among the patients with a DT of more than 16 months, six tumors were in the low-risk group and one tumor was in the very-low-risk group. The changes of the tumor internal echo patterns (from initial to final) were studied. Among the patients with no change of pattern (inhomogeneous to inhomogeneous), one tumor was in the intermediate-risk group and five tumors were in the low-risk group. Among the patients with a change of pattern from homogeneous to inhomogeneous, one tumor was in the intermediate-risk group and two tumors were in the low-risk group. Among the patients with no change of pattern (homogeneous to homogeneous), one tumor was in the low-risk group and one tumor was in the very low-risk group (Table 7). All 12 patients are alive with no evidence of recurrence and metastasis until now.

### DISCUSSION

Criteria for distinguishing benign from malignant GIST, or at least to identify those lesions more likely to metastasize, have been sought, analyzed, and disputed for many years. Many parameters have been proposed but the morphological features that have gained greatest acceptance as being predictive of outcome are mitotic rate and tumor size. Miettinen et al. studied 1765 cases with long-term follow-up GIST. They reported that outcome was strongly dependent on tumor size and mitotic activity. Only 2–3% of tumors <10 cm and <5 mitoses/50 HPF metastasized, whereas 86% of tumors >10 cm and >5 mitoses/50 HPF metastasized. However, tumors >10 cm with mitotic activity <5/50 HPF and those <5 cm with mitoses >5/50 HPF had a relatively low metastatic rate (11% and 15%). So, categorization of the GIST as high-risk, intermediate-risk, low-risk, and very low-risk tumors was made on histological tumor size and the mitotic rate. Then, we investigated the relationship between the clinical parameters and the risk category of GIST. Among

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**Table 6.** Follow-up study of EUS appearance of relatively small gastrointestinal stromal cell tumor (GIST) without treatment \((n = 2)\) or with treatment after 6 months or longer follow up \((n = 10)\)

<table>
<thead>
<tr>
<th>EUS features</th>
<th>Initial EUS ((n = 11))</th>
<th>Final EUS ((n = 12))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size (mean ±SD) (mm)</td>
<td>23.1 ± 8.5</td>
<td>29.6 ± 10.5</td>
</tr>
<tr>
<td>Border</td>
<td>Irregular 1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Regular 10</td>
<td>11</td>
</tr>
<tr>
<td>Cystic area</td>
<td>Present 0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>None 11</td>
<td>12</td>
</tr>
<tr>
<td>Growth</td>
<td>Extra 6</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Intra 3</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Endo 2</td>
<td>3</td>
</tr>
<tr>
<td>Internal echo</td>
<td>Inhomogeneous 6</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Homogeneous 5</td>
<td>3</td>
</tr>
</tbody>
</table>

Follow-up period ranged from 6 to 98 months (mean ±SD: 37.4 ± 33.1 months). In one patient, only radiographic examination was performed initially. Finally, radiographic examination and EUS were performed. Final EUS features of this patient were as follows: 17 mm diameter, a regular border, no cystic area, endogastric growth, homogeneous internal echo.

**Table 7.** Relationship between risk category and doubling time (DT), and change of echo pattern of relatively small gastrointestinal stromal cell tumor (GIST) without treatment \((n = 2)\) or with treatment after 6 months or longer follow up \((n = 10)\)

<table>
<thead>
<tr>
<th>GIST</th>
<th>High-risk ((n = 1))</th>
<th>Intermediate-risk ((n = 2))</th>
<th>Low-risk ((n = 8))</th>
<th>Very low-risk ((n = 1))</th>
</tr>
</thead>
<tbody>
<tr>
<td>DT (months)</td>
<td>1†</td>
<td>2</td>
<td>2</td>
<td>6 (2)‡</td>
</tr>
<tr>
<td>More than 16</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Internal echo pattern</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhomogeneous to inhomogeneous</td>
<td>1</td>
<td>5 (1)‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homogeneous to inhomogeneous</td>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homogeneous to homogeneous</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

†In one patient, only radiographic examination was performed initially. Finally, radiographic examination and EUS were performed. So, DT was calculated by radiographic findings in this patient.

‡In two patients, followed up with EUS-fine-needle aspiration (FNA) biopsy was continued without treatment. So, their risk categories were guessed to be low risk by calculating from EUS images and FNA data in this table.

All 12 patients are alive with no evidence of recurrence and metastasis until now.
the EUS features of GIST, a larger diameter, an irregular border, and cystic areas were significantly correlated with higher risk and unfavorable prognosis. Above all, a larger diameter (50 mm ≤) was a significant determinant for the high-risk GIST category. Among the pathological features, a tumor size greater than 50 mm, >10 mitoses per 50 HPF, necrosis, and high-risk category were significant unfavorable prognostic factors. As a result, high-risk parameters on EUS reflected pathological unfavorable prognostic features. Palazzo et al. previously reported that EUS is reliable for predicting the potential malignancy of GIST, with the three most predictive EUS features being irregular margins, cystic areas, and lymph nodes with a malignant pattern. The presence of at least one of these findings had a sensitivity of 91%, a specificity of 88%, a positive predictive value of 83%, and a negative predictive value of 94% for malignancy, while a combination of any two findings had a positive predictive value and specificity of 100%.

