Hong Kong J Radiol. 2012;15:155-61

ORIGINAL ARTICLE

Gastrointestinal Stromal Tumours: Role of Computed Tomography in Predicting Tumour Behaviour

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ABSTRACT

Objectives: *To describe the clinical and imaging features of the gastrointestinal stromal tumours and the role of computed tomography in predicting malignant potential.*

Methods: *The medical records and imaging features of the patients diagnosed with gastrointestinal stromal tumours at our institution were reviewed retrospectively. Imaging features were correlated with their clinical course, including the presence or subsequent development of metastatic disease.*

Results: *In all, 28 patients (mean age, 65.2 years) with pathologically proven gastrointestinal stromal tumours were included in the study. The stomach was the most common site followed by small bowel. The mean tumour diameter was 7.5 cm. Metastatic disease developed in nine patients. Computed tomography showed necrotic masses (n = 8) and heterogeneous contrast enhancement (n = 17). Large tumour size, heterogeneous enhancement and necrosis were independently associated with an increased risk of metastatic disease.*

Conclusion: *Gastrointestinal stromal tumours have fairly characteristic imaging features on computed tomography and the diagnosis can be suggested by imaging features. Computed tomography is potentially a valuable tool in the initial evaluation of such tumours and predicting their potential for malignant behaviour.*

Key Words: *Gastrointestinal neoplasms; Proto-oncogene proteins c-kit; Tomography, X-ray computed*

中文摘要

胃腸道間質瘤：電腦斷層造影在預測腫瘤方面的應用

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目的：描述胃腸道間質瘤的臨床及影像特徵，以及電腦斷層造影在預測腫瘤惡性程度所扮演的角色。

方法：回顧本院胃腸道間質瘤患者的臨床紀錄及影像特徵，並探討這些影像特徵是否與病人的臨床病程有關，包括癌症轉移的出現或狀況。

結果：共回顧了28名病理證實患有胃腸道間質瘤的病人紀錄。患者平均年齡65.2歲，最普遍患癌的位置為胃部，其次為小腸。腫瘤平均直徑為7.5 厘米。其中9名患者有癌症轉移。電腦斷層造影顯示

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Submitted: 30 Apr 2012; Accepted: 16 Aug 2012.

8人有壞死性腫瘤，另17人有不均勻強化的顯影增強。大腫瘤、不均勻強化現象、和壞死均獨立與高風險癌症轉移相關。

結論：胃腸道間質瘤在電腦斷層造影表現有一定的特徵性，醫生可憑這些造影特徵作診斷。電腦斷層造影對胃腸道間質瘤的初步評估以及預測腫瘤惡性程度有重要價值。

INTRODUCTION

Gastrointestinal stromal tumours (GISTs) are rare mesenchymal tumours of the gastrointestinal tract. In 1983, they were recognised as a separate entity from gastrointestinal smooth muscle tumours.[1] They can arise anywhere in the gastrointestinal tract, mesentery or omentum, but the majority are located in the stomach and small intestine.[2,3] They usually arise from the muscularis propria of the bowel wall and grow subserosally or submucosally. They are believed to originate from malignant degeneration of interstitial cells of Cajal,[4] which are normally located in the enteric plexuses of the bowel wall that have a role in gastrointestinal motility. Although these tumours show variable cell differentiation, spindle cell differentiation is histologically the most common feature noted in 70 to 80% of the cases.[5] The hallmark of these tumours is the presence of cell-surface antigen CD117 (also known as KIT antigen), which can be readily detected by immunohistochemistry.[6] This surface antigen is present in more than 95% of GIST regardless of their site of origin.[7,8] As they possess tyrosine kinase receptors, KIT gene activation is believed to play a critical role in GIST oncogenesis.[9]

GISTs can affect all age-groups; the mean age at presentation is 60 years, and males are more often affected than females.[10] Patients with GIST have variable clinical presentations, including abdominal pain, gastrointestinal bleeding, anaemia related to chronic gastrointestinal blood loss, and intestinal obstruction, but many remain asymptomatic and the tumours are discovered incidentally.[10,11]

GISTs have a continuous spectrum of degree of malignancy from benign local disease to aggressive tumour with distant metastasis. Determining tumour malignancy has been notoriously difficult and traditionally depended on pathological features such as size and number of mitoses per high power field (HPF).[12]

Imaging plays an important role in the initial evaluation and diagnosis of these patients because of their clinical presentations. Although several studies have described the radiological features of these tumours and the possible role of imaging in monitoring disease response to treatment, few tried to predict tumour malignancy based on imaging.[13-17] In addition to familiarising radiologists and clinicians with the radiological features of GIST, this study aimed to explore the potential role of contrast-enhanced computed tomography (CT) in predicting GIST behaviour and potential malignancy.

