GIST (Gastrointestinal Stromal Cell Tumor): Basics and Beyond

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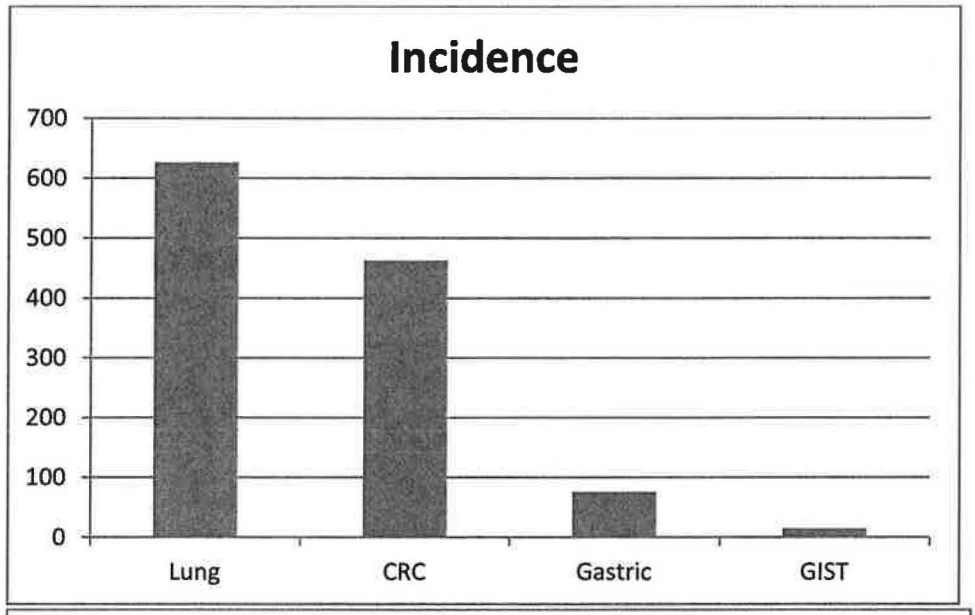
This is to acknowledge that Udit Verma, M.D. has disclosed that he does not have any financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Verma will be discussing off-label uses in his presentation

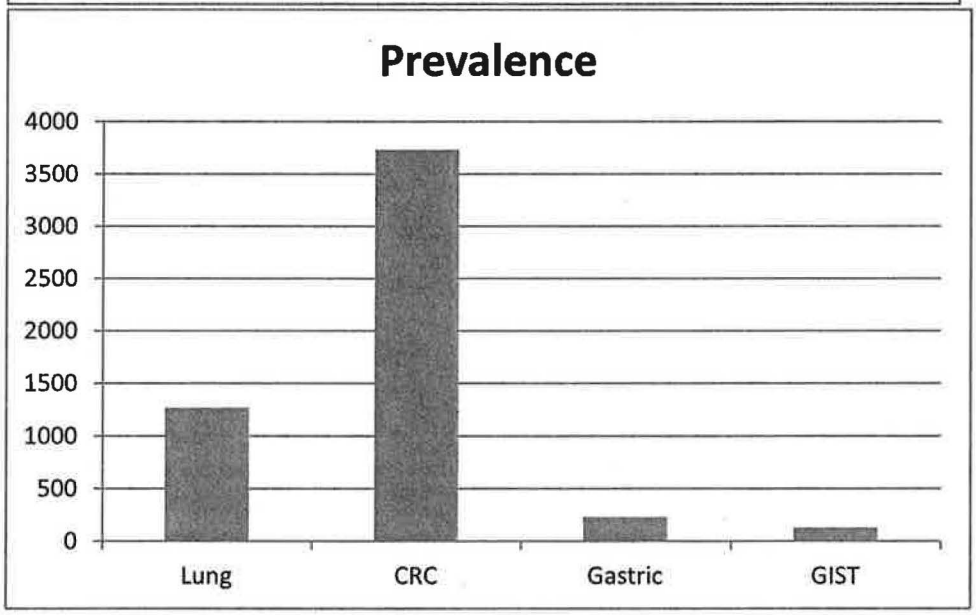
Gastrointestinal stromal cell tumors, better known by acronym GIST are mesenchymal tumors of gastrointestinal tract with likely origin from interstitial cell of Cajal. These tumors are characterized by activating mutations of c-kit or PDGFR-α, c-kit (CD 117) overexpression and dramatic response to receptor tyrosine kinase (RTK) inhibitors. Gastrointestinal stromal cell tumors differ from other solid tumors in several ways including molecular pathogenesis, clinical presentation, response to therapy and overall clinical course. Tremendous progress has been made in understanding of these aspects in last 10-15 years, sparking a keen interest in this disease by scientist, physicians and patients alike. I plan to review current state of knowledge with emphasis on clinical aspects of disease and future directions.

There has been much confusion in histogenesis, nomenclature and classification of these tumors since initial descriptions in 1940s and the subject is reviewed elsewhere.[1,2] Spindle cell and later epitheloid cell stromal cell tumors of GI tract were described in 1940s and were thought to arise from smooth muscle. These were classified as leiomyomas, leiomyosarcomas, leiomyoblastomas and several other names. The term GIST was coined by Mazur and Clark in 1983 to describe gastrointestinal non-epithelial neoplasms that lacked the immunohistochemical features of Schwann cells or ultra-structural characteristics of smooth muscle cells [3]. However, these tumors were rarely diagnosed as separate entity from other soft tissue sarcomas till recently. Hirota et al identified gain of function mutation in c-kit in most of the GIST. [4] Advent of gain of function mutations in c-kit and subsequent demonstration of remarkable efficacy of receptor tyrosine kinase inhibitor Imatinib[5] in treatment of these patients has led to intense interest in this disease. Over last decade, enormous progress has been made in biology and treatment of gastrointestinal stromal cell tumors

EPIDEMIOLOGY

Gastrointestinal stromal cell tumors constitute 3-6% of soft tissue sarcomas and are most common mesenchymal tumors of GI Tract. Clinically significant GISTs constitute <1% of GI tumors though small incidental GISTs (microGISTs) are very common and seen in up to 20-30% of normal populations.[6] It is thought that cancer registry based data under estimate frequency of these tumors. In one study examining the Surveillance, Epidemiology, and End Results (SEER) registry, the incidence is reported to be 3.2/million/year and the prevalence rate of 16.2.[7] A population based study from Sweden[8] found incidence of clinically detectable GIST to be 14.5/million/year and prevalence rate of 129/million. Similar results were seen in several other population based studies from other countries. Currently, it is estimated that 4000 to 6000 new cases of GIST are diagnosed each year in US. Frequency of GIST in relation to other common cancers is shown in Figure 1.





GIST tends to occur in 40-70 year age group with median age of 58 years. There is slight male preponderance but otherwise both males and females are affected. Vast majority of GISTs are sporadic. Several kindred's with familial GIST are described where this is inherited in autosomal dominant fashion. GISTs are also seen in patient with NF-1 and as part of Carney Triad

CLINICAL PRESENTATION

GIST can arise anywhere along gastrointestinal tract with stomach being the most common site. Relative distribution along GI tract is given in Figure 2.

