Gastrointestinal Stromal Tumors: Computed Tomographic Features and Prediction of Malignant Risk from Computed Tomographic Imaging

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Background: Gastrointestinal stromal tumors (GISTs) are specific, generally Kit (CD117)-positive, mesenchymal tumors of the gastrointestinal tract encompassing a majority of tumors previously considered gastrointestinal smooth muscle tumors. Our aim was to characterize the computed tomographic findings and predict malignant risk from computed tomography for the evaluation of GISTs.

Methods: The computed tomographic images of 39 patients with pathologically and immunohistochemically proven GISTs were reviewed by 2 radiologists, and the final interpretations were reached by consensus. Images were assessed for the size, contour, growth pattern, boundary, degree of enhancement, and necrosis of the tumors. The presence of calcification within the lesions, abdominal lymphadenopathy, ascites, and bowel obstruction were also recorded. Categorical variables were compared using Fisher's exact test. Univariate and multivariate logistic regression analyses were used for selection of significant predictors of high-risk malignancy. In addition, the relationships between computed tomographic features and tumor size were assessed by means of nonparametric univariate analysis with the Mann–Whitney *U* test and Kruskal–Wallis test.

Results: Both old age and larger tumor size (≥ 5 cm) were statistically significant in the univariate logistic analysis for high-risk malignant tumors ($p < 0.25$). However, in multivariate logistic regression, only larger tumor size (≥ 5 cm) was found to have final statistical significance for high-risk malignant GISTs ($p < 0.05$). In addition, more exophytic growth pattern ($p < 0.01$), more lobulated appearance ($p < 0.01$), good enhancement ($p < 0.05$), and more necrosis ($p < 0.01$) of masses were more often observed in larger GISTs than small ones on computed tomography.

Conclusion: Larger tumor size (≥ 5 cm) was found to have a predictive value with respect to high-risk malignant GISTs. [*J Chin Med Assoc* 2007;70(9):367–373]

Key Words: computed tomography, gastrointestinal stromal tumor, gastrointestinal tract, neoplasm

Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal (GI) tract.[1] The radiologic findings of GISTs are similar to those of previously described leiomyomas and leiomyosarcomas.[2–4] Recently, immunoreactivity for c-kit (CD117), a tyrosine kinase growth factor receptor, has allowed GISTs to be distinguished from true leiomyomas, leiomyosarcomas, neurofibromas or schwannomas in 95% of patients.[5] The definite identification of GISTs has become increasingly important, because a c-kit selective tyrosine kinase inhibitor, imatinib mesylate, has shown promise as an effective adjuvant therapy treatment.[6]

The radiologic findings of GISTs have been recently described in the radiology literature.[7–9] Few articles have attempted to correlate computed tomography

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(CT) findings with tumor grade. Tateishi et al[8] reported that the most significant CT features that predict a high-grade GIST are an extrinsic epicenter and an unclear boundary. Recently, anatomic site, size (maximum diameter in centimeters), and mitotic rate were suggested as criteria for the prediction of malignancy of GISTs.[10] Kim et al[11] evaluated the correlations between these new criteria and CT features. They reported that only tumor size had predictive value with respect to malignant GISTs of the stomach. However, their cases were limited to tumors of gastric origin. The purpose of this study was to characterize the CT findings of GISTs and determine whether some CT characteristics are useful for predicting malignancy of GISTs, and to compare our results with those of previous reports.

Methods

From August 2000 to September 2004, the medical records at our institution of 65 patients with a histologic and immunohistochemical diagnosis (CD117-positive) of GIST were reviewed. Twenty-six patients were excluded because CT scan was not available. Only 39 patients were enrolled in our study. CT scan data were reviewed on a PACS (picture archiving and communications system; GE Healthcare) for all patients. Clinical data were recorded for patient age, sex, and presenting symptoms. The institutional review board at our hospital did not require approval or informed patient consent for the review of medical records and images.

CT examinations

CT examinations were performed using a Picker PQ6000 or a Picker PQ2000 (Picker International Inc., Cleveland, OH, USA) scanner. Each patient received 100 mL of a nonionic contrast material (Ultravist 370 [iopromide], Schering, Berlin, Germany; Iopamiro 370, Bracco, Milano, Italy) or an ionic contrast material (Telebrix 35, Guerbet, Aulnay, France).