METHODS

Using our hospital tumour registry database, we identified all patients diagnosed with a histopathologically proven GIST between January 2005 and December 2010. Using the hospital electronic medical records, we retrospectively reviewed their clinical presentations, course, and management. All imaging studies performed to establish the diagnosis and evaluate the extent of tumour were reviewed by a board-certified radiologist, using our hospital-installed picture archiving and communication system. The radiologist was blinded to the histopathological grading. From the beginning, this study was approved by our Institutional Ethical Committee.

Each patient's clinical features, including main presenting symptoms, method of initial diagnosis, and subsequent management were recorded, and histopathological reports were reviewed. High-grade malignancy as defined pathologically referred to >5 mitoses per 50 HPFs and low-grade malignancy referred to ≤5 mitoses per 50 HPFs.

All available initial imaging studies used to establish the diagnosis were reviewed by a board-certified radiologist. In all, 26 patients underwent their initial abdominal CT at our hospital and were available for review; CT scan techniques were varied and the initial eight cases entailed using 16-slice CT and the remaining one was performed using a multislice CT utilising 5-mm slice thickness reconstruction (Aquilion 64; Toshiba Medical Systems, Otawara, Japan). Oral contrast was given to most of these patients and all of them also received intravenous contrast. The post-contrast CT was performed during the portovenous phase (70-90 seconds

delay); this phase was used for analysis of the tumour's CT features. Additional pre-contrast and post-contrast arterial phase films were obtained in some of these patients.

The size, location, presence of necrosis and calcification, and the degree and pattern of enhancement were recorded based on the pre-treatment CT. The degree of enhancement was calculated by subtracting tumour density in the area of maximum enhancement pre-intravenous contrast from post-contrast images of the same area using Hounsfield units (HU). The degree of metabolic activity was reviewed based on CT/positron emission tomography (PET) studies using standardised uptake values (SUVs). Ultrasound studies were reviewed for the tumour size, echogenicity, and degree of homogeneity.

The GIST is considered malignant if metastasis was apparent at the time of diagnosis or during the follow-up period. Using multivariate analysis, the following imaging variables on CT were analysed to determine their ability to predict tumour malignancy: tumour site of origin, size, pattern, the degree of enhancement on the post-contrast film, and the presence of necrosis.

Table. Clinical features of the patients.

Clinical feature	No. (%) of patients*
Mean (range) age (years)	65.2 (38-84)
Tumour location	
Stomach	17 (61)
Small bowel	
Duodenum	1 (4)
Jejunum	6 (21)
Ileum	3 (11)
Omentum	1 (4)
Mean (range) size (cm)	7.5 (1-26)
Presenting symptoms	
Asymptomatic	9 (32)
Abdominal pain	9 (32)
Gastrointestinal (GI) bleeding	8 (29)
Anaemia secondary to GI blood loss	4
Gross GI haemorrhage	4
Small bowel obstruction	2 (7)
Metastatic disease	9 (32)
Treatment	
Surgery	18 (64)
Medical treatment	9 (32)
None	1 (4)
Pathological grading	
High-grade	9 (32)
Low-grade	10 (36)
Not available	9 (32)

* Data are shown in No. (%) of patients, except otherwise indicated.

RESULTS

A total of 28 patients with GISTs who presented during the study period were identified from our database. All of them were men, reflecting the veteran affairs population. The mean age of patients at presentation was 65.2 years (range, 38-84 years). The Table summarises the clinical features of the study subjects. Almost one-third of our patients (n = 9, 32%) were asymptomatic and their tumours were discovered incidentally during imaging or endoscopy for various indications. When symptomatic, abdominal pain and gastrointestinal haemorrhage were common presenting symptoms.

Radiology Studies

In all, 26 patients underwent the initial abdominal CTs at our hospital, which were available for review; 21 underwent pre- and post-intravenous contrast CTs, and five underwent only post-intravenous contrast CTs. Among these patients, 11 had CT/PET studies prior to any treatment, nine of which were performed at our hospital and available for review; four patients had an ultrasound and one had a magnetic resonance imaging scan of the liver that also showed the primary tumour.

