



Fishing boats, Mytho, Mekong Delta, Vietnam. Photograph courtesy of J. Bryan Murphy, MD, Clearwater, Florida.

The imaging features of nonmetastasizing and malignant gastrointestinal stromal tumors are reviewed.

Imaging Gastrointestinal Stromal Tumors

Marla R. Hersh, MD, Junsung Choi, MD, Chris Garrett, MD, and Robert Clark, MD

Background: Because of the recent reclassification of mesenchymal tumors, which was based on a better understanding of the genetics and immunophenotype of gastrointestinal stromal tumors (GISTs), only a limited number of studies have described the radiologic appearance of GISTs.

Methods: This study reviews the imaging characteristics of GISTs, with an emphasis on differentiating benign and malignant tumors using positron emission tomography (PET), computed tomography (CT), and magnetic resonance imaging (MRI). We reviewed the data from 53 cases of GISTs treated at our institute. The imaging studies from these cases, which were recorded at our institute from January 1998 through June 2003, included PET, CT, and MRI.

Results: Of the 53 GIST cases, stomach and small bowel tumors accounted for 80% of the tumors. Malignant lesions were larger and more heterogeneous, had ulcerations, and were PET positive. Peritoneal and liver metastases were most common.

Conclusions: PET, CT, and MRI appear to be useful in differentiating nonmetastasizing from malignant GISTs.

Introduction

Gastrointestinal stromal tumors (GISTs) are rare, accounting for less than 3% of all gastrointestinal neoplasms and less than 6% of all sarcomas.¹⁻³ In the past, mesenchymal

tumors of the gastrointestinal tract were usually classified as leiomyomas or leiomyosarcomas,^{4,5} but growing evidence over the last two decades suggests that GISTs are a unique entity and separate from leiomyomas and leiomyosarcomas. GISTs are now defined as spindle cell, epithelioid, and occasionally pleomorphic mesenchymal tumors of the gastrointestinal tract that express the KIT protein (CD117, stem cell factor receptor) detected at immunohistochemistry.^{6,8} This feature differentiates GISTs from leiomyomas, leiomyosarcomas, schwannomas, and neurofibromas, which do not express the KIT protein.

GISTs can originate in the gastrointestinal tract, mesentery, or omentum.^{1,9} They typically arise in the bowel wall, usually from the muscularis propria. The most common sites of presentation for GISTs are the stomach and small bowel. Most GISTs are benign, but pathologic categorization of malignancy is difficult. The three most

From the Department of Radiology at the H. Lee Moffitt Cancer Center & Research Institute, Tampa, Florida. Dr. Clark is now at Seven Rivers Community Hospital in Florida.

Submitted October 28, 2004; accepted January 14, 2005.

Address correspondence to Marla R. Hersh, MD, Department of Radiology, H. Lee Moffitt Cancer Center & Research Institute, 12902 Magnolia Drive, Tampa, FL 33612-9497. E-mail: hershmr@moffitt.usf.edu

No significant relationship exists between the authors and the companies/organizations whose products or services may be referenced in this article.

Abbreviations used in this paper: GIST = gastrointestinal stromal tumor, CT = computed tomography, MRI = magnetic resonance imaging, PET = positron emission tomography.

important factors in determining malignancy are mitotic rate, tumor size, and site.¹⁰

Because of the recent reclassification of mesenchymal tumors, which was based on a better understanding of the genetics and immunophenotype of GISTs, only a limited number of studies have described the radiologic appearances of GISTs. Horton et al¹¹ reviewed computed tomography (CT) imaging of GISTs, and Hasegawa et al¹² described magnetic resonance imaging (MRI) features of 9 cases. Also, four series have been reported: two single-institution studies from Europe^{13,14} and a collection of cases submitted to the Armed Forces Institute of Pathology in the United States.¹⁵ An additional review from Korea of omental and mesenteric GISTs was completed recently.¹⁶

The purpose of our study was to evaluate our experience involving patients with GISTs who were referred to our tertiary cancer center. We describe the imaging features of GISTs with emphasis on CT, MRI, and positron emission tomography (PET), and we evaluate the patterns of metastatic spread and the usefulness of PET and imaging characteristics to differentiate benign from malignant GISTs.