In 34 patients, monophasic helical CT scan (equilibrium phase) was obtained after the finishing of contrast material injection by rapid dripping. The CT scan was performed using the following parameters: an 8- or 10-mm collimation. These patients received about 600 mL diluted oral contrast agent routinely 1 hour before the study, and 300 mL diluted oral contrast agent was added immediately before CT scans. In 5 patients, the biphasic helical CT scans were obtained after 25 seconds (arterial phase) and 120 seconds (equilibrium phase) after the initiation of contrast material injection by an automatic injector at a rate of 3.5 mL/sec. The CT scan was performed using the following parameters: a 5- or 8-mm collimation, 1:1.5 table pitch, and 5- or 8-mm reconstruction interval. Unenhanced images were obtained for 12 patients.

Imaging criteria

Two radiologists reviewed the CT scan images retrospectively, and final interpretations were reached by consensus. CT scans were reviewed to determine the size, contour, boundary, growth pattern, degree of enhancement, and necrosis of the tumors. The presence of calcification within the lesions was also recorded.

Tumor contour was categorized as round, ovoid, or lobulated. The boundary categories were clear (a smooth or lobular contour without surface projections) and unclear (irregular with surface projections). The growth pattern was categorized as endoluminal, exophytic, or equivocal. Endoluminal growth was defined as when the tumor mass was completely confined to the bowel lumen without bulging into the extraluminal space. Conversely, exophytic growth was defined as a mass confined to the extraluminal space without bulging into the bowel lumen, although extrinsic indentation could be found. The degree of tumor necrosis was assessed subjectively and categorized as absent, mild (< 30% necrosis of the tumor), moderate (between 30% and 70% necrosis of the tumor), and severe (> 70% necrosis of the tumor). CT findings were also evaluated for presence of bowel obstruction, abdominal lymphadenopathy, ascites, and distal metastasis.

The pathologic diagnosis, concluded as low-grade or high-grade malignancy, was made by an experienced pathologist.

Statistical analysis

We evaluated the correlation between each CT feature and malignancy. Patients' demographic characteristics, presenting symptoms, and lesion location were also assessed. The statistical methods used included Fisher's exact test for categorical variables and Mann–Whitney *U* test for continuous variables. Univariate logistic regression for malignancy was performed for selected significant factors. The level of significance used for inclusion in the model in multivariate logistic regression was less than 0.25. The final multivariate logistic regression model was made by means of backward stepwise strategy using the significance value $p < 0.05$ to identify significant predictors of a high-grade GIST.

In addition, the relationship between CT features and tumor size was assessed by means of nonparametric

univariate analysis using the Mann–Whitney *U* test for comparison of 2 groups and the Kruskal–Wallis test for comparison of multiple groups. A p value <0.05 was considered statistically significant. Analyses were performed using SPSS version 10.0 (SPSS Inc., Chicago, IL, USA).

Results

Patients' demographic characteristics, presenting symptoms, lesion location, and CT characteristics are shown in Table 1. Of the 39 patients with GISTs, 21 were male (54%) and 18 were female (46%). The mean age

Table 1. Patients' demographic characteristics, presenting symptoms, lesion location, and computed tomographic (CT) characteristics

	Low-grade malignancy ($n=9$)	High-grade malignancy ($n=30$)	p
Demographic characteristics			
Gender			1.000†
Male	5	16	
Female	4	14	
Age (yr)			0.234§
Mean ± SD	53.3 ± 20.2	62.8 ± 13.1	
Range	20–78	35–86	
Presenting symptoms			0.693†
Symptomatic	6	22	
Non-symptomatic	3	8	
Lesion location			0.142‖
Upper location	3	19	
Esophagus	1	1	
Stomach	2	18	
Lower location	6	11	
Small intestine	5	6	
Colon and rectum	1	3	
Omentum and mesentery	0	2	
CT characteristics			
Size*			0.016†
≥ 5 cm	0	20	
< 5 cm	9	9	
Contour*			0.168†
Round	6	11	
Lobulated	2	16	
Ovoid	1	2	
Growth pattern†			0.433†
Endoluminal	4	10	
Exophytic	4	20	
Enhancement			0.465†
Poor	5	12	
Moderate	2	4	
Good	2	14	
Necrosis			0.458†
Absent	4	5	
Mild	3	14	
Moderate	1	4	
Severe	1	7	
Boundary			1.000†
Clear	8	25	
Unclear	1	5	