Many studies have shown that the c-kit mutations occur preferentially in malignant GIST and do not occur in leiomyomas or leiomyosarcomas. These observations suggest that mutations in exon 11 of c-kit might represent a useful molecular marker for malignant GIST. Data on the prognostic value of KIT mutations is currently somewhat contradictory. In some recent studies, KIT mutations have been found in benign, borderline, and malignant GIST at about equal frequency. Corless et al. found KIT mutations in 11 (85%) of 13 of morphologically benign GIST by use of a sensitive mutation-detection method. These findings suggest that KIT mutations are acquired very early in the development of most GIST and that KIT mutations alone may be of limited prognostic importance.

During the last 20 years, the incidence of GIST has been increasing in Japan, largely due to a mass screening system. Nowadays, we clinically diagnose the risk category of GIST from their EUS findings or other modalities. And then surgical treatments are performed. Based on the pathological findings of the surgical specimens, we predict the clinical course of the patients with GIST. If recurrence or metastasis occurs, we perform surgical approach again or use STI-571 (imatinib, Gleevec; Novartis, Basel, Switzerland). A KIT tyrosine kinase inhibitor, STI-571 has recently shown promise in the treatment of metastatic GIST.

The availability of this new drug may shift the focus of prediction of malignancy to the proper selection of patients for this new adjuvant therapy. Actually, the problem that still remains unresolved is that some high-risk GIST less than 50 mm in diameter did not have any cystic areas, an irregular border on EUS images.

Additionally, it is difficult to determine mitotic rate of GIST exactly before surgery. The GIST consensus conference of 20–21 March 2004, under the auspices of the European Society of Medical Oncology, reported the optimal management procedures for patients with GIST in localized and advanced stages, as well as research issues for the future. Complete tumor resection with negative tumor margins is the standard surgical treatment. As every GIST is now considered potentially malignant, all GIST may need to be resected, even small intramural lesions of the gastrointestinal tract. However, as not all intramural lesions of the gastrointestinal tract are GIST, a preoperative pathological diagnosis should be obtained. Therefore, even in cases of small (≤ 20 mm) intramural tumors, shell-out procedures should be avoided, except in difficult locations (esophagus and rectum), provided the patient is informed and a careful follow up is possible. So, when we encounter a patient with small GIST, should we treat this patient immediately? Increasing incidence has occurred in all clinical GIST but the greatest increase has been observed in patients with small tumors as a result of incidental detection by mass screening or at annual health check-up, especially in Japan. Many incidental small GIST have an invariably benign clinical behavior. Patients with GIST have lived long, comfortable, and relatively productive lives without treatment or with delayed treatment. Indolent behavior of many GIST must be considered when recommending various surgical procedures and interpreting their results in relationship to the functional outcome of the patient. According to this clinical evidence, we should judge the clinical risk of patients with GIST and then decide how to manage these patient. Now, in Japan, incidentally detected small GIST, which meet the following criteria: localized tumors, tumor size less than 20 mm in diameter, absence of invasive growth and informed consent of patients, have been mostly monitored with a ‘wait and see’ strategy in order to spare surgery. Monitoring is generally performed every 6 months. The GIST, which increases in size, is resected after some months of observation. Natural history information is important when recommending treatment. Little is known about the natural history and growth rate of asymptomatic small GIST. To better delineate this problem, the authors reviewed the clinical records and EUS studies, and we diagnosed histologically with asymptomatic GIST at our institution. Among GIST that measured 50 mm or less, our EUS study showed that tumors with rapid growth and a change of internal echo (more inhomogeneity) were higher risk, while tumors that did not grow and showed no change of a homogeneous internal echo were lower risk. A patient with an initially small GIST that shows rapid growth and a change of the internal echo (more inhomogeneity) will be at high risk. After a long follow-up period, such tumors will develop cystic areas or irregular border. Thus, EUS performed at one time cannot always determine whether a small GIST is high-risk, intermediate-risk, low-risk, or very low-risk. Accordingly, follow-up assessment is necessary for a patient with a small GIST. Our study confirms that this strategy may be feasible. However, the possible benefit has to be carefully balanced against possible risks.

In conclusion, despite modern pathological techniques, including c-kit mutation analysis, GIST still pose a dilemma in diagnosis, classification, and prognostication. At the present time, we believe that EUS parameters (a larger diameter, an irregular border, and cystic spaces) provide us useful information on how to manage patients with GIST. Tumor growth rate and change of internal echo pattern will be a helpful prognosticator, especially for asymptomatic and incidentally detected small GIST, where the classical EUS high-risk parameters come up against limiting factors. We also strongly advocate that all patients with a GIST be carefully diagnosed, especially when we encounter asymptomatic and incidentally detected small GIST. We hope the more effective prognostic parameters can be established, perhaps on the basis of molecular genetic or mutational analysis.
REFERENCES


