

Pediatric Gastrointestinal Stromal Tumors and Leiomyosarcoma

The St. Jude Children's Research Hospital Experience and a Review of the Literature

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BACKGROUND. With the introduction of molecularly targeted therapy for gastrointestinal stromal tumors (GISTs), it became important to distinguish GISTs from leiomyosarcomas (LMSs). The authors sought to characterize the clinicopathologic features of these tumors in pediatric patients.

METHODS. The authors reviewed the medical records of 11 patients for whom GIST or LMS was diagnosed between March 1962 and July 2002 at St. Jude Children's Research Hospital and reclassified the tumors according to current histologic and immunophenotypic criteria. The authors also reviewed the literature pertaining to pediatric GISTs and LMSs.

RESULTS. Seven patients had GISTs, and four had LMS. The median age of the patients at diagnosis was 11.5 years. At diagnosis, metastases were present in one patient with GISTs and in another with LMS. Unlike the focal distribution of CD117 (KIT) in LMS, diffuse and strong immunostaining was observed in GISTs. Only GISTs expressed CD34. Six patients underwent complete resection (four with GISTs and two with LMS), four patients underwent incomplete resection (three with GISTs and one with LMS), and one patient (with LMS) underwent a biopsy only. Radiotherapy or chemotherapy was used to treat one patient with GISTs and three patients with LMS. One patient with a high-risk GIST (largest dimension of 32 cm and high mitotic count) was treated with adjuvant imatinib mesylate outside the preferred setting of a clinical trial, due to concerns regarding the high risk of tumor recurrence. Four patients with GISTs and two with LMS survived disease-free a median of 10.4 years and 4.3 years after diagnosis, respectively. Tumors in all but one survivor were completely resected.

CONCLUSIONS. KIT staining helped to distinguish GISTs from LMSs. Surgery was the treatment of choice for both entities, and tumor resectability was a key prognostic factor. *Cancer* 2004;101:39-50. © 2004 American Cancer Society.

KEYWORDS: children, *c-kit*, gastrointestinal stromal tumors, gastrointestinal autonomic nerve tumors, imatinib mesylate, KIT, leiomyosarcoma.

Until recently, gastrointestinal stromal tumors (GISTs) were regarded as smooth muscle neoplasms and were categorized as leiomyosarcomas (LMSs), leiomyomas, or leiomyoblastomas.¹ In 1983, Mazur and Clark proposed the term *stromal tumors* to describe the group of mesenchymal neoplasms that lacked ultrastructural and immunophenotypic features of smooth muscle differentiation.² These same authors, along with many others, recognized that at least some stromal tumors of the gastrointestinal (GI) tract expressed neural crest antigens such as S-100 protein and neuron-specific enolase.³ In 1984, Herrera et al.⁴ introduced the term *plexosarcoma* to denote tumors that exhibited clear ultrastructural evidence of autonomic

neuronal differentiation. This subset of GISTs subsequently became better known as the *gastrointestinal autonomic nerve tumors (GANTs)*.⁵ After considerable confusion regarding the histogenesis of GISTs in the early 1990s, it is now recognized that GIST cells exhibit characteristics similar to those of the interstitial cells of Cajal (ICC), the 'pacemaker cells' of the GI tract.^{1,6} ICC and GIST cells express the receptor tyrosine kinase KIT. Therefore, the immunohistochemical marker for KIT (CD117) is now used by pathologists to distinguish GISTs from LMSs and other spindle cell tumors of the GI tract.^{6,7} KIT overexpression due to activating mutations appears to drive the neoplastic growth of GISTs.^{8,9} The recent introduction of the receptor tyrosine kinase inhibitor imatinib mesylate (Gleevec, formerly known as STI-571; Novartis, Basel, Switzerland) provided the first effective treatment for patients with recurrent or metastatic GISTs.^{10,11} As a consequence, the distinction between GISTs and other spindle cell tumors has become crucial in selecting the appropriate therapy.

GISTs occur predominantly in middle-aged or older persons and are uncommon in children.¹² LMS is a malignant smooth muscle tumor that accounts for 7–11% of soft tissue sarcomas in adults^{13,14} and 2–4% of soft tissue sarcomas in children.^{15–17} GISTs and LMS in pediatric patients have not been well described. Available information regarding GISTs is obtained primarily from case reports.^{5,18–29} We reviewed the St. Jude Children's Research Hospital (Memphis, TN) experience over a 40-year period in which 11 pediatric patients were treated for GISTs or LMS, and we reclassified these patients' tumors according to the current histologic and immunophenotypic criteria.^{3,30,31} We determined that 7 of the 11 patients had GISTs and that 4 had LMS. In the current study, we describe the clinicopathologic features of the tumors found in these 11 patients and present a review of the literature pertaining to pediatric GISTs and LMSs.

