

Introduction:

Forming Partnerships in the Multidisciplinary Approach to Gastrointestinal Stromal Tumor (GIST)

▶ **Optimal Management of GIST Requires Expert Collaboration¹**

In recent years our understanding of the biology and treatment of GIST has accelerated exponentially, presenting special challenges to clinicians across many disciplines.² While the era of targeted therapy has transformed the landscape of KIT+ GIST treatment, it has also highlighted important issues ranging from histopathologic and molecular diagnosis to advanced imaging techniques and evolving criteria for risk stratification.

An integrated multidisciplinary approach that depends on partnerships across many clinical professions can best evaluate a growing body of data, recently updated consensus guidelines, and changing standards of patient care.

Presentation

Many GISTs are first identified because they cause nonspecific GI symptoms or they are incidentally discovered during radiologic imaging for an unrelated condition.³ The initial workup can be performed by either a primary care physician (PCP) or a gastroenterologist (GE).

Diagnosis

Because GISTs are relatively uncommon, differential diagnosis can be complicated and requires the expertise of the pathologist in conjunction with nearly the entire team, from radiology to medical oncology.

Treatment

The assessment of the complex issues in GIST—such as risk of recurrence and response evaluation—may be clinically challenging, so collaboration among radiology, surgery, pathology, and medical oncology is crucial. The potential benefits of multidisciplinary management include reducing recurrent disease, optimizing timing of surgery and organ preservation, enhancing response to targeted therapies, and prolonging survival for every patient.¹

The Multidisciplinary Approach: Partnering at All Stages for Patient Benefits

Primary Care Physician	Presentation	Diagnosis	Resection	Risk Stratification	Response Evaluation
Gastro-enterologist	Presentation	Diagnosis	Resection	Risk Stratification	Response Evaluation
As the first physician to see the patient, be sure to refer the case to medical oncology and/or pathology colleagues to confirm the diagnosis and provide treatment options as soon as possible.					
Surgeon	Presentation	Diagnosis	Resection	Risk Stratification	Response Evaluation
After operating on the patient with GIST, do not forget to consult pathology and medical oncology colleagues to ensure the best postresection care possible.					
Radiologist	Presentation	Diagnosis	Resection	Risk Stratification	Response Evaluation
Remember to effectively identify and monitor tumor density and metabolic activity as well as changes in tumor size when evaluating treatment response.					
Pathologist	Presentation	Diagnosis	Resection	Risk Stratification	Response Evaluation
Use of conventional histology in conjunction with immunohistochemistry allows you to confirm GIST and identify type (ie, KIT+), plus conduct mutational analysis if needed. Be sure to partner with your medical oncology colleagues to provide all relevant testing so the best treatment options for your patient's individual tumor characteristics can be considered.					
Medical Oncologist	Presentation	Diagnosis	Resection	Risk Stratification	Response Evaluation
Close collaboration with and feedback from your clinical colleagues at each stage of GIST management may enable you to take advantage of new treatments and emerging standards of care.					

NOTE: Boxes with orange text represent physicians' areas of individual involvement as well as opportunities for collaboration throughout the course of GIST management.

CONCLUSION

The close partnership of various specialties ensures comprehensive patient care.