**Tumor contour and size were difficult to evaluate in 1 patient; †equivocal growth pattern of the lesion was noted in 1 patient; ‡Fisher's exact test; §Mann–Whitney U test; ‖upper vs. lower location, Fisher's exact test.*

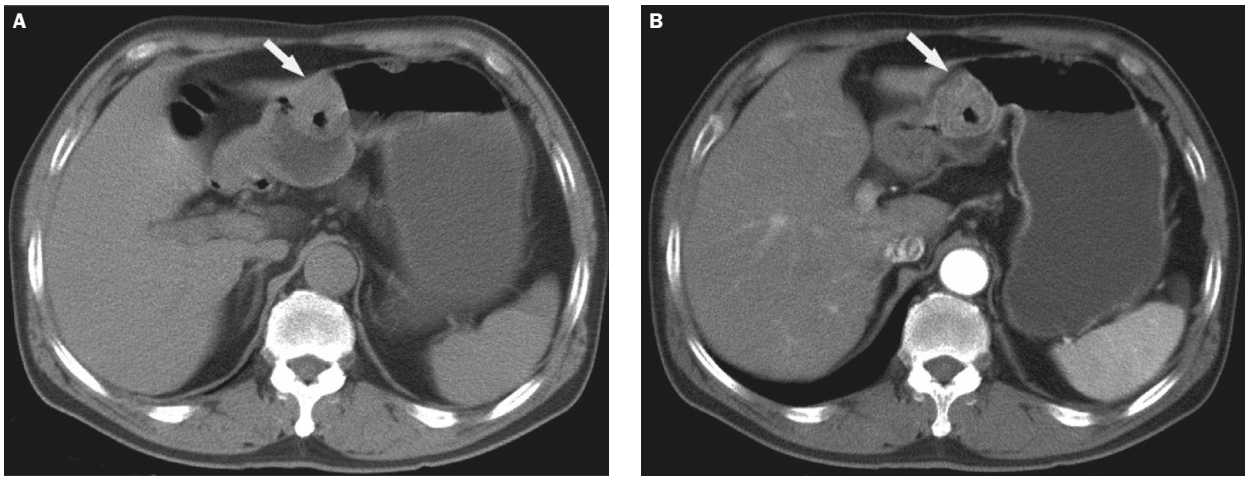

Figure 1. A 58-year-old male with benign gastrointestinal stromal tumor of the stomach incidentally detected during periodic medical check-up. Computed tomography shows well-defined and rounded endoluminal gastric tumor (arrow): (A) non-enhanced; (B) contrast-enhanced.