MATERIALS AND METHODS

We searched the solid tumor database at St. Jude for all patients who had an original diagnosis of LMS, GIST, leiomyoma, or leiomyoblastoma and who were treated between March 1962 and July 2002. No patients with leiomyoma or leiomyoblastoma were identified. Information regarding the clinical characteristics, treatment, and outcome of the 11 patients with LMS or GIST was collected by review of their medical records. For all patients, pathologic material was reviewed by a single author (J.J.J.) to determine histologic diagnosis, tumor grade (for LMS), risk of aggressive behavior (for GIST), and surgical resection margins. Tumors were classified as either GISTs or

LMSs on the basis of current histologic and immunophenotypic criteria.^{3,30,31} We defined LMSs as tumors with typical features of smooth muscle differentiation (i.e., interlacing bundles of packed spindle cells with abundant eosinophilic cytoplasm, frequent paranuclear vacuoles, and a centrally located cigar-shaped or blunt-ended nucleus) and α -smooth muscle actin (A-SMA) or muscle-specific actin expression that was detected by immunohistochemical staining.^{30,31} Tumors located in the GI tract that exhibited a remarkably uniform appearance falling into 1 of 3 categories: 1) spindle cell type, 2) epithelioid type, or 3) mixed type, were classified as GISTs. This diagnosis was supported by unequivocal, diffuse, and strong cytoplasmic CD117 staining for all patients who had pathologic material available for immunohistochemical analysis.³ Tumors that fulfilled the histologic and immunophenotypic criteria for GISTs but were located outside the GI tract were identified as *extra-GISTs*. Immunohistochemical studies of available formalin-fixed, paraffin-embedded tissue sections were conducted using the avidin-biotin complex method. Commercially available antibodies that were used were specific for CD117 (KIT; polyclonal antibody diluted 1:300; Dako, Carpinteria, CA); CD34 (monoclonal antibody [MoAb] diluted 1:400; Dako); muscle-specific actin (Enzo Diagnostics, Farmingdale, NY); and A-SMA (MoAb diluted 1:28,000; Sigma, St. Louis, MO). Immunocytochemical staining was classified as strong (+++), moderate (++), weak (+), or negative; cytoplasmic (C) or membranous (M); and diffuse or focal. A rabbit or mouse universal negative control MoAb was used as the negative control for each specific antibody. The mitotic activity of GIST cells was expressed as the number of mitotic figures per 50 high-power fields (HPF; $\times 40$ objective and $\times 10$ ocular). The mitotic activity of LMS cells was defined as the number of mitotic figures per 10 HPF.

The histologic grade of LMS was determined using the Pediatric Oncology Group (POG) grading system,³² which takes into account the mitotic activity of tumor cells and the extent of necrosis. The risk of aggressive behavior by GISTs was assessed using the criteria derived from the GIST workshop convened by the National Institutes of Health (NIH) in April 2001.^{3,12} In that workshop, it was recommended that GISTs not be categorized according to tumor grade, but rather according to their risk of aggressive behavior. The categories used were *very low risk*, *low risk*, *intermediate risk*, and *high risk*, and these categories were based on tumor size and mitotic count.³

To determine patients' clinical groups, we used the surgicopathologic staging system developed by the Intergroup Rhabdomyosarcoma Study Group.³³ The categories were as follows: Group I, completely re-

TABLE 1
Clinical Features, Treatment, and Outcome Data for 11 Pediatric Patients with GISTs or LMS

Patient no. (yr of diagnosis)	Age (yrs)	Gender	Primary site	Clinical group	TNM status	Surgical resection	Primary therapy	Site of recurrence or progression (time in mos ^a)	Outcome (time in yrs ^a)
GIST									
1 (1981)	17.2	F	Abdominal wall	IV	T2bN0M1	Incomplete (macroscopic residual)	None	LDP (7)	DOD (2.2)
2 (1982)	5.3	F	Colon	I	T1aN0M0	Complete	None	None	NED (9)
3 (1983)	4.3	M	Small intestine	II	T1bN0M0	Incomplete (microscopic residual)	None	Local recurrence (6)	DOD (1.2)
4 (1985)	0.25	F	Small intestine	I	T1bN0M0	Complete	None	Liver (16)	Died ^b (1.6)
5 (1987)	10.2	M	Colon	II	T2bN0M0	Incomplete (microscopic residual)	RT to whole abdomen and pelvis (5990 cGy)	None	NED (11.8)
6 (1989)	11.5	F	Stomach	I	T1bN0M0	Complete	None	Local recurrence (45)	NED (12.7)
7 (2002)	15	M	Stomach	I	T2bN0M0	Complete	Imatinib mesylate	None	NED (1.3)
LMS									
8 (1980)	15.5	M	Retroperitoneum	IV	T2bN0M1	Biopsy	CVAD; DTIC + D	LDP (9)	DOD (1.2)
9 (1989)	9.3	F	Face	II	T2aN0M0	Incomplete (microscopic residual)	VCAD	Lung (3)	DOD (0.75)
10 (1998)	19.8	F	Uterus	I	T2aN0M0	Complete	None	None	NED (4.4)
11 (1998)	14.8	F	Thigh	I	T1bN0M0	Primary reexcision	Brachytherapy with ¹²⁵ I (4480 cGy)	None	NED (4.2)

GIST: gastrointestinal stromal tumor; LMS: leiomyosarcoma; F: female; M: male; A: actinomycin D; C: cyclophosphamide; D: doxorubicin; DTIC: dacarbazine; V: vincristine; DOD: died of disease; LDP: local disease progression; NED: no evidence of disease; RT: radiotherapy; cGy: centigrays.