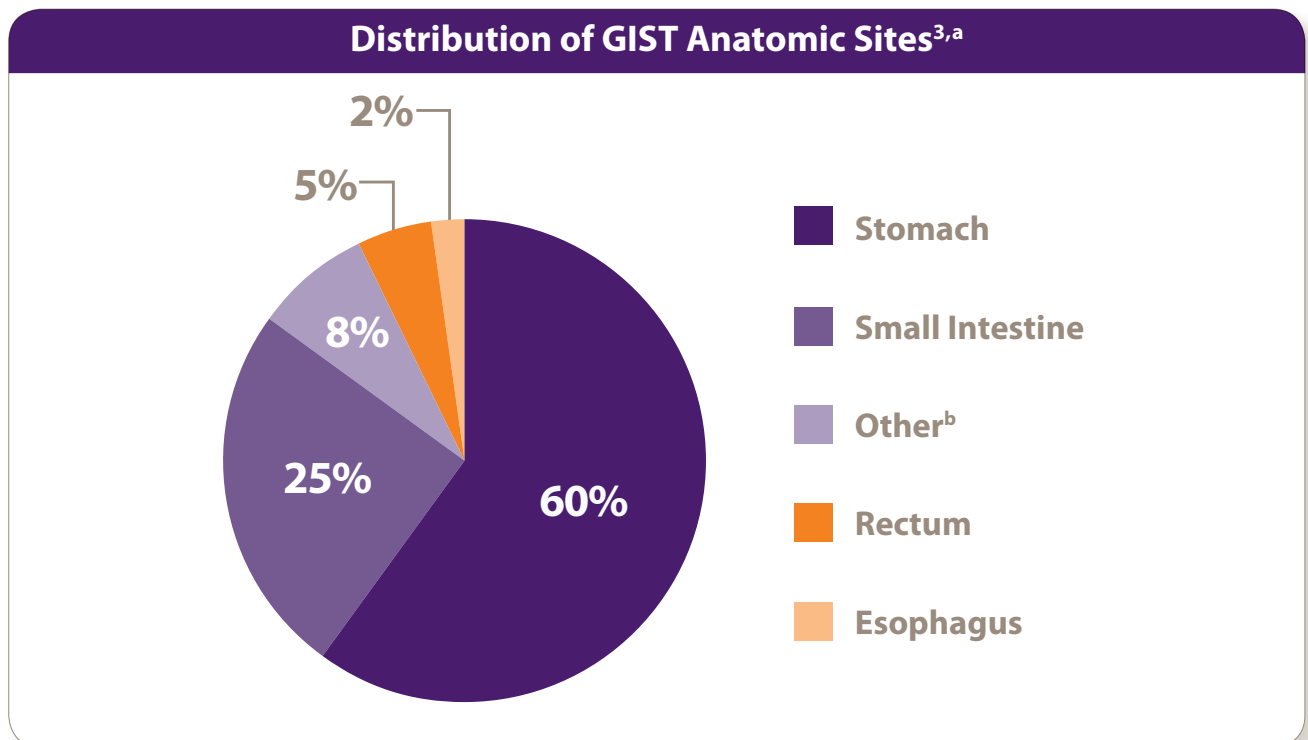
Diagnosis:

The Importance of Identifying Gastrointestinal Stromal Tumors (GISTs)

▶ GIST diagnosis is not always straightforward and can be challenging

- GISTs are uncommon sarcomas—estimated incidence is 1-2 per 100,000 persons annually^{4,5}
- Presentation can be throughout the GI tract—though the majority arise in the stomach³
- Because GIST has only recently been defined at a pathologic and molecular level,⁶ there are not yet standardized steps in diagnosis, so many clinicians may not immediately identify GIST

▶ Maintain a high index of suspicion for GIST during initial evaluation of GI masses



^a Tumor location was reported in 97% of patients and not reported in 3% of patients.

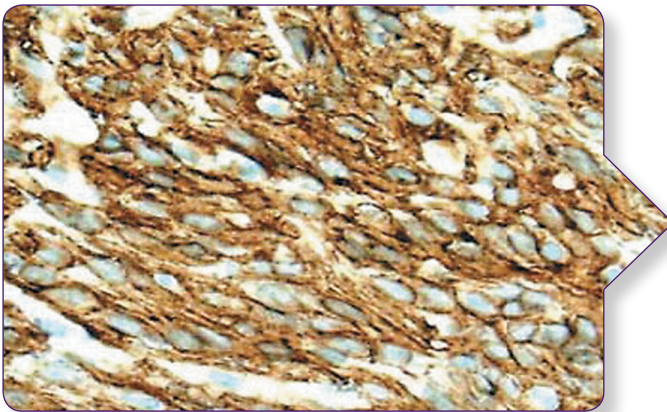
^b Other includes 5% of patients with tumors reported in the appendix, gallbladder, pancreas, mesentery, omentum, and retroperitoneum, and 3% of patients with tumor location that was not reported.

▶ Conventional histology and immunohistochemistry

- Examination of standard histology reveals that most GISTs show 1 of the following 3 patterns³:
 - Spindle cells (most common type, 70% of cases)
 - Epithelioid cells (20%)
 - Mixture of both spindle and epithelioid cells (≈10%)
- However, because GISTs have a relatively broad morphologic spectrum, staining for common tumor markers is integral in confirming a diagnosis of GIST³

▶ KIT (CD117) is the most commonly used tumor marker for GIST

- 95% of GISTs are KIT+¹
- KIT immunostaining provides the most reliable assay in the diagnosis of GIST³
- Staining with KIT gives a strong and diffuse signal²



Immunohistochemical stain of KIT (CD117) in GIST²

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▶ Mutational analysis is useful in KIT– GIST diagnosis¹

CONCLUSION

An accurate diagnosis of GIST depends on careful consideration of several factors. Beginning with factors considered for GIST diagnosis, a multidisciplinary dialogue among all colleagues—from pathologist to oncologist—can also facilitate subsequent steps, such as a thorough assessment of risk of recurrence.

