·Clinical Research·

Correlation of multi-slice spiral CT features to clinicopathologic manifestations of gastrointestinal stromal tumor: a report of 49 cases

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[**Abstract**] **Background and Objective**: Gastrointestinal stromal tumor (GIST) is one of the most common mesenchymal tumors of the digestive system. Imaging examination plays an important role in preoperative diagnosis and postoperative evaluation for it. This study was to describe the multi-slice spiral computed tomographic (MSCT) findings and pathologic features of GIST, and to analyze their correlation. **Methods**: MSCT and pathologic reports of 49 patients with 53 pathologically confirmed GIST lesions were reviewed and compared. **Results**: Of the 53 GIST lesions, 14 were at very low biological risk, 11 at low risk, ten at moderate risk and 18 at high risk; 36 (67.9%) were found in first visit by CT scans. On CT images, the GIST lesions with maximal diameter of ≥50 mm showed irregular shape, invasive growth, presence of cystic area and heterogeneous enhancement, and most of them were at high risk; the lesions with maximal diameter of <50 mm showed regular shape, expansive growth, and homogeneous enhancement, and most of them were at risk of moderate or below. No lymph node metastasis was found. Only three lesions showed S100-positive, which presented infiltration along the gastric wall or bowel ring on CT images. **Conclusions**: CT examination is helpful in risk prediction for GIST, but it is difficult to detect small lesions (< 2 cm) by CT scans. Due to the infiltrative growth of GIST with neural differentiation (S100-positive), it is difficult to distinguish GIST from gastric cancer on CT images.

Key words: gastrointestinal stromal neoplasm, mesenchymom, tomography, X-ray computed, risk, immunohistochemistry

Gastrointestinal stromal tumor (GIST) is the most common mesenchyma-derived tumor in the digestive system, accounting for 1%-3% of all gastrointestinal tumors. It is primarily originated from the digestive system, expresses C-kit protein (CD117) and contains large number of spindle-shaped epithelioid cells (or a small part), and occasionally presents as polymorphic mesenchymal tumors.[1,2] Mesenchymal stem cells can differentiate into either smooth muscle cells or neural cells, or both or neither of them during tumor formation. Tumors with significant neural differentiation are S100-positive.[3] Therefore, GISTs at early stage

are often misdiagnosed as digestive leiomyoma (leiomyosarcoma) or (malignant) neurilemmoma.[4] Existing studies suggested no definite benign behaviors in GISTs, which are thus graded as very low risk, low risk, moderate risk or high risk based on their biological behaviors.[5] Biological risk grading is well correlated to prognostic parameters, such as survival.[6] Our study aimed to compare CT findings and pathologic features, particularly biological risk, of GISTs, and to improve the role of CT examination in its preoperative diagnosis and prognostic evaluation.

Material and Methods

General information. A total of 49 naive GIST patients (with 53 lesions) with complete CT reports, treated in Sun Yat-sen University Cancer Center during 2006-2008, were analyzed. Among these patients, two had two lesions and one had three lesions. All the lesions were confirmed by postoperative pathologic examination and immunohistochemistry. Of these patients, 33 were men and 16 were women, aged between 16-77 years, with a median age of 56 years. Clinical symptoms were mostly abdominal pain, abdominal mass and digestive tract hemorrhage.

Examination method. CT scans were performed using Phillips Brilliance 16 ^{MT} system. At about 30 min before the scan, all patients were orally given 500 mL of 0.5% diluted contrast agent or water to expand the gastrointestinal tract, and another 100 mL was given right before the scan. Routinely, plain scan was performed, followed by biphasic contrast enhanced scan of the upper abdomen, where 80-100 mL of non-ionic contrast agent was intravenously injected at the rate of 2-3 mL/s. During biphasic contrast enhanced scanning, the duration of artery phase scan was 18-25 s, and that of portal vein phase scan was 60-70 s. Scanning was performed under following conditions: 120 kV; 250 mA; matrix 512× 512; slice thickness 5 mm; pitch 1.