^a Measured from the time of diagnosis.

^b Died of surgical complications.

sected tumors; Group II, macroscopically resected tumors with microscopic residual disease at the primary site; Group III, macroscopic residual disease; and Group IV, distant metastases. Disease stage was categorized according to the TNM system of the International Union Against Cancer.³⁴ The information required for this classification included tumor size, lymph node involvement, and the degree of tumor invasiveness. T1 lesions were confined to the organ or tissue of origin and T2 lesions had invaded contiguous organ(s) or tissue(s). Both categories consisted of 2 subcategories that were based on the maximum tumor diameter: subcategory 'a' (≤ 5 cm) and subcategory 'b' (> 5 cm). Lymph node involvement conferred a designation of N1 (no lymph node involvement = N0), and distant metastases at the time of diagnosis conferred a designation of M1 (no metastases = M0).

Surgical procedures were defined as *biopsy*, if an incisional biopsy was performed; *incomplete resection*, if macroscopic or microscopic residual tumor was present after the surgical procedure; or *complete resection*, if surgical margins were free of tumor. Complete resection of GI tumors included resection of the mesentery. Primary reexcision was a repeat surgical procedure performed to achieve surgical margins that were free of tumor.

RESULTS

Patient Characteristics

Of the 276 children with nonrhabdomyosarcomatous soft tissue sarcoma treated at St. Jude Children's Research Hospital during a 40-year period, 7 (2.5%) had GISTs, and 4 (1.4%) had LMS (Table 1). In one patient (Patient 10), LMS was a secondary malignancy that was diagnosed 18 years after a sacrococcygeal germ cell tumor had been treated successfully with chemotherapy and pelvic radiotherapy (5049 centigrays [cGy]).

The median age of the 11 patients was 11.5 years (range, 3 months–19.8 years). Seven patients were female, and nine were white. Six GISTs originated in the GI tract, including the stomach ($n = 2$), small bowel ($n = 2$), and colon ($n = 2$). In patients with GISTs of the GI tract, the most common presenting signs and symptoms included the presence of an abdominal mass ($n = 4$), abdominal pain ($n = 4$), and abdominal distention ($n = 3$). It is noteworthy that one patient had a tumor that fulfilled the histologic and immunophenotypic criteria for GISTs but arose in soft tissue outside the GI tract (extra – GIST). This patient (Patient 1) had an abdominal wall tumor and presented with a 6-month history of abdominal pain, weight loss,

TABLE 2
Tumor Size and Histologic and Immunohistochemical Features of GISTs or LMS in 11 Pediatric Patients

Patient no.	Diagnosis	Tumor size (cm)	Histopathologic features	No. of mitotic figures	Extent of necrosis	Immunohistochemical findings			
						CD117 (KIT)	CD34	Actin	A-SMA
1	Extra-GIST	> 5	Spindle	60 (per 50 HPF)	Minimal, focal	+++/C, M/diffuse	+++/C, M/diffuse	+/C/focal	Neg
2	GIST	< 5	Spindle and epithelioid	250 (per 50 HPF)	Minimal	NA	NA	NA	NA
3	GIST	15 × 16 × 12	Spindle	115 (per 50 HPF)	Extensive	NA	NA	NA	NA
4	GIST	4 × 5 × 6	Spindle	155 (per 50 HPF)	Multiple small foci	+++/C/diffuse	++/C/diffuse	Neg	+--+/C/focal
5	GIST	15 × 9 × 10	Spindle	5 (per 50 HPF)	Extensive	NA	NA	NA	NA
6	GIST	5.5 × 2.5	Epithelioid	25 (per 50 HPF)	None	+++/C, M/diffuse	+++/C/focal	Neg	Neg
7	GIST	32 × 24 × 15	Spindle	250 (per 50 HPF)	Extensive	+++/C/diffuse	+++/C/diffuse	NA	+/C/focal
8	LMS	15 × 13 × 5	Spindle and epithelioid	2 (80 in recurrent tumor) (per 10 HPF)	Minimal, focal (many stellate zones in recurrent tumor)	++/C/focal	Neg	+++/C/focal	+++/C/focal
9	LMS	3 × 2	Spindle and epithelioid	11 (per 10 HPF)	Rare, focal	+++/C/focal ^a	Neg	+++/C/focal	Neg
10	LMS	3.8 × 3.8 × 3.8	Spindle and epithelioid	20 (per 10 HPF)	Minimal, focal	+----/C/focal	Neg	+----/C, M/focal	+++/C, M/diffuse
11	LMS	8 × 8 × 5	Spindle	7 (per 10 HPF)	None	NA	NA	+----+/C	Neg

GIST: gastrointestinal stromal tumor; LMS: leiomyosarcoma; +: weak intensity; ++: moderate intensity; +++: strong intensity; A-SMA: α -smooth muscle actin; C: cytoplasmic; HPF: high-power field; Neg: negative; NA: not available; M: membranous.