Materials and Methods

We performed a retrospective review of medical records of all cases at our institute between January 1998 and June 2003 with a histologic diagnosis of GIST. These cases were identified through our cancer registry, which has coded GISTs only since 1998. The registry search was performed according to a research protocol approved by our Institutional Review Board. All cases had a histologically confirmed diagnosis of GIST and were KIT-positive.

Fifty-three patients had a histologic diagnosis of GIST, consisting of 26 men and 27 women with a mean age of 58.4 years (range 26–82 years). We reviewed all of the available imaging studies for the 53 patients. Imaging studies included examinations obtained at our own institute and those from other institutions. For this reason, no standard protocol was used for the images, and both soft-copy PACS (picture archiving and communication system) and digitized images were reviewed. We recorded the site of the primary tumor in all cases by means of pathologic and surgical reports, and we then confirmed the cancer registry data.

CT and MRI findings for the primary tumors were categorized according to previously reported criteria.¹³ We recorded maximum tumor diameter at presentation (measured by CT) and whether the tumor was predominantly exophytic or endoluminal (defined as whether more or less than half of the tumor lay outside the bowel lumen as determined by CT). The tumor margin was categorized as well defined (a smooth or lobular contour without surface projections), irregular (with surface projections), or clearly invasive (soft tissue of similar attenuation to the tumor breached an adjacent organ or tissue). The presence of intratumoral fluid, gas, or calcification was noted, and we

Site of Primary Tumor in Patients With GISTs:
Summary and Comparison of Reports

Primary Site	Current Study (n=53)	Burkill et al ¹³ (n=116)	Levy et al ¹⁵ (n=64)	Total (n=233)
Esophagus	2 (4%)	0	1 (2%)	3 (1%)
Stomach	19 (36%)	43 (37%)	28 (44%)	90 (39%)
Small Bowel	23 (43%)	49 (42%)	27 (42%)	99 (42%)
Colon-Rectum	5 (9%)	13 (11%)	7 (11%)	25 (11%)
Peritoneum	0	0	0	0
Other-unknown	4 (8%)	11 (9%)	1 (2%)	16 (7%)

visually assessed the homogeneity of the tumor and contrast enhancement. We noted evidence of bowel, biliary, or renal obstruction and/or the presence of ascites. Peritoneal metastasis included peritoneal nodules; ascites was evaluated independently.

PET scans performed with intravenous injection of [¹⁸F]-fluoro-2-deoxy-D-glucose ([¹⁸F]FDG) were reviewed and compared to the most recent CT or MRI examinations. PET scans were categorized as [¹⁸F]FDG-avid or [¹⁸F]FDG-negative by visual assessment. Analysis of metastatic patterns included review of all imaging available prior to and following treatment.

Results

The primary tumor locations are summarized in the Table and compared to two recent large series.^{13,15} Stomach and small bowel accounted for more than 80% of the primary sites. Location of the primary tumor could not be determined for 4 tumors because of extensive peritoneal dissemination. These lesions could have been primary to the peritoneum or metastatic with inability to identify the primary organ.

The mean primary tumor size was 14 cm (range 3–26 cm). CT scans prior to therapy were available for review in all 53 cases, MRI scans were available in 19, and PET scans in 8.

Imaging Features

Of the 53 patients who underwent CT at presentation, all primary tumors were predominantly exophytic except for 4 patients in whom the primary tumor could not be categorized because of peritoneal dissemination. The tumor margin was categorized and defined (ie, smooth or lobular) in 40 of 49 cases, irregular in 5 cases, and invasive in 4 cases. No vascular encasement was identified, and no enlarged lymphadenopathy was noted at presentation. Heterogeneity of the primary tumor by CT or MRI was identified in 40 of 49 cases (Fig 1).