The stomach was the most common site of origin, where 61% (n=17) of the tumours originated, whilst 36% originated in the small bowel (duodenum n = 1, jejunum n = 6, and ileum n = 3) and one originated in the omentum (n = 1). The mean size of these tumours at presentation was 7.5 cm with sizes ranging from 1 to 26 cm. Nine patients had distant metastasis, and the remaining 19 had localised disease. Metastasis was to the liver only in four patients, the peritoneum only in two and to both sites in three.

Eighteen patients underwent surgical resection of the primary tumour; nine had wedge gastric resections, one patient had partial gastrectomy, five had small bowel resections, two had small bowel resections with peritoneal nodule excisions. Another patient had an omental mass resected coupled with a splenectomy and partial pancreatectomy because of direct invasion of these organs by the tumour.

Histopathological grading of the tumours was available for 19 patients, as they had undergone surgical resection or core biopsy before any medical treatment. High-grade malignancy was present in nine patients, and low-grade malignancy in 10. In seven patients, pathological grading was not possible since the initial diagnosis was made by endoscopic or percutaneous ultrasound-

guided fine needle aspiration, and in some of these patients surgical resection was performed after imatinab treatment. In the remaining two patients, surgical resection was performed outside our institution and pathological grading was not available.

Initial CT images of 26 patients included in the study were available, 21 of them being both pre- and post-intravenous contrast. The scans showed predominantly solid soft tissue masses arising from the gastric (Figure 1) or small bowel wall (Figure 2) and were predominantly subserosal (n = 20, 77%) and less commonly submucosal (n = 5, 19%). In one patient, the mass lesion

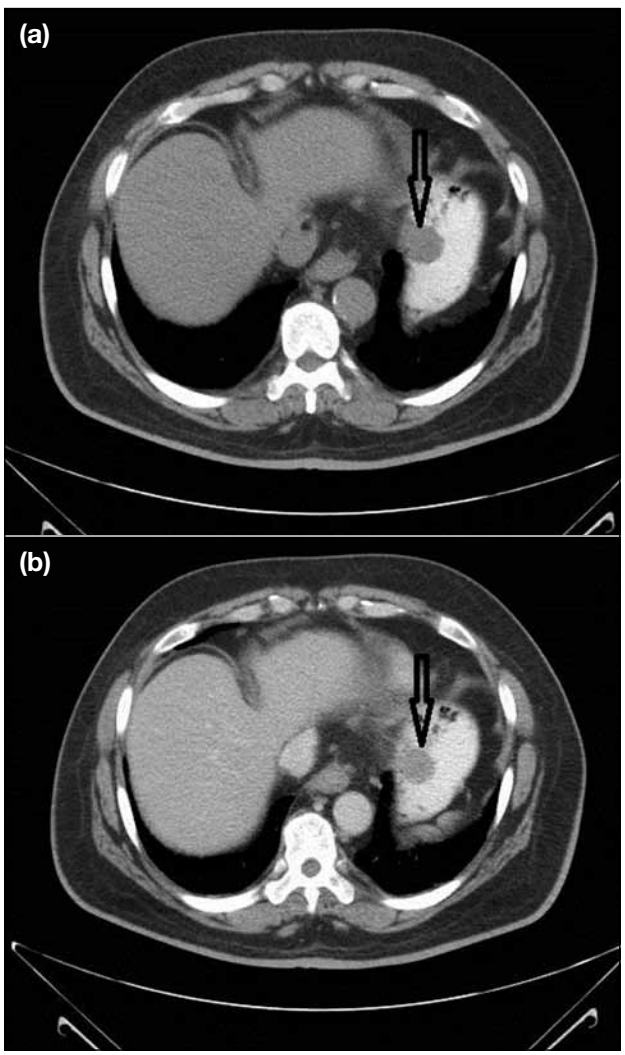

Figure 1. A 66-year-old asymptomatic male patient: (a) non-enhanced axial computed tomographic (CT) image of the upper abdomen shows soft tissue mass lesion (arrow) arising from the gastric wall and growing submucosally into the gastric lumen, and (b) post-contrast CT image shows homogeneous enhancement of the mass (arrow). Endoscopic ultrasound-guided biopsy confirmed pathology of gastrointestinal stromal tumour.