^a Primarily in the spindle cell component.

and nausea. The median duration of symptoms before diagnosis of GISTs for these 7 patients was 1 month (range, 2 weeks–6 months). Four patients with GISTs had clinical Group I disease, two had Group II disease, and one had Group IV disease with peritoneal metastases.

LMS locations included the retroperitoneum, face, uterus, and thigh. Patient 8 presented with a retroperitoneal mass and a 6-week history of abdominal pain, tenesmus, constipation, fever, and weight loss. Patient 9, whose tumor was located in the face, presented with a 2-day history of tooth loosening and facial swelling. Patient 10 had a 5-week history of hematuria, and Patient 11 had a 2-month history of limping at initial presentation. Two patients with LMS had clinical Group I disease, one patient had Group II disease, and one patient had Group IV disease with omental and peritoneal metastases.

Tumor Characteristics

The median greatest dimension of the GIST among 5 of the 7 patients was 15 cm (range, 5.5–32 cm; Table 2).

For the remaining 2 patients with GISTs (Patients 1 and 2), tumor size was documented only as < 5 cm or > 5 cm. Histologic analyses showed that five GIST specimens were of the spindle cell type, one was of the epithelioid type, and another was of the mixed cell type. On the basis of the risk assessment criteria,³ we concluded that all GISTs as well as the extra-GIST fell into the *high risk of aggressive behavior* category, because the largest dimensions of these tumors were > 10 cm and/or the mitotic counts were > 10 mitotic figures per 50 HPF. Immunohistochemical analysis detected CD117 (KIT) in all four GIST specimens evaluated. A pattern of diffuse and strong cytoplasmic staining was observed in most tumor cells. CD34 reactivity was observed in the four tumor specimens analyzed, and focal reactivity of A-SMA was observed in two tumor specimens. Actin staining was weak and focally positive in only one of three tested GIST specimens.

The median maximum dimension of LMS was 5.9 cm (range, 3–15 cm; Table 2). Peritoneal seeding was observed in one patient at presentation (Patient 8).

Microscopy showed that the tumors consisted of spindle cells alone or mixed spindle and epithelioid components. Mitotic activity ranged from 2 to 20 mitotic figures per 10 HPF at initial diagnosis. Using the POG grading system, we determined that all LMSs were Grade III lesions. Immunohistochemical analysis revealed actin positivity in all four tumor specimens, two of which also exhibited strong reactivity for A-SMA. Each of the three tested LMSs exhibited only focal positivity for KIT, and all three were negative for CD34 staining.

Therapy and Outcome

Therapy and outcome data for the 11 patients in the current study are summarized in Table 1. GISTs/extra-GISTs were completely resected in four of seven patients and incompletely resected in two (both had microscopic residual disease). Macroscopic residual disease due to peritoneal metastasis was present in one patient after resection.

Three of the four patients with clinical Group I disease were treated with surgery alone. Two of these three patients (Patients 4 and 6) experienced tumor recurrence. Patient 4, whose primary tumor was located in the small intestines, experienced tumor recurrence in the liver and died of postoperative complications after partial hepatectomy. Patient 6, whose tumor recurred at the primary site (stomach), underwent a total gastrectomy and received adjuvant chemotherapy (vincristine, ifosfamide, doxorubicin, and etoposide). At the time of the current report, this patient was alive and free of disease 12.7 years after the initial diagnosis. One patient with clinical Group I disease (Patient 7) was considered to have a high risk of tumor recurrence because of the large size of the tumor (32 cm × 20 cm × 10 cm) and its high mitotic count. After complete tumor resection, this patient received adjuvant therapy with imatinib mesylate and is alive and free of disease 1.3 years after surgery. It is important to note that there is no evidence in the literature to support the use of adjuvant imatinib mesylate. Therefore, this form of treatment should be used in the context of a clinical trial. Although no clinical trials of adjuvant therapy were available for pediatric patients with GISTs, the treating oncologist elected to offer adjuvant therapy due to concerns regarding the high risk of tumor recurrence. Two children with GISTs had Group II disease. One child (Patient 3) who underwent an incomplete resection and who received no further therapy experienced local tumor recurrence 6 months after diagnosis and died 14 months after initial diagnosis, despite re-resection and salvage chemotherapy. Patient 5 received radiotherapy to the whole abdomen and pelvis (5990 cGy)

and was alive and free of disease 11.8 years after diagnosis. Radiation-induced enteritis that required resection of a large portion of this patients' small intestines eventually developed, and he consequently experienced severe malabsorption due to short-bowel syndrome.