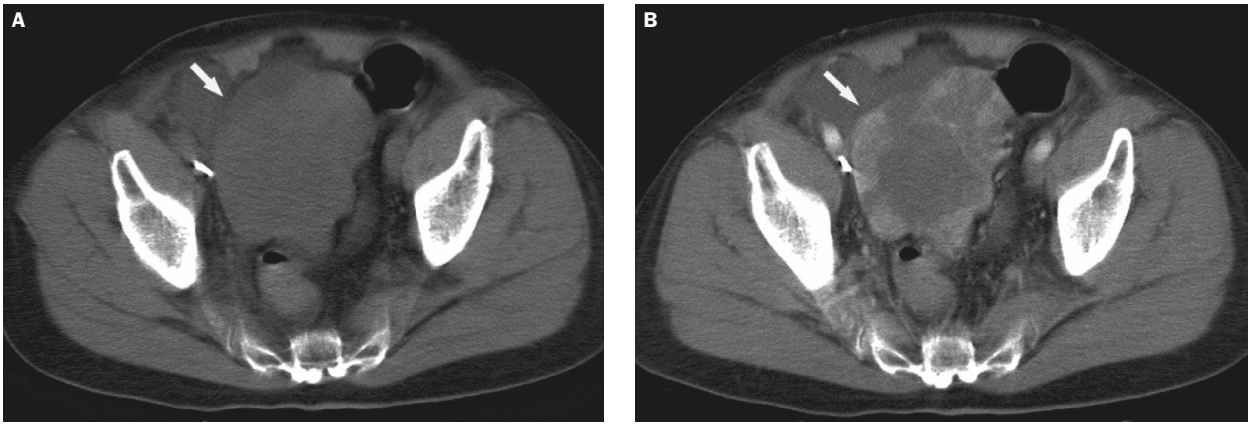

Figure 2. A 70-year-old male with malignant gastrointestinal stromal tumor of the small intestine presenting with gastrointestinal bleeding. (A) Non-enhanced computed tomography (CT) shows a large well-defined soft tissue mass in the pelvic cavity (arrow). (B) Contrast-enhanced CT obtained during arterial phase shows a lobulated hypervascular tumor with severe central necrosis (arrow).

at the time of presentation was 61 years (range, 20–86 years). The most common symptoms were GI bleeding in 14 patients (36%), followed by abdominal pain or discomfort in 9 patients (23%), changed bowel habits in 2 patients (5%), chest tightness in 1 patient (3%), dysphagia in 1 patient (3%), and palpable mass in 1 patient (3%). In 11 patients (28%) who were asymptomatic, tumors were detected during a periodic medical check-up. When the tumor location was divided into upper location and lower location, no significant correlation between lesion location and malignancy could be identified.

Thirty-six patients underwent surgical removal of their tumor. Biopsy was performed in 2 patients because they were not suitable for surgery. In 1 patient, the tumor mass was scattered over the mesentery and omentum. Due to extensive tumor spreading and the easy bloody ooze of the tumor surface, only partial omentectomy was done. Nine (23%) cases were classified as benign (Figure 1) and 30 (77%) as malignant (Figures 2 and 3). The sizes of benign tumors ranged from 2.5 to 5.0 cm (mean, 3.8 ± 0.9 cm), and those of malignant tumors ranged from 2.5 to 22.0 cm (mean, 8.2 ± 5.3 cm).

A primary mesentery GIST in 1 patient presented with numerous nodules scattering over the mesentery, and its contour and size were difficult to evaluate. Another 78-year-old female with a GIST of the jejunum presented with GI bleeding, and the growth pattern in this patient was equivocal. The sizes of 39 tumors ranged from 2.5 to 22.0 cm (mean, 7.2 ± 5.0 cm). Exophytic growth pattern was present in 24 tumors (62%). Central fluid attenuation was present in 30 tumors (77%). Calcification ($n = 1$),

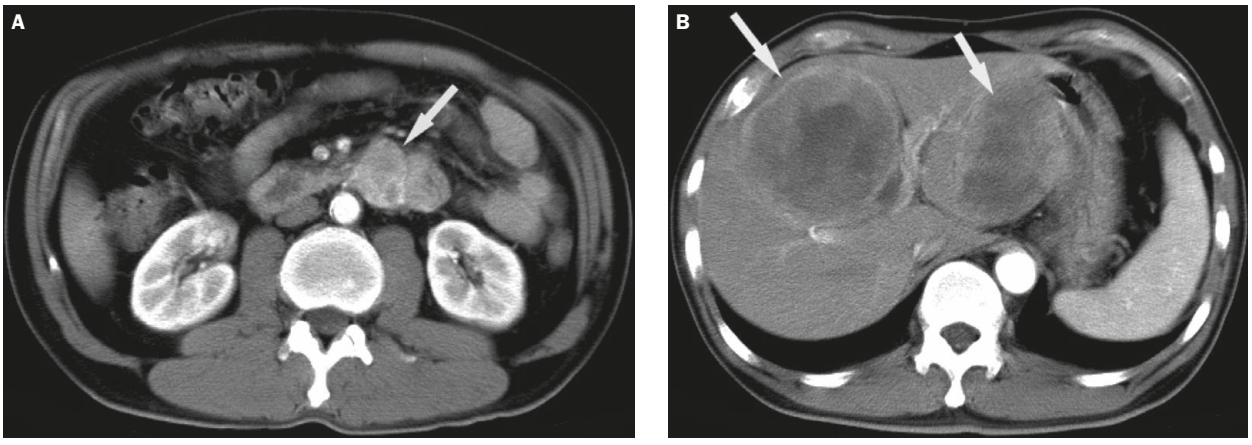

Figure 3. A 49-year-old male with a pathologically proven malignant gastrointestinal stromal tumor incidentally detected for clinical indications of other diseases. (A) Contrast-enhanced computed tomography (CT) obtained during arterial phase shows a solid and lobulated hypervascular mass in the proximal jejunum (arrow). (B) Contrast-enhanced CT obtained during arterial phase shows metastatic liver masses (arrows) with peripheral heterogeneous enhancement and central fluid attenuation.