Heterogeneous contrast enhancement was identified by CT or MRI in 39 of 49 cases. Areas of nonenhancement (ie, avascular tumor, necrosis, or fluid) were present in 32

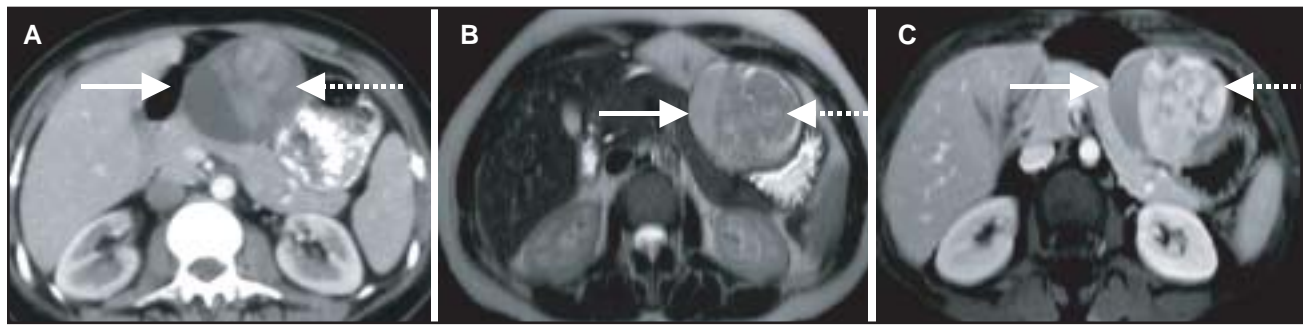


Fig 1A-C. — Gastric GIST. (A) CT demonstrates an exophytic mass with a well-defined margin, heterogeneous contrast enhancement (dotted arrow), and a homogeneous low-density area without enhancement (solid arrow). (B) T2-weighted MRI without contrast enhancement demonstrates an exophytic mass with a well-defined margin, heterogeneous signal in the area of CT contrast enhancement shown in (A) (dotted arrow), and a homogeneous higher signal region (solid arrow). (C) T1-weighted MRI with gadolinium contrast enhancement demonstrates heterogeneous enhancement (dotted arrow), corresponding to the area of CT enhancement shown in (A), and homogeneous low-density region without enhancement (solid arrow), also corresponding to the CT shown in (A).

of 49 tumors (Fig 1), while central gas was seen in 5 (Fig 2) and central calcification in 1 (Fig 3). The 9 homogeneous tumors tended to be smaller than heterogeneous tumors (Figs 4 and 5), with a mean diameter of 7 cm (range 3–12 cm).

PET scans prior to any therapy were [¹⁸F]FDG-negative in 4 cases (Figs 4 and 5) and [¹⁸F]FDG-avid in 4 cases. The 4 negative cases were smaller, homogeneous tumors with a mean diameter of 6 cm (range 3–8 cm), and none showed evidence of metastatic spread. The 4 [¹⁸F]FDG-avid cases were larger, heterogeneous tumors with a mean diameter of 15 cm (range 12–18 cm), and all had evidence of metastatic spread (Fig 6).

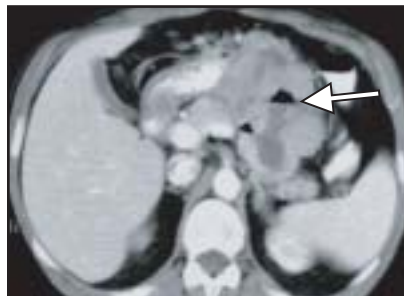


Fig 2. — Small bowel GIST with central gas. CT demonstrates an exophytic mass with an irregular margin, heterogeneous contrast enhancement, and central gas within the tumor with a gas-fluid level (arrow).



Fig 3. — Small bowel GIST with calcifications. CT demonstrates an exophytic mass with an irregular margin, heterogeneous contrast enhancement, and central calcifications (arrow).

Patterns of Metastatic Spread

The mean time of clinical follow-up for the 53 patients was 2.6 years (range 0.5–5.5 years). Eighteen patients had no metastases and were thus considered to have non-metastasized tumors. All of the 9 patients with homogeneous tumors exhibited no metastases. Direct invasion of surrounding tissues or organs occurred in 16 patients at presentation. Tumor spread to regional lymph nodes occurred in 4 patients. Only 1 patient had enlarged nodes (greater than 1 cm short axis) by CT. Distant metastases occurred in 15 patients; sites included liver in 12 patients, peritoneum in 5 patients (Fig 7), lung in 2 patients, and bone in 1 patient. Some patients had multiple sites of spread. Four patients had ascites (Fig 8). No cases of visceral obstruction were identified radiologically, but 1 patient with extensive peritoneal metastases developed bowel obstruction as a terminal event.