Patient 1, who had Group IV disease, underwent incomplete resection as a result of peritoneal seeding. The family declined chemotherapy, and the patient died of local disease progression 2.2 years after diagnosis. Imatinib mesylate, which was approved by the U.S. Food and Drug Administration in October 2002 for the treatment of metastatic and/or unresectable GISTs, was not available at the time that Patients 1, 3, and 5 were treated.¹¹

Four of the 7 patients with GISTs were alive and free of disease a median of 10.4 years (range, 1.3–12.7 years) after diagnosis. Three of these four patients did not experience treatment failure, and one was treated successfully after disease recurrence. Three patients died after progressive or recurrent disease a median of 1.6 years after diagnosis.

Two of the 4 patients with LMS were alive > 4 years after diagnosis. Patient 10 received a complete resection of a uterine LMS, and Patient 11 underwent primary reexcision of a thigh mass followed by brachytherapy with ¹²⁵I (4480 cGy).

At initial presentation, Patient 8 had extensive retroperitoneal disease and metastases to the omentum and abdominal wall. This patient underwent biopsy followed by multiagent chemotherapy and died of progressive disease. Patient 9, whose tumor originated in the face, underwent incomplete resection and subsequently was treated with multiagent chemotherapy. Metastatic lung disease developed 3 months after diagnosis, and the patient died despite undergoing thoracotomy, chemotherapy, and radiotherapy.

Tumor resectability had a notable association with survival. Three of the four patients with GISTs and both patients with LMS who underwent complete resection survived, whereas only one of the three patients with GISTs and none of the patients with LMS who underwent incomplete resection or biopsy survived. Radiotherapy may have contributed to the long-term survival of Patient 5, who had microscopic residual disease.

DISCUSSION

To our knowledge, the current review is the first in the English-language biomedical literature to report the characteristics of GISTs occurring in pediatric patients and to differentiate such tumors from true LMSs.

TABLE 3
Cases of Pediatric GIST Reported in the Literature

Reference	Patient age (yrs)	Patient gender	Original diagnosis	Primary tumor site (metastatic site)	Morphology	KIT staining	CD34 staining	Treatment	Outcome (time ^a)
Walker and Dvorak 1986 ⁵	16	M	GANT (Carney triad)	Stomach	Spindle	ND	ND	CR	NED (9 mos)
Tortella et al., 1987 ²⁰	16	M	GANT (Carney triad)	Stomach	Spindle	ND	ND	CR	NED ^b
Perez-Atayde et al., 1993 ¹⁸	16	F	GANT (Carney triad)	Multicentric; stomach and duodenum	Spindle and epithelioid	ND	ND	CR	NED (2.5 yrs)
Lauwers et al., 1993 ²²	10	F	GANT	Stomach	N/A	ND	ND	Surgery ^c + chemotherapy	NED (1.3 yrs)
Kodet et al., 1994 ²³	15	F	GANT	Stomach (liver)	Spindle and epithelioid	ND	ND	IR + chemotherapy	AWD (10 mos)
Wu et al., 1999 ²⁶	1 day	M	GIPACT	Jejunum	Spindle	Pos	Pos	CR	NED (12 mos)
Kerr et al., 1999 ²⁴	10	F	GANT	Stomach	Spindle and epithelioid	ND	Pos	CR	NED (8.7 yrs)
Kerr et al., 1999 ²⁴	11	F	GANT	Stomach (LN)	Spindle and epithelioid	ND	Pos	CR	NED (19 mos)
Kerr et al., 1999 ²⁴	13	F	GANT	Stomach	Spindle and epithelioid	ND	Pos	Primary reexcision	NED (8 mos)
Kerr et al., 1999 ²⁴	16	F	GANT	Stomach	Spindle and epithelioid	ND	Pos	Primary reexcision	NED ^d (9 yrs)
Terada et al., 2000 ²⁷	4	F	GIST	Colon	Spindle and epithelioid	Neg	Pos	CR	NED (12 mos)
Varan et al., 2000 ²⁵	45 days	F	GANT	Colon	Spindle and epithelioid	ND	ND	CR	NED (8 mos)
Bates et al., 2000 ²¹	14 days	F	GIST	Jejunum	Spindle and epithelioid	Neg	Neg	CR	NED (12 mos)
Shenoy et al., 2000 ²⁸	1 day	M	GIST	Ileum	Spindle	ND	Pos	CR	NED (12 mos)
Johnston et al., 2001 ²⁹	17	F	GIST	Multicentric; stomach and retroperitoneum	NA	Pos	Pos	Chemotherapy (no response) followed by CR	NED (13 mos)
Li et al., 2002 ¹⁹	12	F	GIST	Stomach (liver)	Epithelioid	Pos	Pos	CR	NED ^b

AWD: alive with disease; CR: complete resection; GANT: gastrointestinal autonomic nerve tumor; GIPACT: gastrointestinal pacemaker cell tumor; GIST: gastrointestinal stromal tumor; IR: incomplete resection; LN: lymph nodes; NA: not available; ND: not done; NED: no evidence of disease; Neg: negative; Pos: positive.