Analysis of CT images. All data were put into Visual FoxPro 6.0 software to build up a database and describe lesion sites. Based on the maximal diameter of the lesion on CT images, they were assigned into <50 mm and ≥ 50 mm groups. Analysis was performed on tumor margin, growth pattern, density, enhancement pattern and metastasis. All these CT findings were compared with pathologic results (biological risk and immunohistochemical results).

Analysis of pathologic results. Biological risk grading of GIST was based on maximal diameter and mitotic figure count of the lesions:[5] for very low risk tumor, the maximal diameter was <2 cm, and mitotic figure count <5/50 HPF; for low risk tumor, the maximal diameter was 2-5 cm, with a mitotic figure count of <5/50 HPF; for moderate risk tumor, the maximal diameter was 5-10 cm, with a mitotic figure count of <5/50 HPF, or a maximal diameter of <5 cm with a mitotic figure count of 6-10/50 HPF; in high risk tumor, mitotic figure count was above 10/50 HPF at any tumor volume, or a maximal tumor diameter of >10 cm or of >5 cm with a mitotic figure count of >5/50 HPF. With CD117, CD34, S100 and HHF35 as parameters, immunohistochemical analysis was performed in all lesions.

Statistical analysis. Statistical analysis was performed using statistical software SPSS 13.0. CT findings of GISTs (size, morphology, growth pattern, density and enhancement pattern) were compared with biological risk grade by chi-square test and exact test. Test level was set to α =0.01; A P≤0.01 indicated significance.

Results

CT findings in gastrointestinal stromal tumor. The 53 lesions included two (3.8%) esophageal submucosal lesions, 31 (58.5%) gastric lesions, 12 (22.6%) intestinal lesions, two (3.8%) colorectal lesions, two (3.8%) mesenteric lesions and four (7.5%) post-peritoneal lesions. A total of 36 lesions were detected by CT examinations, with CT presentations list in Table 1.

In 18 lesions with maximal diameter of <50 mm, 11 showed well-defined boundary, even density and expansive growth (seen as

Table 2 Comparison between CT features and biological risk of 36 GIST lesions

Item	Biological risk (lesions)				χ^2	P
	Very low	Low	Moderate	High	value	value
Diameter					21.876	<0.001
<50 mm	3	9	4	2		
⩾50 mm	0	0	4	14		
Shape					16.435	<0.001
Regular	3	6	1	1		
Irregular	0	3	7	15		
Growth pattern					14.304	0.001
Expansive	3	7	4	2		
Invasive	0	2	4	14		
Density					34.315	<0.001
Homogeneous	3	8	0	0		
Cystic or necrosis	0	1	8	16		
Enhancement pattern					34.315	<0.001
Homogeneous	3	8	0	0		
Heterogeneous	0	1	8	16		

protuberance into the cavity or out of the gastrointestinal wall), with mild homogeneous enhancement (Fig. 1); seven showed blurred boundary, uneven density, cystic degeneration and necrosis, with heterogeneous enhancement. Two patients had liver metastatic lesions. In 18 lesions with maximal diameter of ≥ 50 mm, all showed irregular boundary, with uneven density, cystic degeneration, necrosis, and heterogeneous enhancement; 13 showed infiltrative growth, of which two infiltrated along the gastric wall and one along the intestinal ring, another five showed expansive growth. Two patients had liver metastasis and one had spleen metastasis. in one case. No calcification or lymph node metastasis was observed.

Pathologic results of gastrointestinal stromal tumor. In the 53 lesions, 14 (26.4%) were graded as very low risk, 11 (20.8%) as low risk, 10 (18.9%) as moderate risk and 18 (33.9%) as high risk. Both esophageal submucosal lesions were graded as very low risk; among 31 gastric lesions, 11 were graded as very low risk, eight as low risk, five as moderate risk and seven as high risk; among 12 intestinal lesions, one was graded as very low risk, three as low risk, four as moderate risk and four as high risk; in two colorectal lesions, one was graded as moderate risk and one as high risk; both mesenteric lesions and four post-peritoneal lesions were high risk lesions.