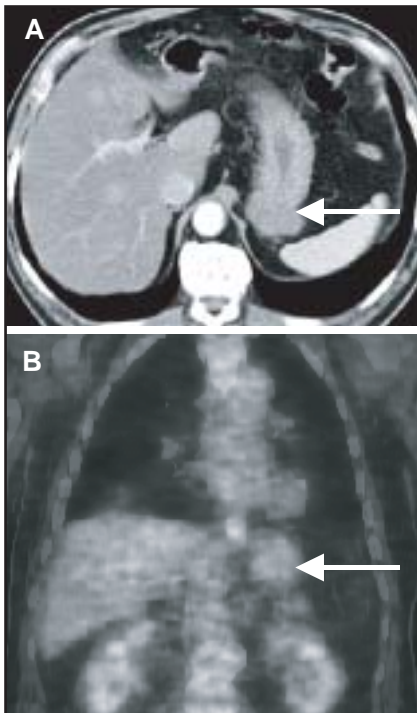


Fig 4A-B. — Gastric GIST with negative PET scan. (A) CT demonstrates an exophytic mass with a well-defined margin (arrow) 5 cm in diameter, with homogeneous contrast enhancement. (B) Coronal CT-PET scan shows no uptake of [¹⁸F]FDG tracer in the gastric GIST (arrow).

Discussion

Our study has several limitations. First, this was a retrospective review of cases collected over 5 years at a single institution. All such studies, including ours, suffer from biases, including referral bias. Since our institute is a tertiary cancer care center, our referral patterns may be biased toward the more aggressive lesions. Referral bias may explain why two thirds of the tumors in our series were malignant and only 34% had no signs of metastases. It may also explain the absence of endoluminal GISTs, which tend to be smaller and nonmetastasizing. Tumors found incidentally are smaller and have a better prognosis than those that cause symptoms. In

one report, asymptomatic tumors found incidentally had a mean diameter of only 1.5 cm.¹⁷ Referral bias may have skewed our series toward more small bowel primary tumors as well, since small bowel GISTs tend to have a more aggressive behavior and a worse prognosis than tumors originating in other gastrointestinal sites.^{6,18} The predominance of large primary tumors in our experience probably reflects this bias toward more malignant GISTs.¹⁹

Second, misclassification of the site of origin is possible with large, malignant GISTs. Unlike most other reports, the small bowel rather than the stomach was the most common primary site in our study; gastric lesions that invade other structures, such as small bowel, could be misclassified. Similarly, the GIST cases with diffuse peritoneal dissemination in our study could have originated from the peritoneum, mesentery, or any other part of the gastrointestinal tract (Fig 8).

Third, we were unable to review a standardized set of imaging examinations in every case. Scans reviewed included those from our own center as well as those from other institutions in which different imaging techniques and different follow-up surveillance periodicity were used. Moreover, we did not always have access to soft-copy scans, with the added benefits of electronic measurement and attenuation assessment. The final limitation of our study is the lack of long-term clinical follow-up in all patients. With longer follow-up, more thorough analysis of metastases and clinical outcomes would be possible. However, most, if not all, of these problems are unavoidable because of the rarity of this type of tumor.

Our experience is similar to that reported elsewhere in several respects. The mean age at presentation in our study was greater than 50 years, similar to other series.^{3,17,19,20} The stomach and small bowel account for the majority of cases of GIST in our series, as in other reports.^{3,13,17,19,20} However, our proportion of patients with distant metastases is less than that reported elsewhere. The incidence of metastases at presentation in the largest clinical series of malignant GISTs approached 50%.³ Bowel, biliary, and renal obstructions are rarely reported, and our series confirms that phenomenon. Likewise, ascites is uncommon.