^a Time from resection or diagnosis (as specified in the original report).

^b Length of follow-up not specified.

^c Type of surgery not specified.

^d Local and lymph node recurrences at 3 years and 5 years, respectively.

GISTs

The prevalence of GISTs in the pediatric population is unknown. A search of the English-language biomedical literature revealed published reports of only 16 cases of GISTs, GANTs, or GI pacemaker cell tumors in children (Table 3).^{5,18-29} In the current series, GISTs accounted for 2.5% of nonrhabdomyosarcomatous soft tissue sarcomas treated at St. Jude in the past 40 years. Whereas GISTs are distributed equally among adults of either gender,³⁵ 4 of 7 patients in the current study and 12 of the 16 pediatric patients described in the literature were female. Three reports described GISTs in the context of the Carney triad, which is typically found in young females and is characterized by the unlikely occurrence of two or three of the following rare neoplasms: gastric epithelioid tumor (a GIST), pulmonary chondroma, and extraadrenal paraganglioma.¹⁸ No patient in the current study had a GIST as part of the Carney triad.²⁰

In the current series, the six GISTs that originated

in the GI tract were distributed equally among the stomach, small bowel, and colon. This distribution differs somewhat from the one described in the literature for pediatric patients. In literature reports, most tumors were located in the stomach (11 of 16), whereas only a few patients had tumors that were present in the small bowel (3 of 16) or colon (2 of 16). In adults, GISTs also reportedly occur most frequently in the stomach (50–60% of lesions) and less frequently in the small bowel (20–30%), large intestine (10%), and esophagus (5%).³ The most common symptoms for patients in the current study were abdominal masses and pain; these findings are similar to what is described in the pediatric case reports. One of the seven patients with GISTs in the current study presented with metastatic disease (to the peritoneum), and another patient had a tumor that metastasized to the liver after complete resection. Metastases in the liver or lymph nodes were present at diagnosis in 3 of the 16 pediatric patients described in the literature,

and multicentric lesions were observed at initial presentation in 2 others. Fifteen to 50% of adult patients present with overt metastatic disease,³⁶ and the most common sites of metastasis are the peritoneum and the liver. Regional lymph node metastases are extremely rare.³⁵

As was noted in patients in the current study, GISTs characteristically stain strongly for the CD117 antigen, an epitope of the receptor tyrosine kinase KIT. KIT typically is found throughout the entire tumor, with staining observed most commonly in the cytoplasm. Smooth muscle neoplasms (e.g., leiomyoma and LMS), neurogenic tumors (schwannomas), and desmoid fibromatoses typically do not exhibit positive expression of CD117. Cells from the four analyzed GIST specimens in the current study expressed CD34, a sialylated transmembrane glycoprotein also found on hematopoietic progenitor cells and endothelial cells. In adults, 60–70% of GISTs are reportedly positive for CD34.³ A pattern of focal staining for A-SMA was found in two of four specimens in the current study. In adults, \leq 40% of GIST specimens stain positively for A-SMA. GIST specimens rarely express desmin, an intermediate filament protein typical of muscle, or S100, a neural (Schwann) cell marker. Therefore, strong KIT expression in the absence of smooth muscle differentiation-related proteins is characteristic of GISTs. These features aid in distinguishing between GISTs and most other types of GI mesenchymal tumors.^{3,35} Of the five pediatric cases for which results of CD117 immunohistochemical analysis were reported, three cases involved tumors that were positive for KIT, whereas two involved tumors that were negative for KIT. Tumors in 9 of the 10 reported cases for which CD34 immunohistochemical analysis was conducted expressed CD34.

The most intriguing finding in the current study was the observation of a lesion that was located outside the GI tract but fulfilled the histologic and immunohistochemical criteria for classification as a GIST. Other authors have reported lesions that are identical to GISTs but occur in extra-GI locations, primarily the mesentery, omentum, and retroperitoneum.^{37,38} The observation of KIT expression in these lesions has helped to confirm the existence of extra-GISTs, particularly in exceptional sites, such as the gallbladder³⁹ and bladder.⁴⁰ It is unclear whether these lesions are identical to GISTs found in the GI tract or whether they represent a different class of mesenchymal tumors that also express KIT.

Traditionally, the three key prognostic factors for patients with GISTs have been mitotic activity, tumor size, and tumor site. The criteria proposed by participants in the GIST workshop held in April 2001 at the

NIH define tumors with a high risk of aggressive behavior as measuring > 5 cm and having a mitotic count > 5 per 50 HPF, measuring > 10 cm (irrespective of mitotic count), or having a mitotic count > 10 per 50 HPF (irrespective of size).^{3,12} On the basis of these criteria, we conclude that all GISTs and extra-GISTs in the current study and 7 of the 16 pediatric tumors reported in the literature had a high risk of aggressive behavior.