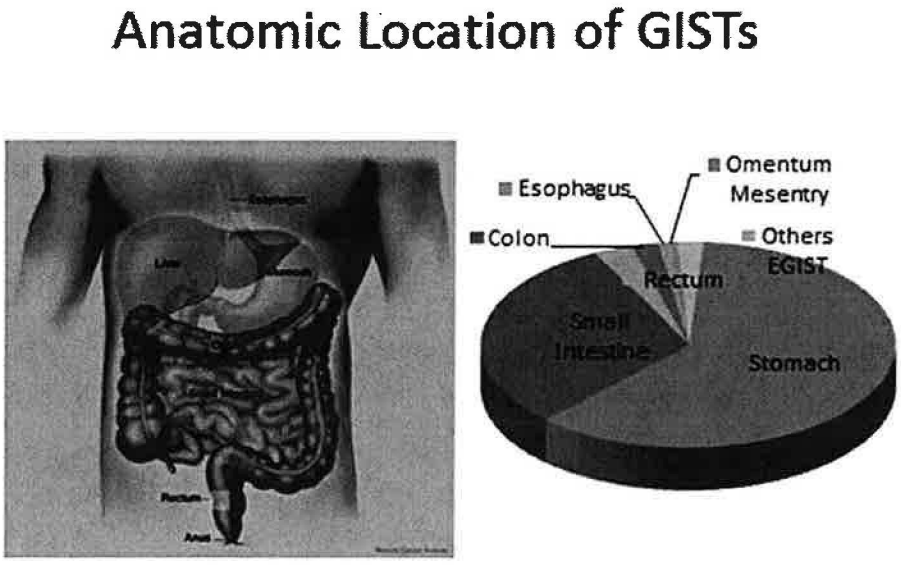


Figure 1. Relative distribution of primary GIST along GI tract

Clinical presentation of GIST varies based on the site of origin. Bleeding is the most common symptom. Bleeding can occur acutely within the lumen or in the peritoneal cavity causing pain, hematemesis, melena and symptomatic anemia. Chronic GI blood loss can manifest as iron deficiency anemia. Dysphagia, early satiety, gastric outlet and intestinal obstruction can be other presentations based on location of these tumors. Abdominal mass with or without associated pain is other common manifestation. 20%-30% patients have metastatic disease at the time of diagnosis. Metastatic disease involves liver and peritoneal cavity. Metastasis to lung, lymph nodes or to other distant sites are rarely seen.

PATHOLOGY

GISTs share phenotypic characteristics with and are thought to originate from the interstitial cells of Cajal (ICC)[9] or their precursors. ICCs exists as an intricate system of fusiform cells, mostly within circular and longitudinal muscle layers of muscularis propria. GIST arise within wall of GI tract with a tendency to project within lumen. As initially these tumors are silent, most tumors are fairly large at the time of diagnosis. Median size in RTOG 0132 study was 8.9 cms. [10]

GISTs are well circumscribed and often surrounded by a pseudo capsule. These tumors have a fleshy pink or tan-white cut surface with hemorrhagic foci, central cystic degenerative changes, or necrosis. Surgical resection requires careful handling as tumor tend to rupture and seeding is common.

Microscopically GISTs are composed of monotonous population of cells, with majority of tumors (70%) demonstrating spindle cell morphology. These cells demonstrate pale eosinophilic fibrillary cytoplasm, ovoid nuclei, and syncytial cell borders. Paranuclear vacuolization is frequently seen. The cells are arranged in short fascicles or whorls. About 20% of cases are composed of epitheloid cells with palely eosinophilic to clear cytoplasm and round nuclei. The cells are arranged in nests, sheets, and, less commonly, cords. This morphology is commonly seen in pediatric GISTs. The remaining 10% of GISTs have a mixed spindle and epitheloid cell morphology. Rarely these tumors may have different features.

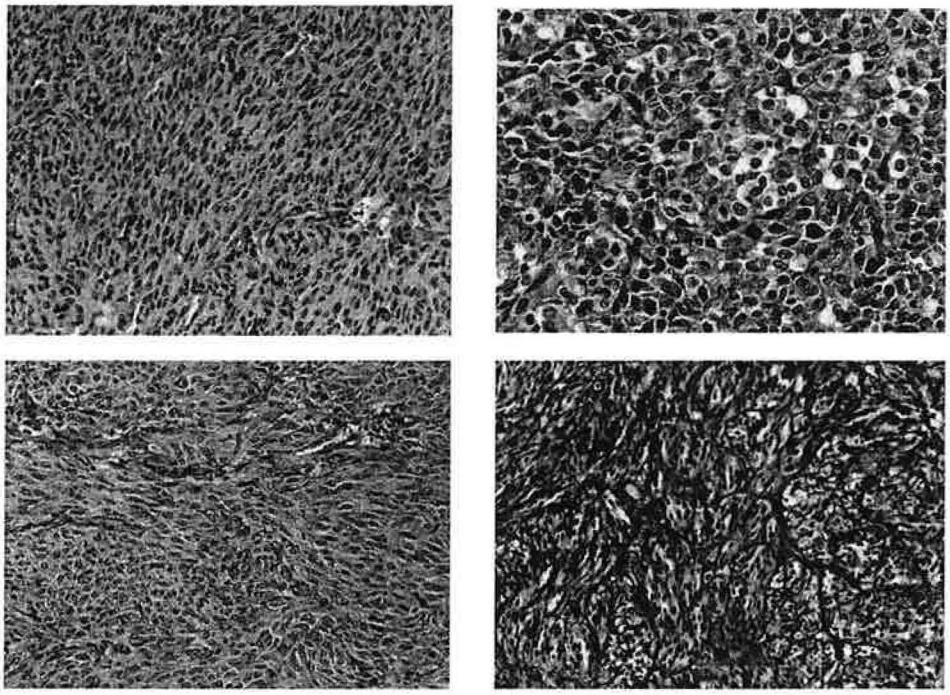


Figure 3. Morphological pattern of GISTs (clockwise from top). Spindle cell type, Epitheloid pattern, nested paraganglioma-like and mixed spindle cell and epitheloid,

Regardless of the cytomorphology, GISTs are variably cellular and can have sclerotic, collagenous, or myxoid stromal changes. Pleomorphism is not common.

Majority of GISTs (95%) express c-kit (CD 117) in a diffuse cytoplasmic pattern. Occasionally there is some variability in expression pattern. Immunoreactivity to DOG 1.1, an antibody to a

chloride channel is other very specific and sensitive marker for GIST. Aside from consistent positivity for KIT (CD117), about 60% to 70% of GISTs show immunopositivity for CD34, 30% to 40% show immunopositivity for smooth muscle actin (SMA), and around 5% show immunopositivity for S-100 protein.

Immunohistochemistry pattern of GISTs as compared to other common tumors is shown in table 1.

Table 1- Immunohistochemistry pattern of GISTs as compared to other common tumors

	KIT		DOG 1.1		CD34		Smooth Muscle Actin		Desmin		S-100		Keratin	
GIST	+++	95	+++	>95	+++	70	+	40	-		-		-	
Leiomyoma	-		-		+/-		+++	80-100	+++	80	-		+/-	
Leiomyosarcoma	-		-		+	10	+++	80-100	++	80	-		+	25
Schwannma	-		-		-		-		-		+++	>95	-	
Fibromatosis	-		+/-		-		++		-		+		-	
Melanoma	+	50	-		-		-		-		+++	>95	-	
Carcinoma	-		+/-		-		+/+++		-		-		+++	25-100

Currently, expert opinion favors that GIST diagnosis should be restricted to lesions with cytoarchitectural features consistent with GIST which are positive for CD117[11]. Certain tumors which are CD117 negative where it appears that CD117 negativity could be attributed to (1) to some type of fixation artifact (excessive heat during section drying, or very prolonged storage of unstained slides), (2) are KIT negative due to sampling error (e.g., very small needle biopsies showing normal internal control staining for other antigens from tumors in which KIT staining is focal in distribution), (3) have (in rare cases) ceased to express KIT due to some form of clonal evolution, perhaps following Imatinib therapy. Some of the tumors which are c-kit negative but otherwise stain positive for DOG 1.1 can be classified as true GIST.