In immunohistochemical evaluation, 45 lesions were CD117-positive, 48 were CD34-positive, eight were HHF35-positive and 3 were S100-positive.

Comparison between CT findings and pathologic results of gastrointestinal stromal tumors. Among 21 GISTs with a maximal diameter ≤ 20 mm as indicated by pathologic results, only eight were detected by CT examinations, of which four were correctly diagnosed, three were misdiagnosed as lymph node metastasis, and one was misdiagnosed as unexpanded intestine with liver metastatic lesion detected at initial diagnosis and diagnosed as GIST by postoperative pathology (Fig.2). Among 32 lesions with maximal diameter >20 mm as indicated by pathologic results, 28 were detected by CT examinations. Of them, four post-peritoneal lesions were large with maximal diameters of 38-112 mm (Fig.3). Those four undetected lesions presented as nodules on the gastric wall which were undistinguishable from unexpanded gastric wall due to poorly-expanded gastric cavity. Among 36 lesions detected by CT examinations, 33 were CD117-positive, 32 were CD34-positive, 3 were HHF35-positive and 3 were S100-positive. Among those S100-positive lesions, two infiltrated along the gastric wall (Fig. 4), and one along intestinal ring; pathology revealed infiltration in all layers of gastric or intestinal wall, with extensive suppuration.

Among 36 lesions detected by CT examinations, three were graded as very low risk, nine as low risk, eight as moderate risk and 16 as high risk. In 18 lesions with maximal diameter <50 mm, 16 were graded as very low or low or moderate risk, and two as high risk. In 18 lesions with maximal diameter ≥ 50 mm, four were graded as moderate risk, and 14 as high risk. In 11 lesions with regular boundary, 10 were graded as very low or low or moderate risk, only one as high risk; among 25 lesions with irregular boundary, 10 were graded as very low or low or moderate risk and 15 as high risk. In 16 lesions with expansive growth, 14 were graded as very low or low or moderate risk, and two as high

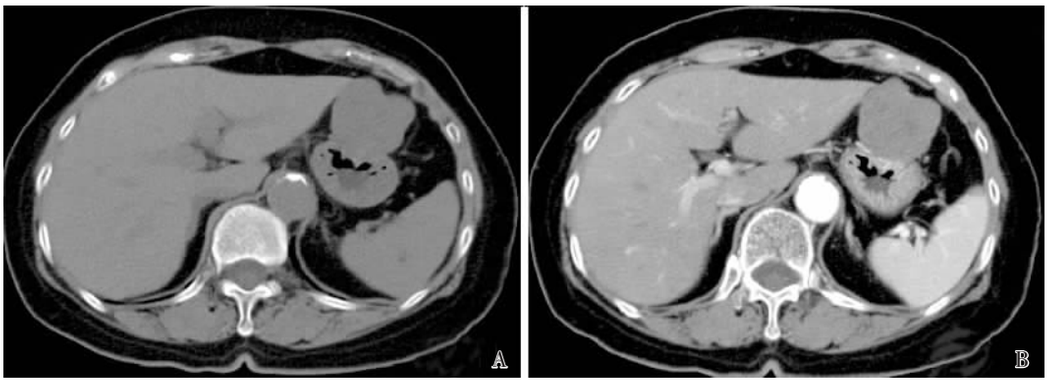

Figure 1 CT features of gastrointestinal stromal tumor (GIST)

A: Unenhanced CT scan shows a 40-mm mass with smooth margin, homogeneous density, and expansive growth (arrow) which extends anterior to the stomach.

B: Contrast-enhanced CT scan shows the mass with homogeneous enhancement at arterial venous phase.