In adults, the characteristic cytogenetic finding in GISTs is monosomy 14. Loss of chromosome 22 also is common.⁴¹ The best-characterized genetic alterations associated with GISTs are found in the *c-kit* gene, located at 4q11–12. Most mutations are in-frame deletions or single-nucleotide substitutions within exon 11, but alterations have also been found in exons 9 and 13.^{12,41–43} In children, no cytogenetic abnormalities or alterations of exons 9, 11, or 13 have been found in the few studies that assessed these features.^{19,24} Because of the unavailability of pathologic material, cytogenetic studies and *c-kit* mutation analysis could not be performed in the current study.

Surgical resection has been the mainstay of therapy for GISTs. The primary goal of surgery is complete resection of disease with the avoidance of tumor rupture. GISTs rarely metastasize to lymph nodes. Therefore, lymphadenectomy is seldom warranted.³⁶ In a recent analysis of 200 adult patients with GISTs, 80 patients with nonmetastatic disease underwent complete macroscopic surgical resection. Their 5-year disease-specific survival rate was 54%.⁴⁴ In the current series, 3 of 4 patients with GISTs who received complete resection survived, with a median survival of 9 years. In contrast, only one of three patients who received incomplete resection survived. Most pediatric patients in the literature (14 of 16) received complete resection, and $> 90\%$ of these patients survived without evidence of disease (median survival, 12 months).

Observation has been the standard of care after the complete resection of primary GISTs.³⁶ Recurrent GISTs develop in 40–80% of adult patients despite complete surgical resection of the primary tumor.^{35,44} As observed in patients in the current study, initial tumor recurrence typically involves the primary site, followed by the liver and the peritoneal surface.^{35,44} Until recently, treatment options for recurrent disease have been limited and included systemic or intraperitoneal chemotherapy, surgery, arterial embolization, and radiotherapy.³⁶ It is difficult to accurately determine the response rate of GISTs to conventional chemotherapeutic agents, but it appears to be extremely low ($< 10\%$).^{36,45} A recent Phase II study of temozolo-

mide in adults with advanced GISTs found a response rate of 0%, verifying the chemoresistance of GISTs.⁴⁶

The use of imatinib mesylate represents a major paradigm shift in cancer therapy, as this treatment targets the specific molecular abnormalities that are critical in the development of a particular type of malignant tumor. Treatment with imatinib mesylate yielded response rates of 40–54% and was well tolerated in 2 large multicenter trials of adult patients with unresectable or metastatic GISTs.^{10,47,48}

An activating mutation in *c-kit* was found in 86% of GIST specimens. The type of mutation appeared to be correlated with treatment response.^{49,50} Patients with exon 11 mutations had a response rate of 72%, whereas patients with mutations in exon 9 or wild-type *c-kit* alleles had response rates of 31.6% and 11.8%, respectively.⁴⁹ A study³⁶ evaluating the benefit of adjuvant imatinib mesylate therapy in adults whose GISTs were completely resected but had a high risk of aggressive behavior (such as the GIST in Patient 7) is underway. Although surgery remains the main treatment option for primary GISTs, patient outcome may be improved by neoadjuvant or adjuvant imatinib mesylate therapy.

The reported overall 5-year survival estimates for adult patients with malignant GISTs range from 28% to 54%. For patients with recurrent or metastatic disease, the reported median length of survival is only 17–22 months.^{44,51,52} In the current patient population, 3 of the 7 patients with GISTs died within 2.2 years after diagnosis, but the remaining 4 patients were alive and free of disease for a median of 10.4 years after diagnosis. All but one of the pediatric patients described in the literature survived free of disease, but the duration of follow-up was too short (median, 12 months) to allow determination of whether children with GISTs have a better prognosis than do adults with the same tumor type.

LMS

Although LMS reportedly represents 2–4% of soft tissue sarcomas in the pediatric population,^{2,3} we believe that the true incidence is even lower, because earlier series did not distinguish between LMSs and GISTs. The occurrence of LMS as a secondary malignancy (as observed in Patient 10) is well recognized and has been observed after chemotherapy and/or radiotherapy.^{53–55} LMS also is commonly found in patients who are immunocompromised because of hematopoietic stem cell transplantation,⁵⁶ solid organ transplantation,^{57,58} or congenital^{59,60} or acquired immune deficiencies.^{61–64} LMS is the second most common malignancy in children with human immunodeficiency virus (HIV) infection.^{61,65,66} HIV testing was performed

for only one of the patients with LMS at St. Jude and revealed negative findings.