MOLECULAR GENETICS

In 1998, Hirota et al [4] recognized that most GISTs harbor gain of function mutation in proto-oncogene *c-kit*. Subsequently, it was noted that a significant portion of GISTs have *wt c-kit* but have gain of function mutation in *PDGFRα*[12,13] which encodes PDGFRα another type III receptor tyrosine kinase (RTK).

KIT is a type III receptor tyrosine kinase that is closely related to PDGFRα and PDGFRβ, as well as to macrophage colony-stimulating factor receptor (CSF1R) and Fl cytokine receptor (FLT3). These kinases are structurally related with an extracellular ligand-binding domain comprising five immunoglobulin-like repeats, a transmembrane sequence, a juxtamembrane domain, and a cytoplasmic kinase domain split by an insert (Figure **4**).

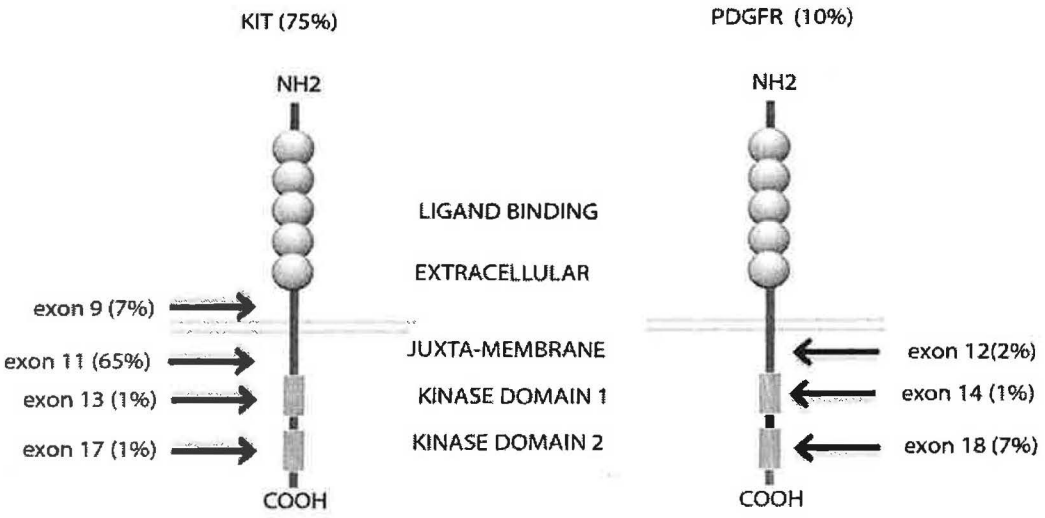


Figure 4. Schematics of Kit and PDGFR α and frequency of mutations in GIST

Binding of KIT ligand (SCF) to KIT results in receptor homodimerization and kinase activation. The resulting phosphorylation of specific tyrosine's on KIT and a number of secondary signaling molecules promotes signaling through several downstream pathways. These include the MAP kinase pathway (RAF, MEK, ERK), the STAT pathway, and the phosphatidylinositol 3 (PI3)-kinase/AKT pathway.

Molecular classification is critical to understanding GIST biology and management. Approximately 75% of GISTs harbor a mutation in *KIT*. *KIT* mutations occur virtually always in one of four out of the 21 exons of the gene (**Figure 4**). Exon 11 mutations (which encodes the intracellular juxtamembrane part of the protein) are most frequent. Mutations involving exon 9 (which encodes extracellular part) are second most common. Rarely mutations in exon 13 or 17(which encode intracellular kinase portion of the protein) are seen. Exon 11 mutations can be deletions or insertions of variable length, combinations of deletions and insertions, or point mutations. Exon 9 mutations tend to be duplications of codons 502 and 503. In ~10% of GISTs, the *KIT* gene is normal but there is a mutation in the platelet-derived growth factor receptor alpha gene, *PDGFRα*. [13] Activating mutations have been detected in *PDGFRα* exons 12, 14, and 18, which correspond to *KIT* exons 11, 13, and 17, respectively.

The majority of GISTs with a *PDGFRα* mutation occur in the stomach and may stain poorly by immunohistochemistry for KIT protein, whereas GISTs with a *KIT* exon 9 mutation usually arise outside of the stomach in the gastrointestinal tract (Table 2).GISTs with a *KIT* exon 11 deletion mutation affecting codons 557 and/or 558, and those with a *KIT* exon 9 mutation, tend to be associated with unfavorable clinical outcome. [14,15] The D842V mutation in exon 18, which accounts for ~60% of all PDGFRA mutations known in GISTs, has shown primary resistance in vitro to all commercially available TK inhibitor drugs Imatinib, Sunitinib, and nilotinib. The D842V mutation in PDGFRα is homologous to the D816V mutation in KIT which is well established as being resistant to Imatinib in vitro.

Distribution of different mutations and their clinical relevance is summarized in table 2. Oncogenic kinase mutations either in c-kit or PDGFRα are critical seminal events, other genetic events are important in progression of these lesions. Two third of GISTs demonstrate either monosomy 14 or partial loss of 14q. [16,17] There appears that tumor suppressor genes on 14q11.2-q12 and 14q23-q24 are important in GIST formation and progression. Loss of long arm of chromosome 22 is observed in 50% GISTs and is associated with progression to more aggressive lesions. [13,16,18,19] Loss of 13q and 15q have also been reported in GISTs. [18,20]

Table 2- Molecular classification of GIST

Gene	Exon	Incidence	Anatomic Distribution	Imatinib sensitivity
Kit Mutations	Exon 9	7%	Mostly non gastric	Higher dose (800 mg/day)
	Exon 11	65%	Gastric or Non Gastric	Sensitive (400 mg/day)
	Exon 13	1%	Gastric or Non Gastric	Variable
	Exon 17	<1%	Gastric or Non Gastric	Variable
PDGFRα				
	Exon 12	1.5%	Mostly Gastric	Sensitive
	Exon 14	0.1%	Gastric or ? Non Gastric	Sensitive
	Exon 18	7%	Mostly Gastric	D482V insensitive, others sensitive
WT GIST	BRAF, SDHA, SDHB,SDHC	10%	Gastric or Non Gastric	Variable
Carney Triad related	Unknown	Rare	Gastric	? Insensitive
Carney-Stratakis	SDHA, SDHB,SDHC	Rare	Gastric	? Insensitive
Neurofibromatosis-1	NF-1	Rare	Small bowel	? Insensitive
Familial	Kit, PDGFR	Rare	Small bowel	Sensitive

In addition to cytogenetic abnormalities noted above, several key genes involved in cell cycle progression are implicated in GIST progression. The tumor suppressor gene *CDKN2A* (p16INK4A) on chromosome 9p is inactivated through several mechanisms in a significant fraction of malignant GISTs. [21-25] Deletions, point mutations and promoter methylation contribute to decreased expression of p16, which is an important inhibitor of the cell cycle. Decreased expression of p16 by immunohistochemistry correlates with aggressive behavior even in tumors classified as low risk by standard morphological criteria . [23,25,26] p27KIP1, is reported to be down regulated in GISTs.[26-28] Various other cell cycle regulatory proteins have been reported to be altered in GIST and may relate to aggressive biology of disease.