lymphadenopathy ($n=1$), and ascites ($n=1$) were seen in malignant lesions. Bowel obstruction was not present in these 39 patients.

Three patients had metastatic lesions on CT scans at first presentation. They were diagnosed with liver metastasis, and 1 of them also had peritoneal tumor seeding. The primary tumor origins of these patients were stomach, duodenum, and jejunum, with tumor sizes of 22.0 cm, 6.0 cm, and 6.8 cm, respectively. Liver metastasis was visualized as a peripheral hypervascular soft tissue component with central fluid attenuation in 1 patient and hypoattenuation in comparison with the normal surrounding parenchyma on equilibrium phase in 2 patients.

Old age and larger tumor size (≥ 5 cm) were statistically significant in the univariate logistic analysis for malignant tumors ($p<0.25$). In multivariate logistic regression by means of backward stepwise strategy, only larger tumor size (≥ 5 cm) was found to have final statistical significance for malignant GISTs ($p<0.05$).

The relationships between CT features and tumor size are listed in Table 2. Exophytic lesions had larger size than endoluminal lesions ($p<0.001$). Lesions with lobulated appearance had larger size than those with round appearance ($p<0.01$). Well-enhanced tumors had larger size than poor-enhanced ones ($p<0.05$). The greater the necrosis of a tumor, the more it presented with larger size ($p<0.01$).

Table 2. Computed tomographic (CT) features and tumor size*

	n	Mean tumor size (cm)	95% CI
CT characteristics			
Growth pattern			
Endoluminal	14	4.2 ± 1.1	3.6–4.8
Exophytic	23	9.2 ± 5.5	6.8–11.6
Contour			
Round	17	4.4 ± 1.3	3.7–5.0
Lobulated	18	9.8 ± 5.8	6.9–12.7
Degree of enhancement			
Poor	16	6.0 ± 4.7	3.6–8.5
Moderate	6	4.6 ± 1.2	3.3–5.8
Good	16	9.3 ± 5.5	6.4–12.2
Necrosis			
Absent	8	3.6 ± 0.8	3.0–4.3
Mild	17	6.1 ± 3.4	4.4–7.9
Moderate	5	8.3 ± 5.1	2.1–14.6
Severe	8	12.3 ± 6.5	6.8–17.7

**Mann–Whitney U test for comparison of 2 groups by Bonferroni method, and Kruskal–Wallis test for comparison of multiple groups. CI = confidence interval.*

Discussion

GISTs, previously classified as leiomyomas or leiomyosarcomas, are the most common mesenchymal tumors of the GI tract.[1] Recent studies suggest that GISTs have unique immunohistochemical and molecular genetic features that set them apart from typical smooth muscle tumors and schwannomas. C-kit (CD117), a tyrosine kinase growth factor receptor, is the most specific and important immunohistochemical marker for GISTs.[12] The availability of the tyrosine kinase inhibitor (STI-571, imatinib [Gleevec]; Novartis, Basel, Switzerland) has altered the clinical approach to GISTs because it has been proven to be effective in the medical treatment of unresectable or

metastatic GISTs.[6] Therefore, the detection of liver metastasis or prediction of tumor malignancy has become more important than ever.

Although some reports in the literature show that GIST has a male predominance,[7,9] others, such as the present study, show no gender predilection.[4,8,11] The most common clinical manifestation of a symptomatic GIST in our series was GI bleeding. This is compatible with previous reports.[1] Patients may present with hematemesis, melena, or signs and symptoms of anemia caused by occult bleeding. In other reports, the most common symptom was abdominal pain.[8,11] Many GISTs are incidentally found during a periodic medical check-up, and some of them may be diagnosed after complaint of abdominal pain or discomfort, but not recorded in the chart, which may provide an explanation for discrepancies concerning the most common symptoms.