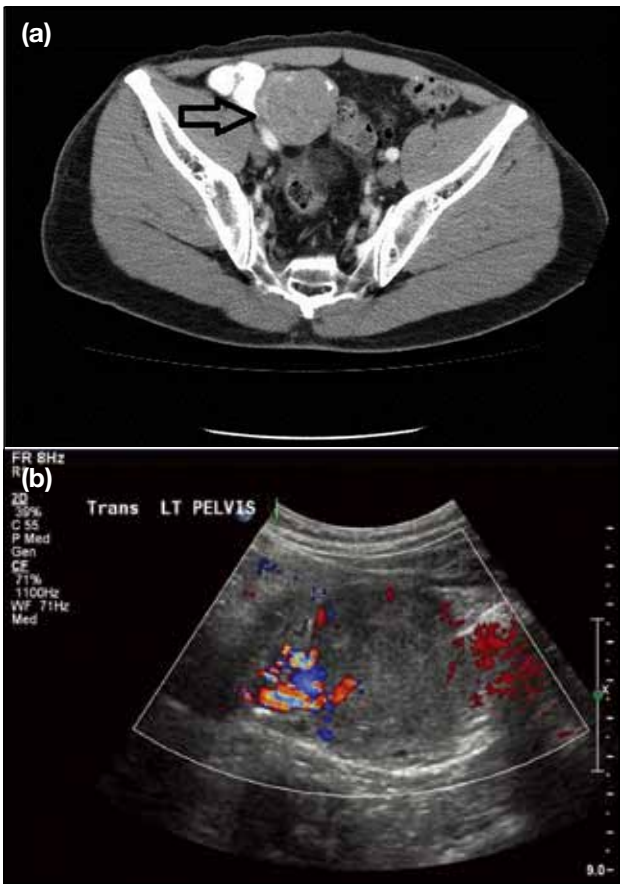

Figure 2. This 70-year-old patient presented with gastrointestinal haemorrhage. (a) Contrast-enhanced abdominal computed tomography demonstrates a hypervascular, homogeneously enhancing soft tissue mass arising from ileal bowel loop (arrow). (b) Abdominal Doppler ultrasound shows a solid, hypervascular, slightly hyperechoic soft tissue mass in the right lower quadrant.

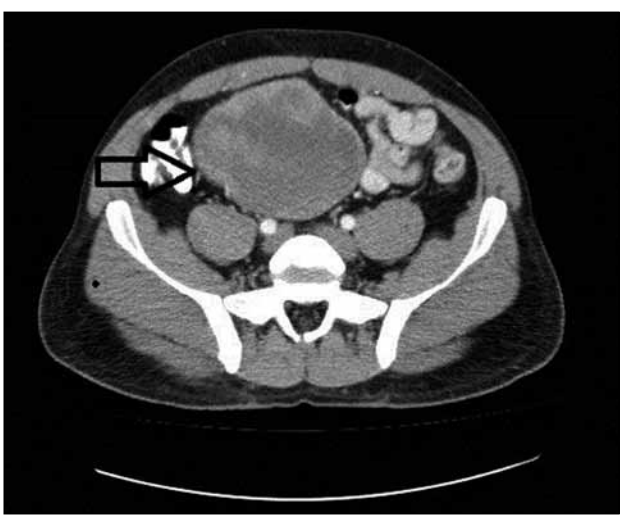

Figure 3. A 38-year-old man with abdominal pain. Physical examination revealed a palpable abdominal mass. Post-contrast computed tomography of the abdomen demonstrates a heterogeneously enhancing soft tissue mass (arrow) arising from the ileum. Surgical excision revealed a low-grade gastrointestinal stromal tumour.