Implications of genetic abnormalities are further discussed under management sections.

DIAGNOSIS AND RISK STRATIFICATION

Although GIST have characteristic imaging characteristics on CT scans and are intensely FDG avid on PET Scans, diagnosis requires histopathological examination either on biopsy or on resected surgical specimen. GIST diagnosis should be restricted to lesions with cytoarchitectural

features consistent with GIST which are positive for CD117[11]. Certain tumors which are CD117 negative but otherwise consistent with GIST should be tested for kit and PDGFRα mutations and GIST diagnosis should be restricted to lesions carrying kit or PDGFRα mutations typically seen in GIST.

An endoscopic ultrasound (EUS) guided biopsy is preferable over percutaneous biopsy secondary to risk of tumor rupture and seeding of tract.

Malignant potential of GISTs is highly variable ranging from slow growing benign lesions to highly aggressive lesions with high risk of metastasis. Risk stratification is important to predict likely course in a given patient and to determine need for adjuvant therapy. Several risk stratification schemes has been proposed and published earlier. [11,29-31] Currently tumor size, tumor site, mitotic rate and presence of tumor rupture are accepted as risk stratification markers. Implication of these on tumor recurrence rate is given in table 3. Mutation type is important in outcome, but thus far not integrated into stratification schemes.

Table 3. Risk Stratification of Primary Gastrointestinal Stromal Tumor (GIST) by Mitotic Index, Size, and Site

Tumor Parameters		Risk for Progressive Disease Based on Site of Origin (%)			
Mitotic Rate	Size, cm	Stomach	Jejunum/Ileum	Duodenum	Rectum
≤5 per 50 HPF	≤2	None (0)	None (0)	None (0)	None (0)
	>2, ≤5	Very low (1.9)	Low (4.3)	Low (8.3)	Low (8.5)
	>5, ≤10	Low (3.6)	Moderate (24)	Insufficient data	Insufficient data
	>10	Moderate (12)	High (52)	High (34)	High (57)
>5 per 50 HPF	≤2	None[d]	High[d]	Insufficient data	High (54)
	<2, ≤5	Moderate (16)	High (73)	High (50)	High (52)
	>5, ≤10	High (55)	High (85)	Insufficient data	Insufficient data
	>10	High (86)	High (90)	High (86)	High (71)

Data are based on long-term follow-up of 1055 patients (54.4%) with gastric GISTs, 629 patients (32.4%) with small-intestine GISTs, 144 patients (7.4%) with duodenal GISTs, and 111 patients (5.7%) with rectal GISTs. [31]

MANAGEMENT

(A) Localized Disease. Complete Surgical resection remains the gold standard for treatment of localized non-metastatic GISTs. Surgical resection should involve en-bloc removal of tumor

with its pseudo capsule. Wide surgical margins are not needed. Regional lymph node resection is or extensive lymphadenectomy is not required, as nodal metastasis are rarely if ever seen. In certain cases, based on location, total gastrectomy, pancreaticoduodenectomy or an abdominoperineal resection may be needed. Every attempt should be made for intact removal of tumor as tumor rupture is associated with an increased risk for development of peritoneal metastasis. Joensuu et al [32] assessed key prognostic factors in an observational cohort study based on ten published population based studies of GIST patients undergone surgery and did not receive adjuvant systemic therapy. Impact of tumor rupture observed in this analysis is shown in figure 5

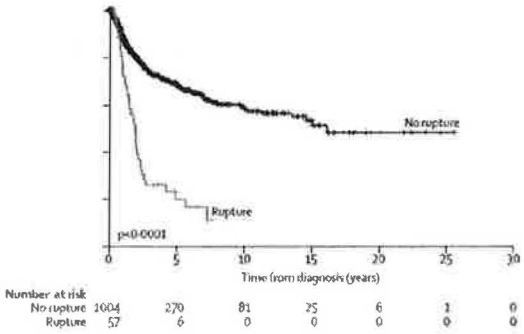


Figure 5. Recurrence free survival by rupture

(B) Neoadjuvant treatment for borderline resectable cases. Borderline resectable cases may become resectable after neoadjuvant therapy with Imatinib or it may become feasible to perform less extensive or less morbid surgery after pre-operative treatment with Imatinib. There are no large randomized trials to address this but several groups have reported institutional experience with neoadjuvant therapy. [10,33-36] In a study by Andtbacka et al,[37] patients with recurrent or metastatic GIST who had radiological PR to neoadjuvant Imatinib therapy (n=11) had a significantly higher complete resection rate (91% vs. 4%; p<.001) compared with patients who had progressive disease (n=24).

(C) **Adjuvant Therapy**. A significant portion of GIST patients recur after complete surgical resection of primary tumor. Recurrence free survival after complete surgical resection as reported by Joensuu et al is shown below in figure 6.