Anatomic site, size (maximum diameter in centimeters), and mitotic rate were recently suggested as criteria for the prediction of GIST malignancy.[10] In our series, the most common location was the stomach (51%), followed by small intestine (28%), colorectum (10%), esophagus (5%), and omentum and mesentery (5%). The results were similar to those of previous studies.[13,14] According to previous reports, the criteria for malignancy differed according to whether tumors were gastric or intestinal. It has been reported that GISTs arising in the small intestine show more malignant behavior than GISTs arising in the stomach.[10,15] However, in our series, no significant correlation existed between lesion location and malignancy. One possible explanation is the small sample size in our series. In a previous report, most (approximately 70%) gastric GISTs behaved in a benign fashion.[16] However, in our series, the incidence of high-grade malignant gastric GISTs was 90%, higher than in most of the previous reports. Such a high incidence of malignant gastric GISTs was also observed in the study of Kim et al.[11] This can explain why location was not a significant predictor of malignancy in our series.

Some authors have postulated no correlation between CT findings and malignant potential unless an obvious local invasion or metastatic lesion is seen.[1,17] The liver is the most common metastatic site at both presentation and disease relapse.[7] In our series, 3 patients had metastatic lesions on CT scans at first presentation. The pathologic diagnoses of these 3 GISTs were all malignancy. Horton et al[16] reported that imaging during the portal venous phase was usually adequate for detecting liver metastasis. In addition, arterial phase imaging may be helpful for evaluation of tumor enhancement or surgical planning. However, we may have missed some liver lesions that may have been isodense on portal venous or equilibrium-phase images. This is a limitation of our study.

Chun et al[4] observed that CT features of size, contour, enhancing pattern, mesenteric fat infiltration, ulceration, regional lymphadenopathy, and exophytic growth pattern could be used to differentiate between malignant and benign tumors. Multivariate analysis was not performed in their report. Tateishi et al[8] and Kim et al[11] performed univariate and multivariate analyses of CT features to differentiate between malignant and benign tumors. Tateishi et al[8] reported that an extrinsic epicenter and an unclear boundary were the most significant predictors of high-grade GIST. Kim et al[11] reported that presence of an ulcer, mesenteric fat infiltration, direct organ invasion, and metastasis were more frequently observed in GISTs of the stomach with a high mitotic rate, but tumor size was the only significant predictor of a high mitotic rate; however, their cases were limited to tumors of gastric origin. In our series, however, multiple logistic regression analysis showed that larger tumor size (≥ 5.0 cm) was the only predictor of malignant GIST. The average tumor size in our series was 7.2 ± 5.0 cm. The average tumor sizes in our series and the study by Kim et al are larger than that of the study by Tateishi et al, and tumor size was the only significant predictor concerning malignancy in our series and the study of Kim et al. We boldly assume that the larger the tumor mass, the more important is lesion size as a predictor concerning malignancy. This hypothesis can be roughly proven in the study by Kim et al,[11] who reported that, for a subgroup of 36 tumors ≤ 5 cm, differentiation of benign from malignant was not possible using CT, including by tumor size.

Our results also showed that larger tumors had a tendency to grow exophyticly and show lobulated contour, whereas smaller ones tended to grow endoluminally and show round contour. This is compatible with a previous report.[11] Good enhancement was also observed in the larger tumors in our series.

In the study by Tateishi et al,[8] statistically significant CT findings of high-grade tumors included heterogeneous enhancement pattern. The series by Chun et al[4] also demonstrated the same result. However, in the study by Kim et al,[11] heterogeneous enhancement pattern was not a significant predictor of malignancy. We used tumor necrosis as a predictor instead of enhancement pattern because biphasic helical CT scans were obtained in only 5 patients in our series. We assumed that the degree of necrosis would affect the

enhancement pattern. We graded necrosis as absent, mild, moderate, or severe. To our knowledge, no previous reports graded necrosis from CT imaging as a predictor. Although in the multivariate analysis in our series, tumor necrosis was not a significant predictor of malignancy, in the later statistical analysis, we found the larger tumor masses were more necrotic.