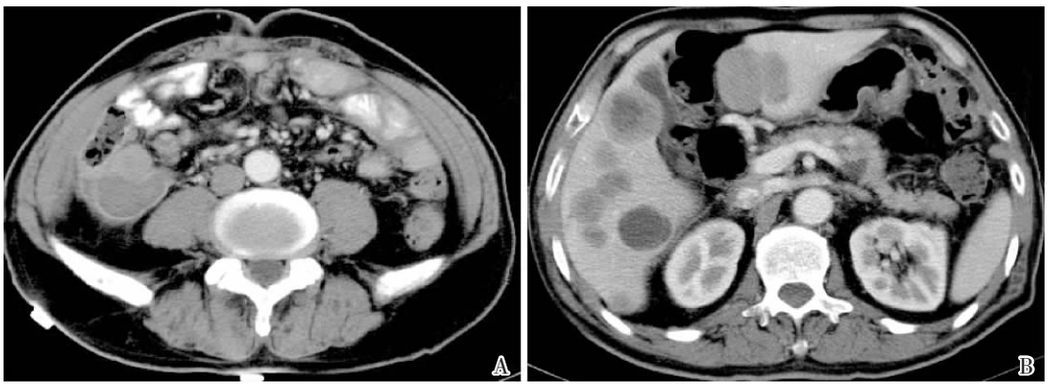

Figure 2 CT features of small mesenteric GIST with multiple liver metastases

A: Contrast-enhanced CT scan shows a 20-mm mass with round shape and homogeneous enhancement arising from the small mesenteric.

B: Contrast-enhanced CT scan shows multiple liver metastases with rim enhancement.

risk; in 20 lesions with infiltrative growth, 6 were graded as very low or low or moderate risk and 14 as high risk. All those 11 lesions with even density and homogeneous enhancement were graded as low or very low risk; in 25 lesions with cystic degeneration and necrosis and heterogeneous enhancement, one was graded as low risk, eight as moderate risk and 16 as high risk.

As shown in Table 2, four biological risk levels showed significant differences between varied tumor volume, shape, growth pattern, density and enhancement pattern as revealed by CT examinations (all $P \leq 0.01$). At higher risk level, the tumor showed larger volume, irregular shape, infiltrative growth and uneven density, with heterogeneous enhancement in contrast-enhanced scanning.

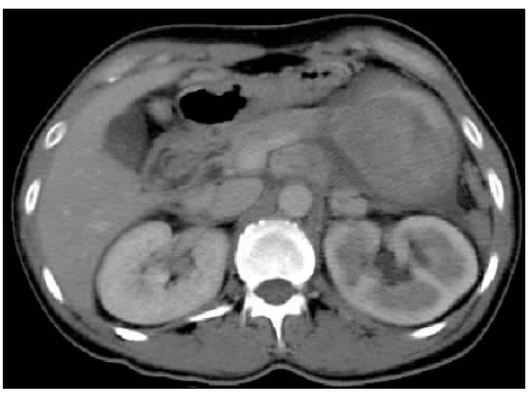

Figure 3 CT features of retroperitoneal GIST

Contrast-enhanced CT scan shows a mass with heterogeneous enhancement and complete envelope.

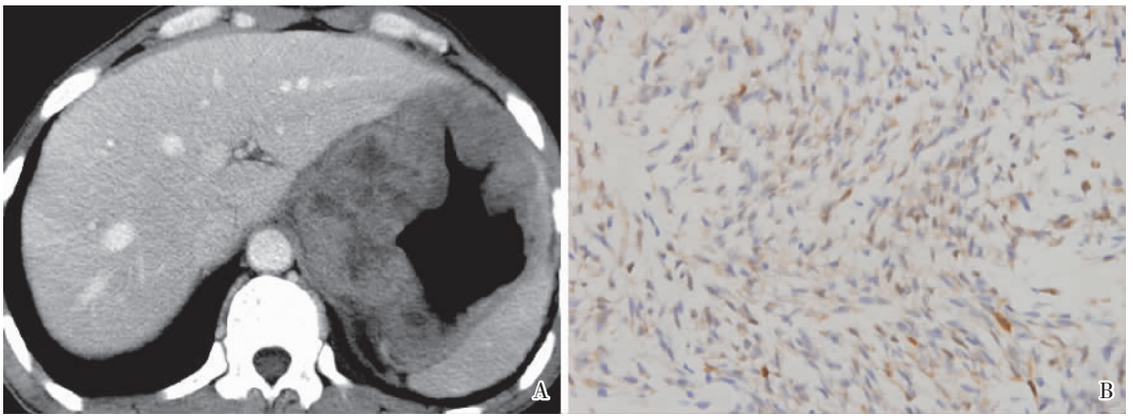

Figure 4 CT features and morphology of S100-positive GIST

A: Contrast-enhanced CT shows a mass with infiltrative growth, heterogeneous enhancement and necrosis arising from the gastric wall. B: S100 is expressed in the GIST tissue (SP ×400).