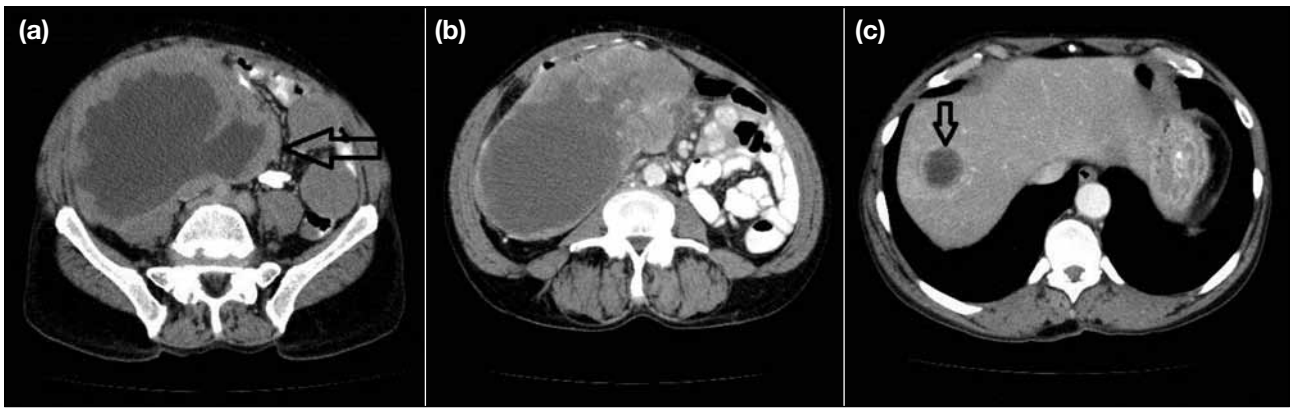

Figure 4. A 59-year-old patient presenting with abdominal pain and weight loss. (a) Non-enhanced computed tomography (CT) of the abdomen shows a large necrotic soft tissue mass (arrow) occupying the right lower quadrant. (b) A post-contrast image shows heterogeneous intense peripheral enhancement with non-enhancing central necrosis. (c) Post-contrast liver CT demonstrates a peripherally enhancing, necrotic soft tissue lesion in the right liver lobe (arrow) consistent with metastasis.

was not related to bowel wall and surgical resection confirmed its omental origin.

The mean density of these tumours was 37 (range, 20-58) HU before administration of intravenous contrast. Calcification was unusual and found in only 8% (2/26) of the patients. All tumours showed significant enhancement on post-contrast CT scans, the mean enhancement being 31 (range, 10-99) HU. Of the 26 patients, 35% of the tumours (n = 9) showed homogeneous enhancement and the rest (n = 17) enhanced heterogeneously (Figure 3). Areas of necrosis (Figure 4), defined as non-enhancing fluid density within the tumour, were seen in almost one-third of the cases (n = 8, 31%).

Presence of metastases was associated with larger primary tumour sizes (mean, 13 cm; 95% confidence interval [CI], 7-19) compared to non-metastasised tumours (mean, 5.1 cm, 95% CI, 3-6). In addition, the presence of necrosis on CT scans was associated with increased risk of metastasis compared to non-necrotic tumours (75% vs. 6%; $p < 0.001$). Heterogeneous enhancement on post-contrast CT scans was also associated with the presence of metastasis (41% vs. 0%; $p = 0.02$). There was no significant association between tumour location, patient age, degree of enhancement, and the presence of metastasis ($p > 0.05$). The presence of necrosis and heterogeneous enhancement could not directly predict the high pathological grade as defined by more than 5 mitoses per 50 HPFs.

Four patients underwent abdominal ultrasonography that showed solid soft tissue masses with variable echogenicity and homogeneity. Doppler ultrasound demonstrated increased tumour vascularity.

Nine patients underwent CT/PET in our department, seven of them showed GIST features (focal area of increased metabolism with SUVs ranging from 2.5-7). Two tumours were metabolically relatively inactive with SUVs of less than 2.5 (Figure 5).

DISCUSSION

GISTs of the gastrointestinal tract are rare. The estimated annual incidence in the USA is approximately 3000 to 6000 cases.[18] Males are more affected than females and the median age at the time of the diagnosis is approximately 60 years.[19] In our study, all the patients were male; a finding also consistent with the fact that the study being performed at a veterans hospital, where the vast majority of the served population was male. The mean age at presentation was 65.2 years in this study, which is close to previously published data.[10]

In our study, the stomach was the most common site of origin (61%) followed by the small bowel in almost one-third of the cases, which was in keeping with previous reports.[3,20] In our study, almost one-third of the patients were asymptomatic and discovered incidentally during imaging or endoscopy for other indications. Most of asymptomatic tumours were of gastric origin. Asymptomatic patients were more common in our study than previously published.[11] When symptomatic, gastrointestinal bleeding and abdominal pain were the most common presenting symptoms.