Our study had an additional limitation. This was a retrospective study in which data were gathered over a period of years, with substantial variations in CT equipment and method. Nevertheless, given the relatively low frequency of occurrence of GISTs at any single institution, the prospective acquisition of a similar number of cases may require a large multi-institutional study conducted over many years.

In conclusion, we observed statistically significant difference in CT findings between malignant and benign GISTs. Larger tumor size (≥ 5 cm) was found to have predictive value with respect to GIST malignancy.

References

1. Levy AD, Remotti HE, Thompson WM, Sobin LH, Miettinen M. Gastrointestinal stromal tumors: radiologic features with pathologic correlation. *Radiographics* 2003;23:283–304.
2. McLeod AJ, Zornoza J, Shirkhoda A. Leiomyosarcoma: computed tomographic findings. *Radiology* 1984;152:133–6.
3. Megibow AJ, Balthazar EJ, Hulnick DH, Naidich DP, Bosniak MA. CT evaluation of gastrointestinal leiomyomas and leiomyosarcomas. *AJR Am J Roentgenol* 1985;144:727–31.
4. Chun HJ, Byun JY, Chun KA, Rha SE, Jung SE, Lee JM, Shinn KS. Gastrointestinal leiomyoma and leiomyosarcoma: CT differentiation. *J Comput Assist Tomogr* 1998;22:69–74.
5. Hirota S, Isozaki K, Moriyama Y, Hashimoto K, Nishida T, Ishiguro S, Kawano K, et al. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. *Science* 1998; 279:577–80.
6. Demetri GD, von Mehren M, Blanke CD, Van den Abbeele AD, Eisenberg B, Roberts PJ, Heinrich MC, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. *N Engl J Med* 2002;347:472–80.
7. Burkill GJ, Badran M, Al-Muderis O, Meirion Thomas J, Judson IR, Fisher C, Moskovic EC. Malignant gastrointestinal stromal tumor: distribution, imaging features, and pattern of metastatic spread. *Radiology* 2003;226:527–32.
8. Tateishi U, Hasegawa T, Satake M, Moriyama N. Gastrointestinal stromal tumor. Correlation of computed tomography findings with tumor grade and mortality. *J Comput Assist Tomogr* 2003; 27:792–8.
9. Ghanem N, Altehoefer C, Furtwangler A, Winterer J, Schafer O, Springer O, Kotter E, et al. Computed tomography in gastrointestinal stromal tumors. *Eur Radiol* 2003;13: 1669–78.
10. Miettinen M, El-Rifai W, Sobin LH, Lasota J. Evaluation of malignancy and prognosis of gastrointestinal stromal tumors: a review. *Hum Pathol* 2002;33:478–83.
11. Kim HC, Lee JM, Kim KW, Park SH, Kim SH, Lee JY, Han JK, et al. Gastrointestinal stromal tumors of the stomach: CT findings and prediction of malignancy. *AJR Am J Roentgenol* 2004; 183:893–8.
12. Fletcher CD, Berman JJ, Corless C, Gorstein F, Lasota J, Longley BJ, Miettinen M, et al. Diagnosis of gastrointestinal stromal tumors: a consensus approach. *Hum Pathol* 2002; 33:459–65.
13. Miettinen M, Sarlomo-Rikala M, Lasota J. Gastrointestinal stromal tumors: recent advances in understanding of their biology. *Hum Pathol* 1999;30:1213–20.
14. Miettinen M, Monihan JM, Sarlomo-Rikala M, Kovatich AJ, Carr NJ, Emory TS, Sobin LH. Gastrointestinal stromal tumors/ smooth muscle tumors (GISTs) primary in the omentum and mesentery: clinicopathologic and immunohistochemical study of 26 cases. *Am J Surg Pathol* 1999;23:1109–18.
15. Emory TS, Sobin LH, Lukes L, Lee DH, O'Leary TJ. Prognosis of gastrointestinal smooth-muscle (stromal) tumors: dependence on anatomic site. *Am J Surg Pathol* 1999;23:82–7.
16. Horton KM, Juluru K, Montogomery E, Fishman EK. Computed tomography imaging of gastrointestinal stromal tumors with pathology correlation. *J Comput Assist Tomogr* 2004;28:811–7.
17. Horton KM, Fishman EK. Current role of CT in imaging of the stomach. *Radiographics* 2003;23:75–87.