Table 1 CT features of 36 gastrointestinal stromal tumor (GIST) lesions

Item	Largest diameter (lesions)		Total
	<50 mm	≥50 mm	
Total lesions	18	18	36
Shape			
Regular	11	0	11
Irregular	7	18	25
Growth pattern			
Expansive	11	5	16
Invasive	7	13	20
Density			
Homogeneous	11	0	11
Cystic or necrosis	7	18	25
Enhancement pattern			
Homogeneous	11	0	11
Heterogeneous	7	18	25
Blood metastasis			
Liver	2	2	4
Spleen	0	1	

Discussion

Pathological features of gastrointestinal stromal tumor. In 1983, a group of gastrointestinal mesenchymal derived tumors were named gastrointestinal stromal tumor by Mazur et al.[7] Recent studies suggested GIST originated from interstitial stem cells of gastrointestinal tract named Cajar cells,[5, 8] which was a member of myelocyte-like stem cells and carried c-kit proto-oncogene (CD117- and CD34-positive). In our study, 45 patients were CD117-positive and 48 CD34-positive, 8 were HHF35-positive, but only 3 were S100 positive. According to literatures, proto-oncogene c-kit (CD117) was negative or inactive in 2-8% of all GISTs. In our study, eight patients (15.1%) were CD117-negative, with a percentage higher than those reported in literature. It was suggested that efficacy of medical treatment was poor in patients with negative CD117. The volume of GIST and the mitotic figure count are currently recognized as the prognostic predictors for GIST, the risk grading methods for GIST (detailed in Table 1) proposed by Fletcher et al.[5] was therefore used in our study. Among the cases in our study, 14 (26.4%) were graded as very low risk, 11 (20.8%) as low risk, ten (18.9%) as moderate risk and 18 (33.9%) as high risk. Nilsson et al.[9] found that five-year survival rate in patients with high risk tumors was remarkably lower than those in patients with very low or low or moderate risk ones, with significantly increased recurrence. Hence, early determination of lesion risk level was very helpful in prognosis evaluation.

CT findings and differential diagnosis of gastrointestinal stromal tumor. The CT findings of GIST were, to a certain extent, characteristic. Small lesions usually have well-defined boundary and even density, and are often seen as moderately and homogeneously enhanced approximately circular mass protruding into the cavity or out of gastrointestinal wall;

while larger lesions tend to show irregular shape, with frequent necrosis, cystic degeneration, obviously heterogeneous enhancement and significant compression over adjacent structures.[10,11] In our study, among 18 lesions with maximal diameter <50 mm, 11 showed well-defined boundary and even density, and were seen as protuberance into gastrointestinal cavity or out of gastrointestinal wall, with mild and homogeneous enhancement; seven showed cystic degeneration and necrosis. All those 18 lesions with maximal diameter ≥ 50 mm showed irregular boundary, uneven density, cystic degeneration and necrosis, and were heterogeneously enhanced by contrast agent. Infiltrative growth was seen in 13 cases, of which two showed infiltration along gastric wall and one along intestinal ring. Based on literature reports, GISTs tend to metastase to liver, mesentery and lung.[10] In our study, liver metastasis developed in four cases, and spleen metastasis in one case; no mesenteric or lymph node metastasis was seen.