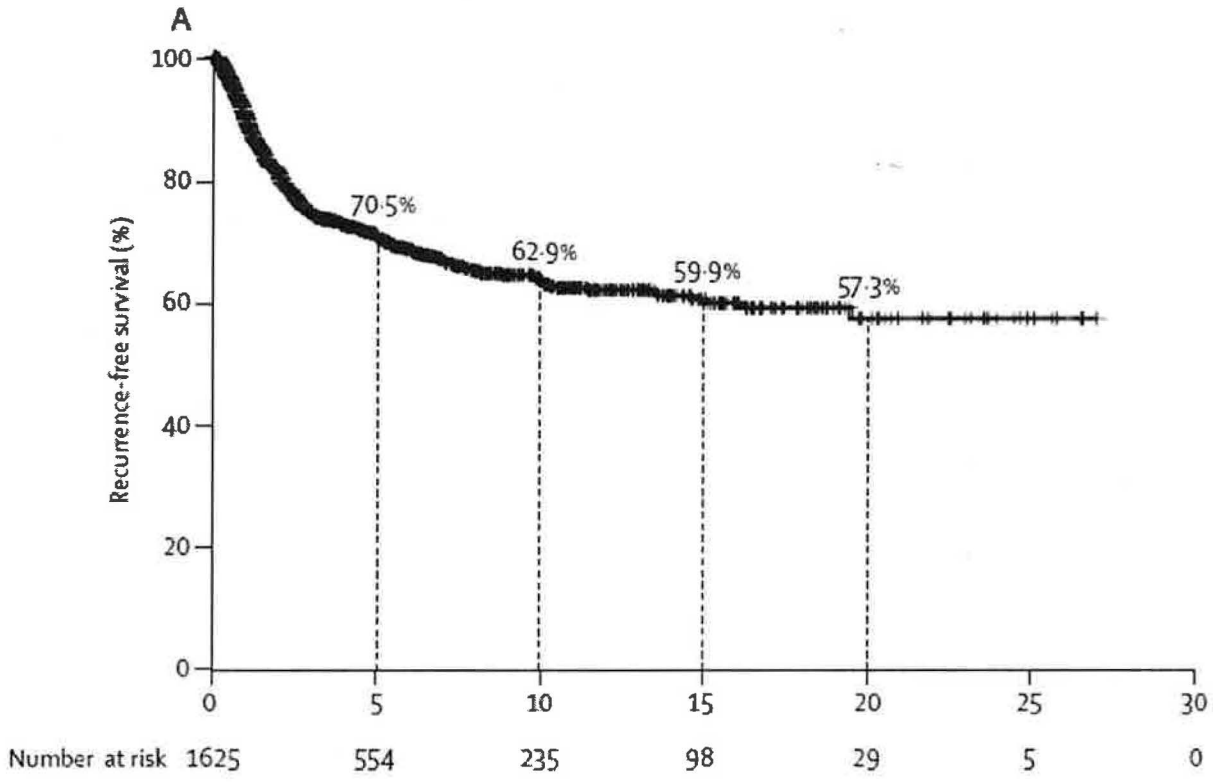
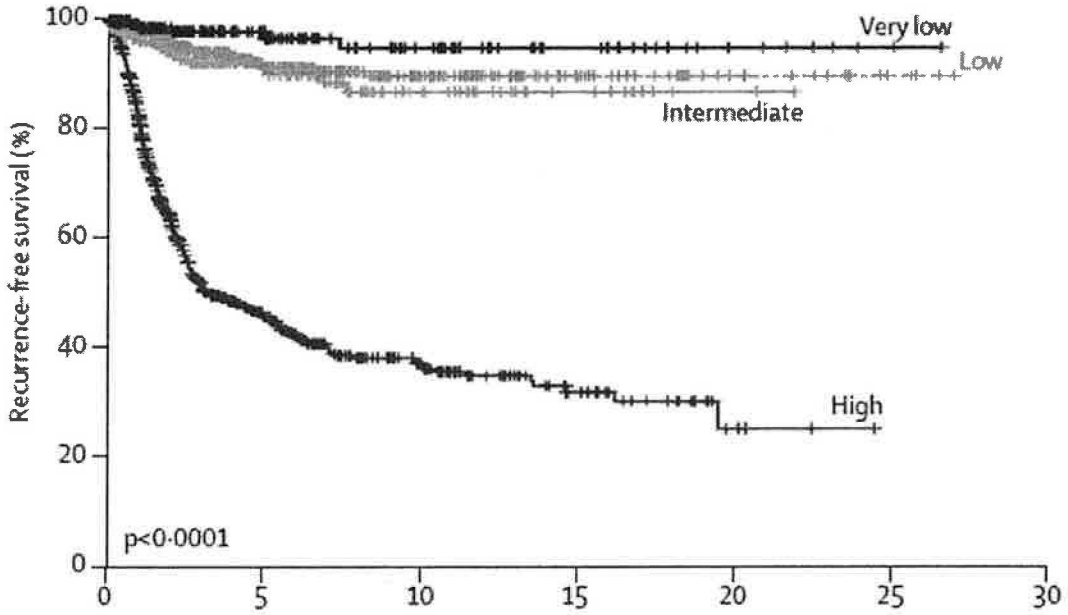


Figure-6 Recurrence free survival after R0 resection of GIST in all comers[32]

Recurrence rate are much higher in high risk groups as defined by tumor size, mitotic rate, and site of origin. Recurrence rates based on NIH modified consensus risk stratification groups as seen in pooled analysis of population based series by Joensuu et al is shown below in Figure -7



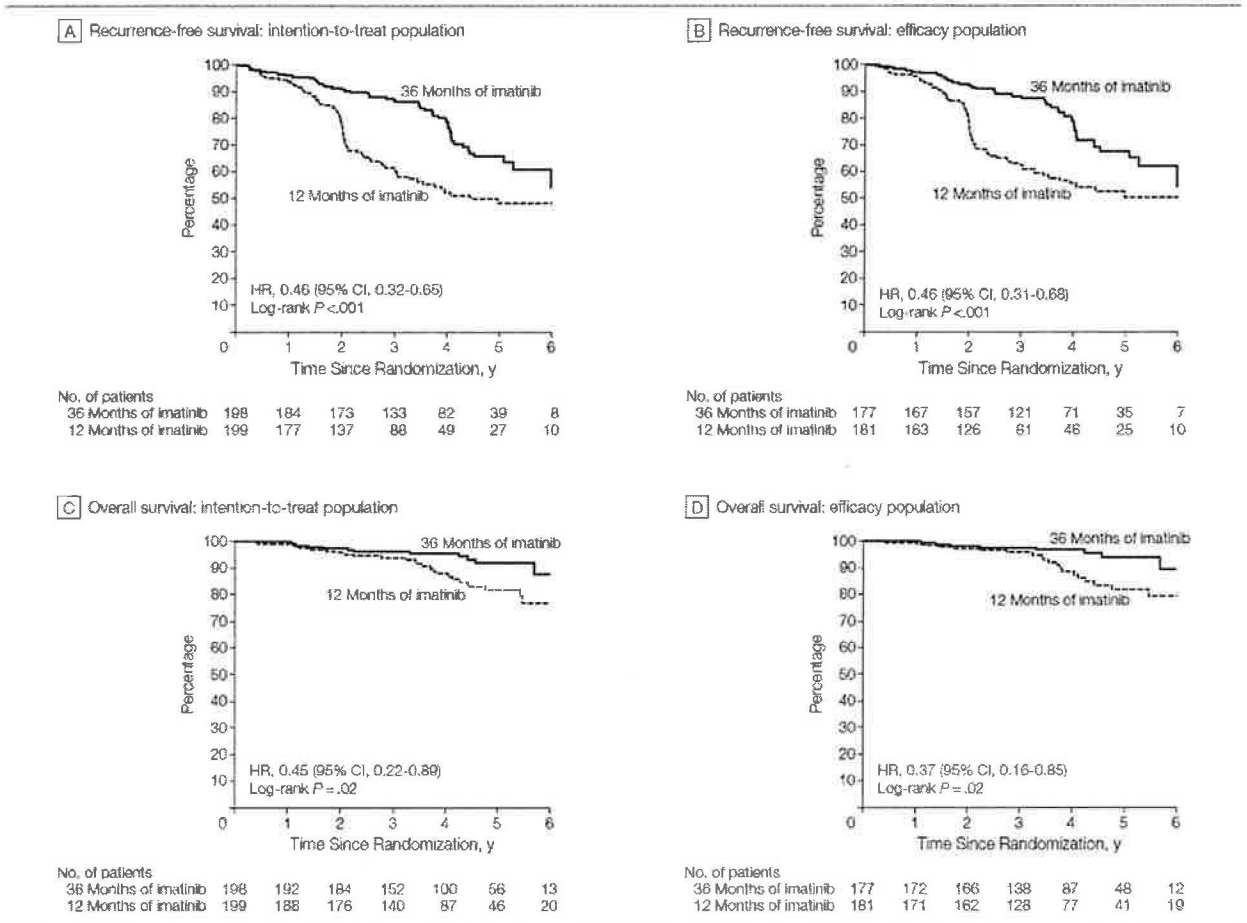
Number at risk							
Very low risk	180	77	43	22	8	1	0
Low risk	435	174	79	34	14	4	0
Intermediate risk	205	86	34	14	2	0	0
High risk	694	171	69	27	4	0	0

Figure -7. Recurrence rates based on NIH modified consensus risk stratification groups as seen in pooled analysis of population based series by Joensuu et al

Role of adjuvant therapy with Imatinib has been addressed in several studies.