Prognosis:

The Risk of Recurrence in Resectable Primary Gastrointestinal Stromal Tumor (GIST)

▶ Risk of recurrence in GIST remains significant, even after complete resection⁴

- 1 in 2 patients experience recurrence of GIST following surgery⁷
- Some high-risk GISTs carry as high a risk of recurrence as 90%¹
- Even resected tumors characterized as low risk may recur^{3,8}
- Only 20% of patients achieve recurrence-free survival at 5 years after removal of a high-risk primary GIST⁹

▶ Mitotic rate and tumor size are very important prognostic factors⁷

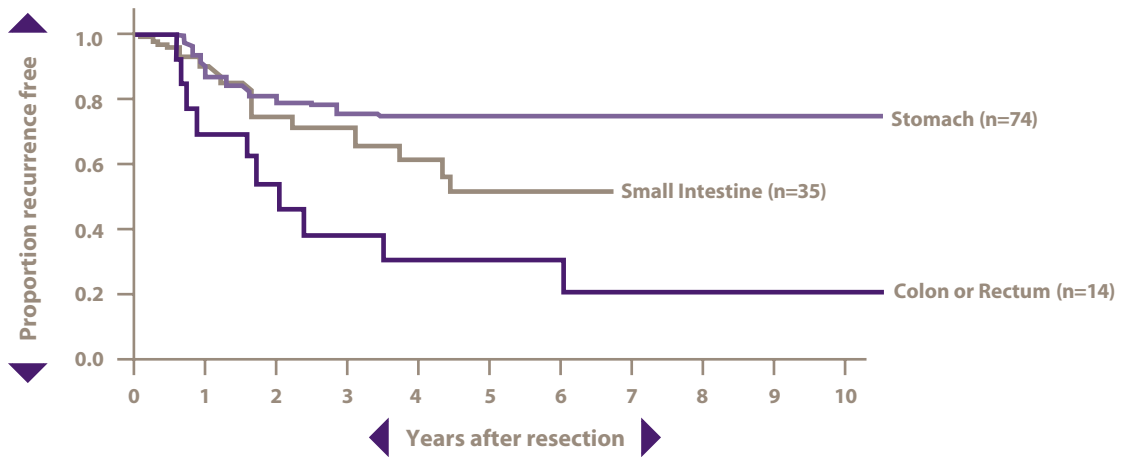
- A mitotic rate of ≥ 5 per 50 high-power fields (HPF) has been found to significantly raise the rate of recurrence (HR 14.6; 95% CI, 6.5-32.4)⁹
- Even lesions that are very small (<2 cm) or with a very low mitotic rate (<5 per 50 HPF) are known to metastasize occasionally¹⁰
- Conversely, some large tumors (>10 cm) with low mitotic activity have a relatively good prognosis based on a recent study of more than 1000 GIST patients⁸

▶ Currently, both ESMO and NCCN guidelines include tumor site as the third factor to consider for risk stratification^{5,7}

- Primary GISTs located outside the stomach (small intestine, colon, or rectum) have a higher risk of recurrence than do gastric GISTs^{1,9}
 - Consideration of tumor site as an additional risk factor can identify patients who may benefit from adjuvant therapy¹¹

▶ Numerous other factors may also play a role in risk stratification, including surgical margins, tumor rupture, and mucosal invasion^{5,11}

Recurrence-Free Survival by Tumor Site^{9,a}



^aBased on 127 patients with completely resected localized GIST.
Adapted from DeMatteo et al, 2008.⁹

▶ **Current consensus criteria for risk stratification are based on tumor size, mitotic rate, and site¹**

Risk for Progressive Disease (%)^{1,12,b}

Mitotic Index (HPF)	Tumor Size (cm)	Gastric	Duodenum	Jejunum/Ileum	Rectum
≤5/50	≤2	0%	0%	0%	0%
	>2 ≤5	1.9%	4.3%	8.3%	8.5%
	>5 ≤10	3.6%	24%	ND	ND
	>10	10%	52%	34%	57%
>5/50	≤2	NONE ^c	HIGH ^c	ND	54%
	>2 ≤5	16%	73%	50%	52%
	>5 ≤10	55%	85%	ND	ND
	>10	86%	90%	86%	71%

ND=not determined.

^bDefined as metastasis or tumor-related death. Data are based on long-term follow-up of 1055 gastric, 629 small intestinal, 144 duodenal, and 111 rectal GISTs.

^cDenotes small numbers of cases.