CT findings were similar between GIST and leiomyoma, leiomyosarcoma and neurilenoma in gastrointestinal tract, which makes it hard to distinguish them. Pathology and immunohistochemistry are necessary to establish the diagnosis. But the incidence of leiomyoma, leiomyosarcoma and neurilenoma in gastrointestinal tract was lower as compared to that of GIST.[1] Some CT findings are common in GISTs, gastrointestinal epithelium-derived tumors and lymphoma, with lower incidence for stromal tumors as compared to the latter two.[12] In three GISTs that showed neural differentiation (S100-positive) in our study, the shape and density on CT images were similar and undistinguishable to those in adenocarcinoma or lymphoma with infiltrative growth. Lymph node metastasis is frequent in gastrointestinal derived adenocarcinoma, and swollen lymph nodes also prevail in lymphoma, whereas lymph node metastasis is extremely rare in GISTs. In addition, mesenteric and post-peritoneal stromal tumors should be distinguished from corresponding malignant tumors, such as leiomyosarcoma, liposarcoma and malignant neurilenoma.

CT diagnosis in relation to pathological results in gastrointestinal stromal tumor. GIST may occur in any site in the gastrointestinal tract, and is also seen beyond gastrointestinal tract.[1,5] In our study, stomach was the most common tumor site, accounting for 58.5% of all cases. Small intestine accounted for 22.6%, but colon-rectal, mesenteric and post-peritoneal lesions were rare. These results were similar to those reported in literature.[13] Among high risk lesions, seven were seen in stomach, four in small intestine, one in colon-rectum, two in mesentery and four post-peritoneally; very low or low or moderate lesions were mostly located in stomach (23) and intestine (8). Therefore, when mesenteric and post-peritoneal lesions are detected by CT scan, the probability of high risk lesions should be noted.

GISTs are concealed at early stages, and are hardly caught by CT examination, particularly when accompanied by other pathologic changes. Most often, they are accidentally found during a surgery. In 21 lesions with maximal diameter of ≤ 20 mm as indicated by pathological results, only eight were detected by CT examinations, with a positive detection rate of 38.1%. And four misdiagnosed lesion were found by MPR reconstruction based the tumor site hinted by pathological results in the retrospective analysis; they were rarely caught by routine scanning. In 32 lesions with maximal diameter >20 mm as indicated by pathological results, 28 were detected by CT examination, with a positive detection rate of 87.5%. Another four nodules in gastric wall were not detected since they were undistinguishable from unexpanded gastric wall. Therefore, CT examination has limitation in detecting small GISTs; as for larger lesions, CT examination is accurate in evaluating tumor volume, shape and its relationship to surrounding tissue, and is capable of revealing distant or lymph node metastasis.

Our study suggested correlations between biological risk and tumor volume, boundary, density and enhancement pattern in CT imaging in GISTs (all $p<0.01$). High risk lesions tended

to have a maximal diameter ≥ 50 mm, with blurred boundary, uneven density, necrosis, cystic degeneration, infiltrative growth and heterogeneous enhancement with contrast agent, while very low or low or moderate risk lesions tended to have maximal diameter <50 mm, with well-defined boundary, even density, expansive growth and homogeneous enhancement with contrast agent. Tateishi et al.[14] revealed a correlation between CT findings of tumor and its risk level; and that exophtically infiltrative growth and blurred boundary were important parameters that predicted high risk lesions. While Yong et al.[15] found that tumor volume (≥ 50 mm) was important in predicting whether the lesion was high risk. Hence, CT findings have certain significance for primary evaluation of biological risk before surgery.

In conclusion, the CT findings of GISTs are characteristic to a certain extent and are helpful in rating biological risk. Large lesions (≥ 50 mm) with blurred boundary, frequent necrosis and cystic degeneration and heterogeneous enhancement are mostly high risk lesions, while small ones (<50 mm) with well-defined boundary, even density and homogeneous enhancement are most probably very low or low or moderate risk lesions. Detecting minor lesions is the weak spot of CT examination. Stromal tumors with neural differentiation tend to show infiltrative growth, which makes them undistinguishable from gastric cancer. Our study had certain limitations, for instant, analysis by tumor sites was not performed due to small sample size. Therefore, relevant conclusions have yet to be further explored.

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