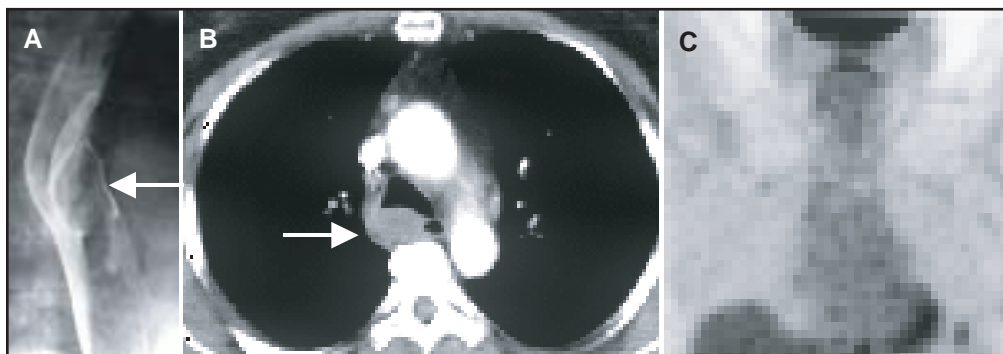


Fig 5A-C. — Esophageal GIST. (A) Air-contrast esophagram shows an intramural lesion (arrow). (B) CT demonstrates an exophytic, well-defined esophageal mass with minimal contrast enhancement (arrow). (C) Coronal PET scan demonstrates no uptake of [¹⁸F]FDG within the mass.

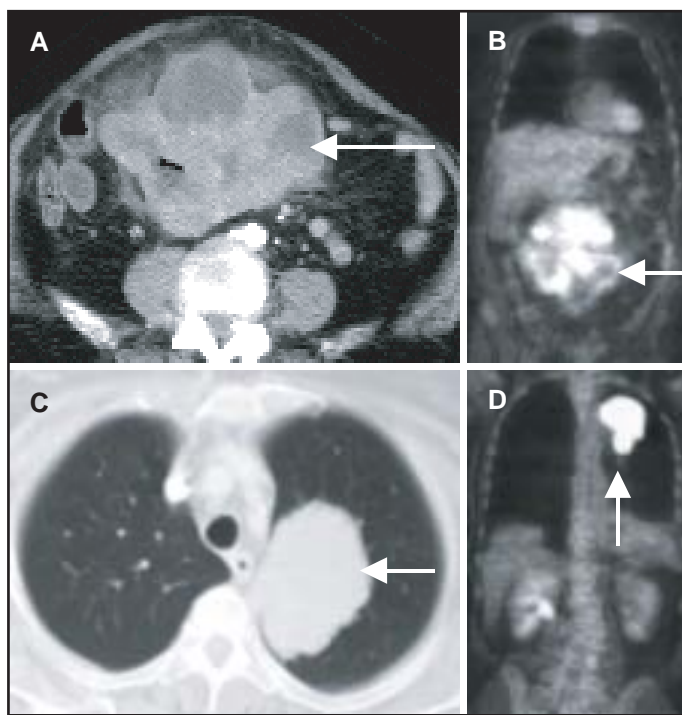


Fig 6A-D. — Small bowel GIST. (A) CT of the abdomen shows a large heterogeneous exophytic mass with central areas of low density and gas (arrow). (B) Coronal CT-PET shows uptake of [¹⁸F]FDG in the abdominal mass (arrow). (C) CT of the thorax shows a large left upper lobe lung metastasis (arrow). (D) Coronal CT-PET shows uptake of [¹⁸F]FDG in the left lung metastasis (arrow).



Fig 7. — Gastric GIST with peritoneal metastasis, 2 years after resection of the primary tumor. CT demonstrates a "drop" metastasis in the pelvic peritoneal cul-de-sac (arrow).



Fig 8. — GIST with diffuse peritoneal dissemination. CT demonstrates multiple peritoneal masses with heterogeneous enhancement and ascites.