Adapted from Miettinen and Lasota, 2006.¹²

CONCLUSION

Enhanced risk stratification criteria can facilitate communication across disciplines like surgery, pathology, and oncology to better serve those GIST patients who will benefit from postsurgical options.¹¹

Assessment:

Evaluating Treatment Response in Metastatic and/or Unresectable KIT+ Gastrointestinal Stromal Tumor (GIST)

▶ Treatment response evaluation in KIT+ GIST can be challenging

Recognizing the pattern of tumor response via conventional computed tomography (CT) scans—the standard imaging modality in KIT+ GIST—is particularly important but can be challenging.¹

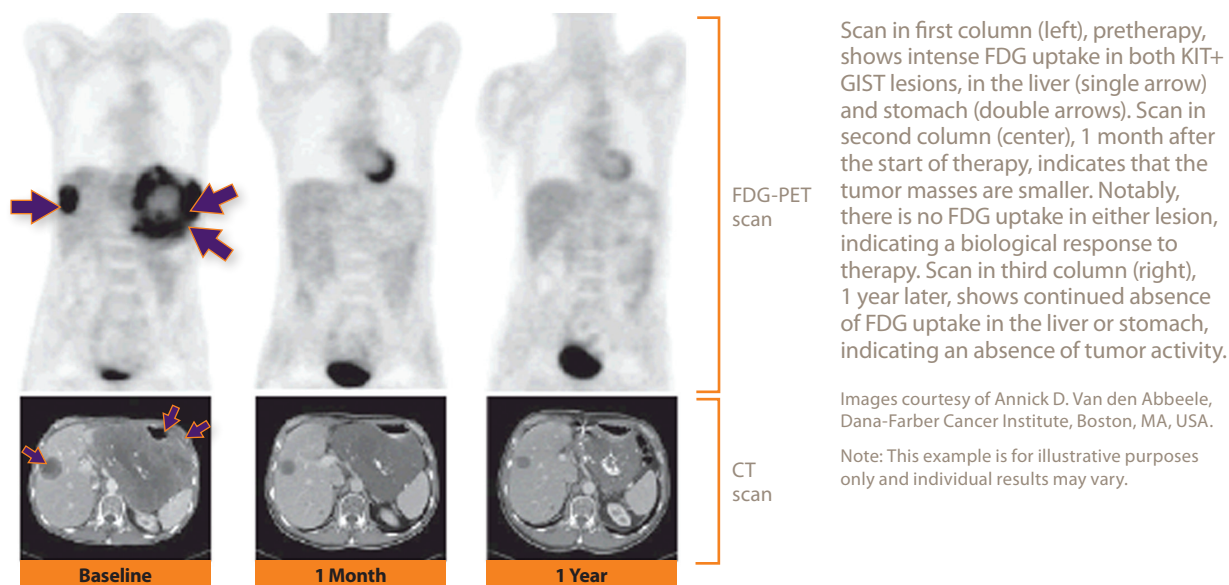
- A decrease in tumor metabolism and tumor density indicates a positive response even in the absence of anatomic tumor shrinkage. Tumor density may be evaluated with contrast-enhanced CT¹
- Fluorodeoxyglucose positron emission tomography (FDG-PET) can be considered if CT findings are inconclusive or inconsistent with clinical findings¹

▶ Evaluating tumor response to tyrosine kinase inhibitors (TKIs) requires careful consideration of tumor metabolic activity and anatomic changes

Changes in tumor metabolic activity often precede anatomic changes; residual tumor masses may appear to persist for months—or even years—on CT despite positive response to TKI treatment.^{1,7}

- A waning tumor may be signified by metabolic changes as well as morphologic ones²
- Patience as well as the careful interpretation of different imaging modes may be critical to the comprehensive assessment of tumor response in KIT+ GISTs⁵

Tumor response to TKI therapy involves morphologic and metabolic changes¹³



Adapted from Sullivan and Kelloff, 2005.¹³

Conventional RECIST response criteria may not accurately identify response¹

In addition to changes in metabolic activity, changes in tumor density are also an early indicator of a good response to TKI therapy.¹

- RECIST criteria—based on change in tumor size—are known to be insensitive in KIT+ GIST response evaluation¹
- Choi response criteria¹⁴:
 - Consider both tumor density and size on CT
 - Have been validated in an independent analysis of patients with recurrent or metastatic GIST
 - Demonstrated to be more sensitive and precise than RECIST
 - Correlated more significantly with time to progression and survival than RECIST

CONCLUSION

Considering activity and density change, in addition to conventional criteria of tumor size only, can ensure more in-depth evaluation of the response of KIT+ GIST to TKI therapy.¹

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