SSG XVIII trial.[38] The Scandinavian Sarcoma Group (SSG) XVIII trial compared 36 vs. 12 months of Imatinib in 400 high risk patients based on NIH modified consensus criteria. At 54 months of follow-up, 36 months treatment was associated with a significant improvement in RFS (66% vs. 48 %; HR 0.46, 95% CI 0.32 to 0.65) and overall survival (92% vs. 82%; 85% CI 0.22 to 0.89). Relapse free and overall Survival Curves from this study are shown below in Figure 8

ACOSOG Z9001.[39] Role of adjuvant Imatinib was addressed phase III double blind multicenter ACOSOG Z9001 study. In this study 713 patients with completely resected GIST of at least 3 cms in diameter were randomly assigned to receive either 400 mg daily of Imatinib or placebo. The one year relapse free survival was 98% in Imatinib group vs. 83% in placebo group (HR for RFS 0.35, 95% CI 0.22 to 0.53).



Comparison of recurrence-free survival in the modified intention-to-treat population (A) and the efficacy population (B). Comparison of overall survival in the modified intention-to-treat population (C) and the efficacy population (D). The 3-year survival rates of patients assigned to 36 months of imatinib and those assigned to 12 months of imatinib are 86.6% vs 60.1% (A), 88.1% vs 62.1% (B), 96.3% vs 94.0% (C), and 97.6% vs 95.8% (D), respectively, and the 5-year survival rates, 65.6% vs 47.9% (A), 67.4% vs 50.3% (B), 92.0% vs 81.7% (C), and 93.9% vs 81.7% (D).

Figure 8. Comparison of recurrence free and overall survival in groups treated with 12 months versus 36 months of Imatinib[38]

In a later analysis, the absolute benefit was greatest in patients with high risk disease with relapse rate of 47% in placebo group versus 19% in Imatinib group. [40]

Another intergroup study EORTC 62024 looking at adjuvant Imatinib versus observation alone for two years has completed accrual with overall survival as primary end point. Data are awaited. Another single arm study PERSIST5, looking at 5 years of adjuvant Imatinib has completed accrual and data are awaited.

Based on results thus far, general consensus including guideline from NCCN is that

(1) High risk GIST patient should be treated with adjuvant Imatinib for at least three years or perhaps for indefinite period
(2) It is unclear whether a higher dose of Imatinib is needed in certain patients based on kinase genotype. Patients with exon 9 mutations do better with Imatinib dose of 800 mg/day in studies

conducted in advanced GIST. Whether these patients with exon 9 mutations will do better with 800 mg dose in adjuvant setting is unclear.

(3) Kinase genotype is not integrated in risk stratification schemes and it is unclear whether patients with high risk genotypes irrespective of other features need systemic adjuvant therapy

(4) Kit negative tumors were not included in these studies

(D) **Management of Advanced Disease**. Prior to introduction of Imatinib in 2000, there was no known effective therapy for unresectable or metastatic GISTs. Responses to systemic chemotherapy were very poor. Finding of gain of function mutation in c- KIT[4] or PDGFRα[13] revolutionized the field by opening the door for effective systemic therapy in the form of small molecule RTK inhibitor Imatinib.[41]

Imatinib induces dramatic responses with sustained clinical benefit in GISTs patients. Systemic therapy with Imatinib is associated with marked improvement in overall survival.

Prior to Imatinib, outlook for patients even after complete surgical resection was poor as shown below in figure 9

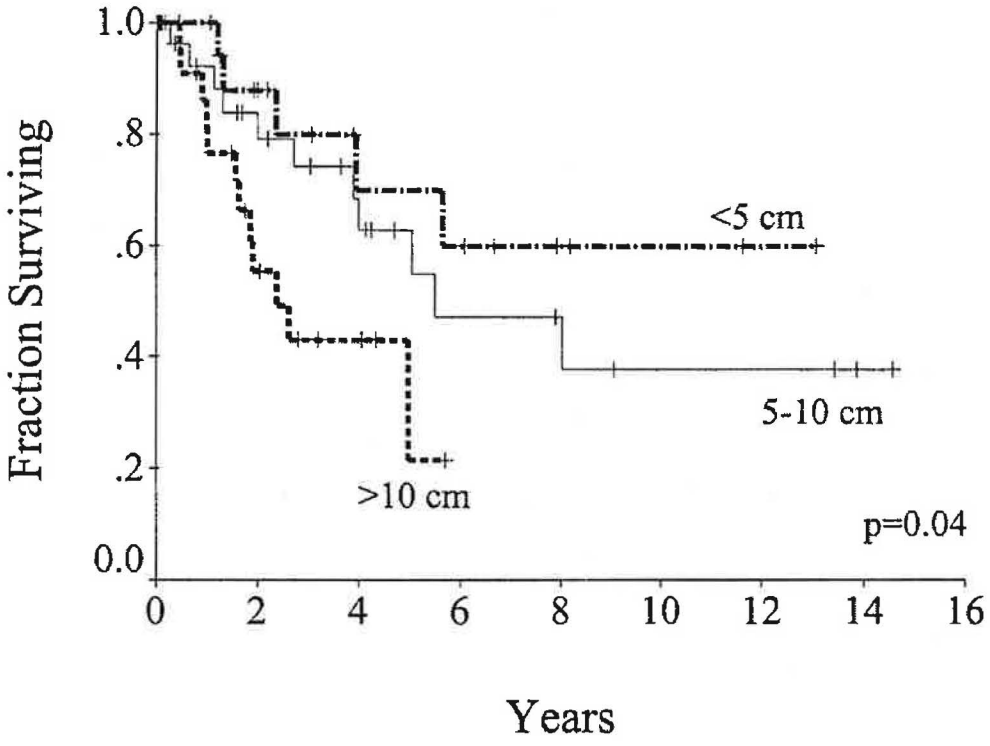


Figure 9. Disease-specific survival after complete resection of primary GIST based on tumor size[42]

Both systemic chemotherapy and radiation treatment were ineffective in treatment of metastatic GIST with response rates consistently less than 20%.

Joensuu et al reported first patient with metastatic GIST treated with Imatinib.[43] The patient had CD117 positive tumor and contained an exon 11 mutation in the c-kit gene. The patient had progressive widely metastatic disease after failing extensive previous therapy including multiple surgeries, chemotherapy, and even investigational antiangiogenic therapy. The patient had major objective response after initiation of daily oral STI-571 (Imatinib) which was maintained for more than 18 months. On subsequent serial biopsies, the tumor demonstrated myxoid degeneration and fibrosis.

Encouraging results in the first patient combined with rational scientific basis led to a rapid adaptation of Imatinib into treatment of patients with advanced GIST. Several studies were conducted which established marked efficacy of Imatinib in these patients. Two studies conducted by US-Finland Collaborative GIST study group and EORTC were presented in ASCO 2001 annual meeting. Both of these studies demonstrated marked efficacy of Imatinib in GIST patients. The results from these two studies and from other large studies are given in Table 4

Study Sponsor/Ref	Phase	N	CR	PR	SD	PD
EORTC[44]	I	35	0	54	37	9
US-FINLAND B2222[45]	II	147	1.4	67	16	12
EORTC[46]	II	27	4	69	18	
Intergroup S0023[47]	III	746	3	45	26	13
EORTC/ISG/AGITG[46]	III	946	5	47	32	11

Table 4. Results from major studies evaluating efficacy of Imatinib in patients with advanced GIST. Only updated results from B2222 and Intergroup S0023 are shown.