The distribution of metastases in our study is similar to that in other reports, with the liver and peritoneum dominating.^{3,13,19} The liver is the most common metastatic site at both presentation and disease relapse.³ Metastases to bone and the lung have been previously described, but they are distinctly uncommon, as was the case in our study.^{3,13} We found only one case of enlarged lymph nodes according to CT criteria in 4 patients with regional lymph node disease. A number of other investigators have reported no metastatic disease to the lymph nodes.^{13,17}

Complete surgical excision of the primary tumor offers the best chance of cure.^{3,17} However, the high rates of local and distant recurrence indicate the need for effective nonsurgical treatment. Until recently, chemotherapy response rates have been disappointing.^{3,21,22} A promising new tyrosine kinase inhibitor, STI-571 (imatinib mesylate; Gleevec), is currently undergoing clinical trials following encouraging initial reports.²³ PET imaging in patients with GISTs undergoing therapy with STI-571 may detect metabolic improvement before morphologic or structural change is apparent. PET imaging may improve the assessment of tumor behavior by highlighting early functional changes in tumor glucose metabolism that appear to correlate closely with metabolic tumor response to STI-571.²⁴ A multicenter phase II clinical trial is currently evaluating the role of PET in assessing tumor response to STI-571 (Neoadjuvant and Adjuvant Imatinib Mesylate in Patients With Primary or Recurrent Potentially Resectable Malignant Gastrointestinal Stromal Tumor — ACRIN-6665)

CT or MRI scans can suggest a diagnosis of GIST by the presence of a large exophytic tumor with heterogeneous contrast enhancement, arising from the stomach or small bowel. Metastases, if present, are usually to the liver or peritoneum. Lymph node enlargement is uncommon.

The differentiation of GISTs from other primary gastrointestinal malignancies can often be made on the basis of these specific findings. Lymphomas tend to be circumferential with homogeneous enhancement and/or lymph node enlargement. Carcinoid tumors are usually found in the distal ileum, or root of the mesentery, and they commonly stimulate a desmoplastic reaction with calcifications. Large carcinomas are more likely to cause visceral obstruction. The diagnoses that are more difficult to differentiate from GISTs are those of other soft tissue tumors, including leiomyoma, leiomyosarcoma, fibrosing mesenteritis, mesenteric lymphangioma, plexiform neurofibromatosis, and malignant tumors of nerve sheath and vascular origin.

Conclusions

Our study showed that malignant lesions enhance heterogeneously, have ulcerations, and tend to be larger (mean 15 cm compared with 7 cm for nonmetastasizing). Direct invasion, peritoneal spread, and metastasis at presentation are also found in malignant tumors. In our preliminary experience

of only 8 cases, PET imaging of malignant GISTs demonstrated uptake of [¹⁸F]FDG, while nonmetastasizing GISTs did not. PET imaging may also detect metabolic improvement early and aid in evaluating response to therapy.