To our knowledge, since 1966, five pediatric series of LMS have been published in the English-language biomedical literature (Table 4).^{31,67–70} Two series^{31,70} were limited to LMS in extravisceral locations, and three^{67–69} included tumors of the GI tract (possibly GISTs). In these pediatric series and the current one, LMS occurred more frequently in adolescents (age range, 11.5–14.2 years). In adults, peak incidence occurs in the sixth decade of life (age range, 54–57 years).^{71,72} Studies of pediatric and adult patients have found a slight female preponderance.^{71–73} In pediatric patients, the most common location of LMS is head and neck (19 of 73 cases).^{70–72} In contrast, the most common locations in adults are the lower extremities and the retroperitoneum.⁷² Although one patient in the current study (Patient 10) had a uterine LMS, LMSs rarely occur at this location in pediatric patients.⁷⁴ In contrast, in adults, the uterus is one of the most common locations for smooth muscle tumors.⁷⁵ Immunohistochemical analysis and electron microscopy are crucial in differentiating LMSs not only from GISTs but also from rhabdomyosarcomas, malignant peripheral nerve sheath tumors, synovial sarcomas, and myofibroblastic proliferations.³⁰ LMSs express vimentin, desmin, A-SMA, and actin, but they do not express neural markers, myoglobin, cytokeratin, CD34, or KIT (CD117). KIT immunostaining revealed only focal positivity in three patients with LMS in the current study and was not performed for any patients with LMS in previously published pediatric series.

Complete surgical resection is the treatment of choice for LMS, and chemotherapy may be beneficial for patients with residual disease. Objective tumor responses have been observed with regimens containing doxorubicin and/or ifosfamide in adults with LMS.^{76–78} The benefits of radiotherapy are well documented only for uterine LMS; postoperative administration appears to have an impact on locoregional disease control and survival.⁷⁹

Overall, 39 (59%) of the 66 patients with LMS described in 5 reports of pediatric series survived and were free of disease for 5 months–21 years after diagnosis. Four patients reported on in the literature had disease that remained in second complete remission at the time of article publication.^{31,67} In adults, the overall 5-year survival estimates ranged from 29% to 64%.^{14,71–73,76} For soft tissue LMS, the best predictors of outcome were tumor size and anatomic location. Retroperitoneal and deep-seated tumors tended to be larger at diagnosis, and patients with these tumors had a poor prognosis. In contrast, more superficial tumors, such as those

TABLE 4
Summary of Clinical Characteristics of Pediatric Patients with LMS in Five Published Series

Characteristic	Lack, 1986 ⁶⁸	Swanson et al., 1991 ⁷⁰	Hwang et al., 1997 ⁶⁹	de Saint Aubain Somerhausen and Fletcher, 1999 ³¹	Ferrari et al., 2001 ⁶⁷
No. of patients	10	6	21	20	16
Median age in yrs (range)	12.5 (2.5–15)	11.5 (0.6–18)	14.2 (0.01–21.7)	12 (4–15)	12 (2–21)
Male:female ratio	1:1	1:2	1:1.1	1:1.2	1:1.3
Disease site		Soft tissue only		Soft tissue only	
Gastrointestinal tract	6	—	5	—	5
Genitourinary tract	3	—	—	—	—
Head and neck	1	3	5	5	5
Extremities	—	1	7	7	2
Trunk	—	2	4	8	4
Primary treatment					
Surgery, not further specified	10	—	—	17 ^a	—
Complete resection	—	3	10	—	9 (primary reexcision in 4 cases)
Incomplete resection	—	2	11	—	4
Biopsy	—	1	—	—	3
Adjuvant therapy					
Chemotherapy	2	1	5	2 ^a	9
RT	—	1	1	2 ^a	—
Chemotherapy + RT	4	1	8	1 ^a	3
Outcome					
Follow-up duration in yrs (range)	0.4–18	0.8–2.2	0.1–21	0.6–12.1	3–18
NED	3	2	8	15 (2 cases in second remission)	11 (2 cases in second remission)
AWD	3	—	4	—	1
DOD	4 ^b	2	9	—	4
NA	—	2	—	5	—

LMS: leiomyosarcoma; AWD: alive with disease; DOD: died of disease; NA: not available; NED: no evidence of disease; RT: radiotherapy.

^a Treatment information was available for only 17 of 20 patients.

^b One patient died of a second malignancy.

located in the dermis or subcutis, tended to be smaller, and patients with such tumors had a more favorable prognosis.^{31,72,73} Other prognostic factors identified in adult patients with soft tissue LMS included age, extent of necrosis, extent of vascular invasion, and mitotic activity.¹⁴ Limited experience suggests that the POG grading system³² is reasonably predictive of the clinical behavior of soft tissue LMS, but not visceral LMS, in children.³⁰

In conclusion, GISTs and LMS rarely affect pediatric patients. Surgery remains the mainstay of therapy for GISTs and LMS, and tumor resectability is an important prognostic factor. However, the distinction between GISTs and LMSs is important, because GISTs, which are virtually unresponsive to chemotherapy and radiotherapy, can be effectively treated with the tyrosine kinase inhibitor imatinib mesylate. Immunohistochemical staining to detect KIT and CD34 aids in distinguishing between GISTs and LMSs. Studies that

include immunohistochemical analysis, electron microscopy, cytogenetic analysis, and *c-kit* mutation analysis are required to further characterize GISTs and LMS in the pediatric population and to determine whether such tumors differ from their counterparts in the adult population.

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