Median time to achieve response to Imatinib is 12-15 weeks. Many patient notice subjective improvement in symptoms within days. FDG avidity of lesions on PET-CT may decrease as early as 24 hours after first dose of Imatinib. However, decrease in size of tumor may take several months to a year to satisfy RECIST criteria for partial response (PR). Early after initiating therapy with Imatinib, most responding lesions become hypo dense and do not enhance on CT without significant change in size. At times lesions may even appear larger than initial size. Thus, response evaluation by RECIST criteria, particularly early in the course is of limited value. Modified response evaluation criteria as proposed by Choi[48] or evaluation based on metabolic imaging with PET-CT[49] are more likely to predict response to therapy.

Responses induced by Imatinib are durable with median response duration of ≥2 years. Progression free and overall survival on meta-analysis[50] performed on 1640 patients included in

Intergroup S0023 and combined EORTC/ISG/AGITG are shown below in Figure 10. These patients were either treated with Imatinib 400 mg/day or 800 mg/day. There was no difference in either RFS or OS between these two groups.

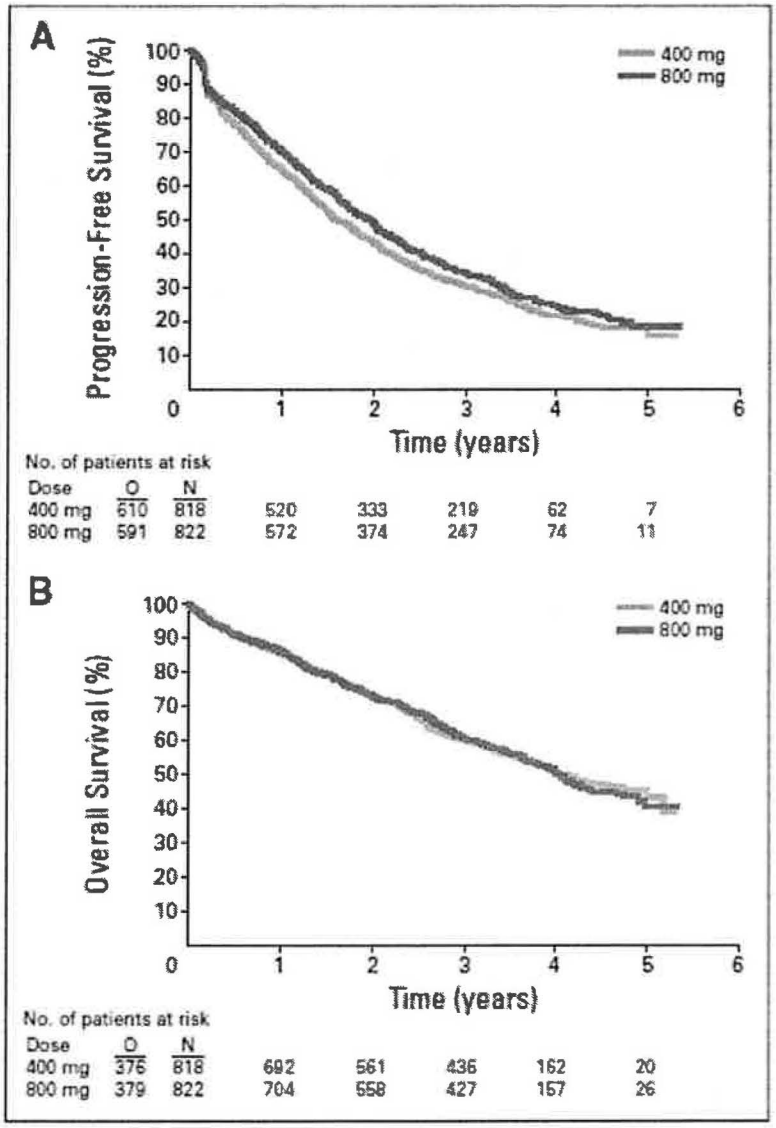


FIGURE 10. Progression Free and Overall Survival in patients with advanced GIST treated with 400 mg or 800 mg dose of Imatinib

Response rates and duration of response to Imatinib varies in patients with different kinase mutations.

	Kit 8	Kit 9	Kit 11	Kit 13	Kit 17	PDGFRα 12	PDGFRα 18	WT
CR/PR/SD	100 (1)	75 (24)	82.3(233)	60 (3)	75(3)	100 (1)	75 (3)	65.7(44)
PD		9.4 (3)	6.4 (18)	20(1)	25(1)		25 (1)	17.9(12)
NA		15.6 (5)	11.3 (32)	20(1)				16.4(11)

Table 5. Response rates based on kinase genotype. Adopted from data reported by Heinrich et al. [51]

In the study reported above, most patients had kit exon 11, kit exon 9 or wt phenotype. The number of patients with other c-kit or PDGFRα mutations was small. Nonetheless results from this and other reported literature suggest that Imatinib should be considered as initial therapy in most patients with advanced GIST irrespective of mutational status. All known patients with PDGFRα D842V has shown primary resistance to Imatinib and perhaps these patients should be considered for alternative therapies if available.

Question of optimal Imatinib dose has been evaluated in two large studies and analyzed further in a meta-analysis. Overall no significant difference either in response rates or duration of response was observed with 400 mg/day versus 800 mg/day dose of Imatinib. However, when results were analyzed based on kinase genotype, patients with kit exon 9 mutation did better with higher dose of Imatinib including improved overall survival. Progression free survival and overall survival with 400 mg Imatinib versus 800 mg Imatinib are shown below in Figure 11.

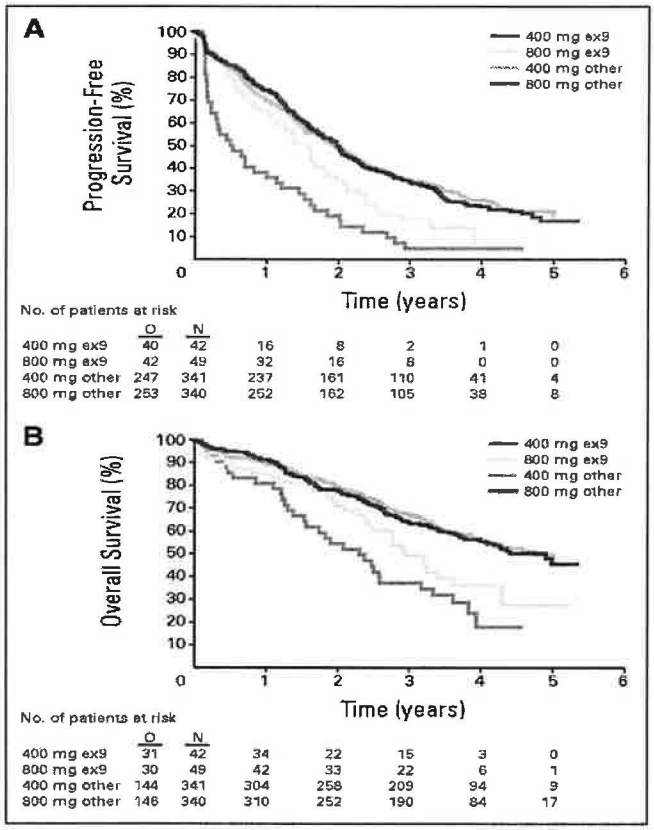


Figure 11. Progression free and overall survival in patients with exon 9 mutations treated with standard versus high dose Imatinibex9, exon 9; N, number of patients; O, events

(E) Imatinib Resistant Disease. Though most patients with advanced/metastatic GIST respond to initial therapy with Imatinib, 50% of responding patients will progress within two years and eventually most of the other patients develop disease refractory to Imatinib.