References

1. Licht JD, Weissmann LB, Antman K. Gastrointestinal sarcomas. *Semin Oncol.* 1988;15:181-188.
2. Lewis JJ, Brennan MF. Soft tissue sarcomas. *Curr Probl Surg.* 1996;33:817-872.
3. Dematteo RP, Lewis JJ, Leung D, et al. Two hundred gastrointestinal tumors: recurrence patterns and prognostic factors for survival. *Ann Surg.* 2000;231:51-58.
4. Clark RA, Alexander ES. Computed tomography of gastrointestinal leiomyosarcoma. *Gastrointest Radiol.* 1982;7:127-129.
5. Pannu HK, Hruban RH, Fishman EK. CT of gastric leiomyosarcoma: patterns of involvement. *AJR Am J Roentgenol.* 1999;173:369-373.
6. Miettinen M, Lasota J. Gastrointestinal stromal tumors: definition, clinical, histological, immunohistochemical, and molecular genetic features and differential diagnosis. *Virchows Arch.* 2001;438:1-12.
7. Kindblom LG, Remotti HE, Aldenborg F, et al. Gastrointestinal pacemaker cell tumour (GIPACT): gastrointestinal stromal tumors show phenotypic characteristics of the interstitial cells of Cajal. *Am J Pathol.* 1998;152:1259-1269.
8. Fletcher CD, Berman JJ, Corless C, et al. Diagnosis of gastrointestinal stromal tumors: a consensus approach. *Hum Pathol.* 2002;33:459-465.
9. Miettinen M, Monihan JM, Sarlomo-Rikala M, et al. Gastrointestinal stromal tumors/smooth muscle tumors (GISTs) primary to the omentum and mesentery: clinicopathologic and immunohistochemical study of 26 cases. *Am J Surg Pathol.* 1999;23:1109-1118.
10. Miettinen M, El-Rifai W, Sobin LH, et al. Evaluation of malignancy and prognosis of gastrointestinal stromal tumors: a review. *Hum Pathol.* 2002;33:478-483.
11. Horton KM, Juluru K, Montgomery E, et al. Computed tomography imaging of gastrointestinal stromal tumors with pathology correlation. *J Comput Assist Tomogr.* 2004;28:811-817.
12. Hasegawa S, Semelka RC, Noone TC, et al. Gastric stromal sarcomas: correlation of MR imaging and histopathologic findings in nine patients. *Radiology.* 1998;208:591-595.
13. Burkill GJ, Badran M, Al-Muderis O, et al. Malignant gastrointestinal stromal tumor: distribution, imaging features, and pattern of metastatic spread. *Radiology.* 2003;226:527-532.
14. Ghanem N, Altehoefer C, Furtwangler A, et al. Computed tomography in gastrointestinal stromal tumors. *Eur Radiol.* 2003;13:1669-1678.
15. Levy AD, Remotti HE, Thompson WM, et al. Gastrointestinal stromal tumors: radiologic features with pathologic correlation. *Radiographics.* 2003;23:283-304.
16. Kim HC, Lee JM, Kim SH, et al. Primary gastrointestinal stromal tumors in the omentum and mesentery: CT findings and pathologic correlations. *AJR Am J Roentgenol.* 2004;182:1463-1467.
17. Ludwig DJ, Traverso LW. Gut stromal tumors and their clinical behavior. *Am J Surg.* 1997;173:390-394.
18. Emory TS, Sobin LH, Lukes L, et al. Prognosis of gastrointestinal smooth-muscle (stromal) tumors: dependence on anatomical site. *Am J Surg Pathol.* 1999;23:82-87.
19. Crosby JA, Catton CN, Davis A, et al. Malignant gastrointestinal stromal tumors of the small intestine: a review of 50 cases from a prospective database. *Ann Surg Oncol.* 2001;8:50-59.
20. Pithorecky I, Cheney RT, Kraybill WG, et al. Gastrointestinal stromal tumors: current diagnosis, biologic behavior, and management. *Ann Surg Oncol.* 2000;7:705-712.
21. Edmonson J, Marks R, Buckner J, et al. Contrast of response to D-MAP + sargramostim between patients with advanced malignant gastrointestinal stromal tumors and patients with other advanced leiomyosarcomas. *Proc Annu Meet Am Soc Clin Oncol.* 1999;18:541A. Abstract.
22. Plaat BE, Hollema H, Molenaar WM, et al. Soft tissue leiomyosarcomas and malignant gastrointestinal stromal tumors: differences in clinical outcome and expression of multidrug resistance proteins. *J Clin Oncol.* 2000;18:3211-3220.
23. Van Oosterom AT, Judson I, Verweij J, et al. Safety and efficacy of imatinib (STI571) in metastatic gastrointestinal stromal tumours: a phase I study. *Lancet.* 2001;358:1421-1423.
24. Van den Abbeele AD, Badawi RD. Use of positron emission tomography in oncology and its potential role to assess response to imatinib mesylate therapy in gastrointestinal stromal tumors (GISTs). *Eur J Cancer.* 2002;38(suppl 5):S60-S65.
25. Jager PL, Gieterma JA, van der Graaf WT. Imatinib mesylate for the treatment of gastrointestinal stromal tumours: best monitored with FDG PET. *Nucl Med Commun.* 2004;25:433-438.
26. Goerres GW, Stupp R, Barghouth G. The value of PET, CT and in-line PET/CT in patients with gastrointestinal stromal tumours: long term outcome of treatment with imatinib mesylate. *Eur J Nucl Med Mol Imaging.* 2005;32:153-162.