GISTs have a variable clinical course with a spectrum

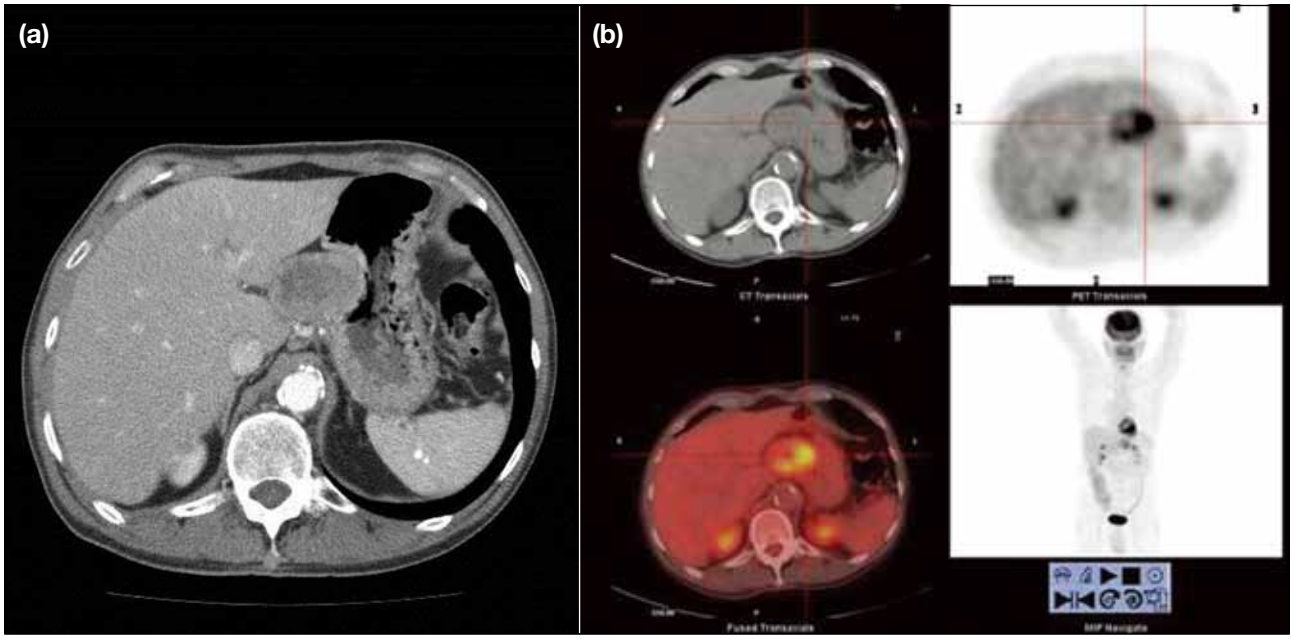

Figure 5. A 73-year-old man presenting with vague epigastric pain. (a) Contrast-enhanced abdominal computed tomography (CT) shows a large solid soft tissue mass arising from the lesser curvature of the stomach with heterogeneous, predominantly peripheral enhancement and central necrosis. (b) CT / positron emission tomography images show a hypermetabolic mass with a maximum standardised uptake value of 5.4.

of aggressiveness ranging from localised benign disease to metastasising malignant lesions. The most reliable established system to predict GIST malignancy takes into account the number of mitoses per 50 HPFs and tumour size.[21,22] Tumours larger than 5 cm in diameter and having >5 mitoses per 50 HPFs tend to metastasise. Tumours less than 2 cm and containing ≤5 mitoses per 50 HPFs tend to remain localised and less likely to develop distant metastasis.[12]

CT is usually the initial imaging modality to evaluate gastrointestinal symptoms related to GISTs. The features of GISTs include appearance of solid soft tissue mass lesions related to the gastric or bowel wall that are mostly extraluminal. Presences of necrosis (heterogeneous enhancement, ulceration) and large tumour size have been described as features suggesting aggressive behaviour.[17,20] Our study also showed that tumour size, heterogeneous enhancement, and the presence of tumour necrosis on CT were independent indicators of possible aggressive tumour behaviour and subsequent development of metastasis. The liver and peritoneum were the most common metastatic sites.

In general, tumour enhancement is partially dependent on the timing of the contrast injection, such that the pattern may differ during the arterial and portovenous phase. Tumour size may also affect the pattern of enhancement and the presence of necrosis. Therefore, a prospective study with a CT protocol that includes both arterial and portovenous phases and analysis of tumour features in both phases is necessary.

CT/PET is currently being utilised to evaluate disease extent of GISTs and follow-up of responses to medical treatment.[23,24] Some studies also suggest a possible correlation between SUVs and tumour pathological risk.[25] Most of the tumours in our series showed increased metabolic activity and SUVs of more than 2.5. Metastatic lesions were also seen as metabolically active soft tissue masses.

A limitation of our study was the small number of patients, partially related to the rarity of this tumour. The study was also performed retrospectively, allowing variation in CT techniques including the amount and timing of contrast injection, both of which could affect tumour appearance on post-contrast images.

CONCLUSION

Imaging, especially CT, plays an important role in the diagnosis of GIST by revealing the typical radiological appearance. CT can also assist in predicting the behaviour and prognosis of these tumours based on

their sizes, degree of heterogeneous enhancement, and features of necrosis — all of which can potentially affect treatment planning.

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