Early or primary resistance to Imatinib is mostly seen in patients with wt kit, kit exon 9 mutations and PDGFRα D842V mutation. Secondary Imatinib is seen through (a) acquisition of a secondary mutation in the kit or PDGFR genes (b) genomic amplification of kit and overexpression of the protein and (c) activation of other RTKs. Secondary mutations in c-kit or PDGFRα, are almost always involve same earlier mutated allele.

Patient may demonstrate focal resistance to Imatinib with limited progression of disease. In such patients, ablative approaches to lesion demonstrating progression such as surgical resection, embolization or RFA combined with continued therapy with Imatinib may provide meaningful benefit.

Patients demonstrating generalized progression of disease may benefit from treatment with a different small molecule RTK inhibitor.

Sunitinib, a small molecule multi tyrosine kinase inhibitor (Kit, PDGFR, VEGFR, FLT-3 and RET) demonstrated substantial activity in patients with advanced GIST with disease progression on Imatinib. In a pivotal phase III trial,[52] 312 patients were randomized to receive either Sutent or placebo in 2:1 ratio in blinded manner with time to tumor progression as primary end point. Results obtained are shown in Figure 12

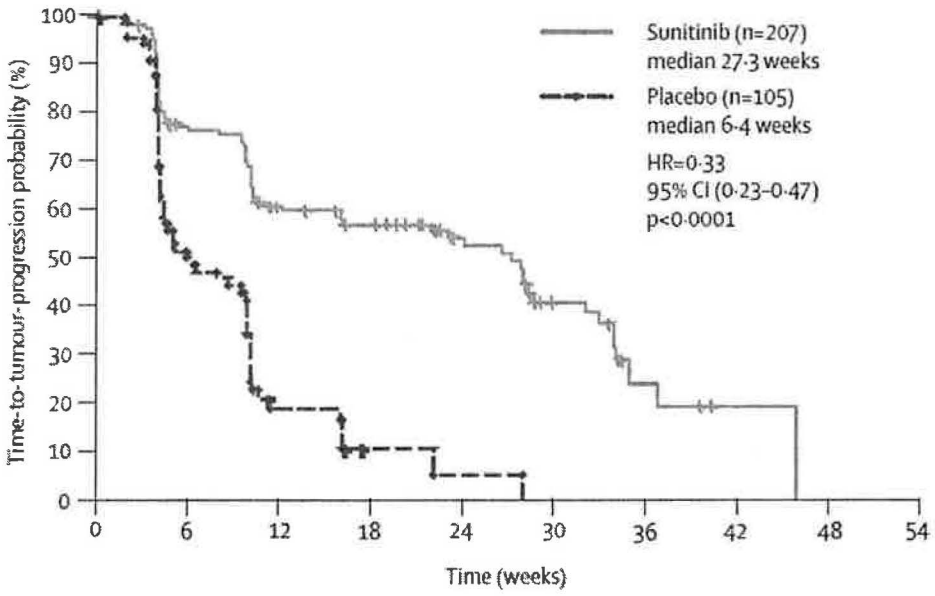
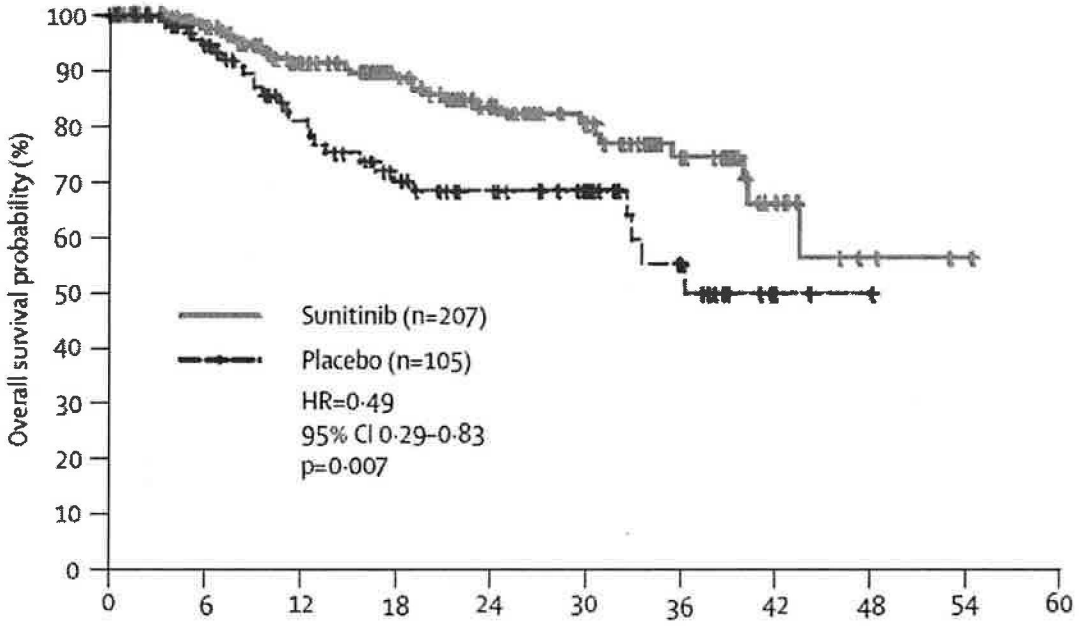


Figure 12. Kaplan-Meier estimates of time to tumor progression in patients treated with Sunitinib versus placebo[52]

Sunitinib increased the median time to tumor progression four-fold compared with placebo (from 6.4 to 27.3 weeks). Overall survival prior to permitted cross over is shown below in Figure 13.



Number at risk											
Sunitinib	207	167	117	97	71	50	31	11	3	1	0
Placebo	105	85	57	43	31	22	13	3	1	0	0

Figure 13. Kaplan-Meier estimates of overall survival in patients treated with Sunitinib versus placebo[52]

Based on these results, Sunitinib was approved by FDA for treatment of GIST after disease progression on Imatinib or in patients intolerant to Imatinib.

Benefit seen with Sunitinib is modest at best. It is possible that patients with localized progression of disease will do better with continued therapy with Imatinib in combination with ablative therapy to lesions demonstrating progression. However, this remains to be resolved.

Several other TKIs are being evaluated in patients with GIST either in first line setting as compared to Imatinib or in patients with who have progressed on Imatinib and Sunitinib.

Sorafenib, another multi TKI with kinase inhibitor profile similar to Sunitinib (more active at RAF) was evaluated in phase II study. 38 were enrolled. 13 % PR, 55% SD giving rise to a Disease control rate (PR + SD) of 68%. Median progression-free survival was 5.2 months and Median overall survival 11.6 months. These results demonstrate significant activity of Sorafenib in this patient population and warrants further study.

Regorafenib, a multi TKI, structurally related to sorafenib was evaluated in GIST patients after failure of Imatinib and Sunitinib. Regorafenib demonstrated impressive activity in phase II trial as shown below in Figure 14[53]

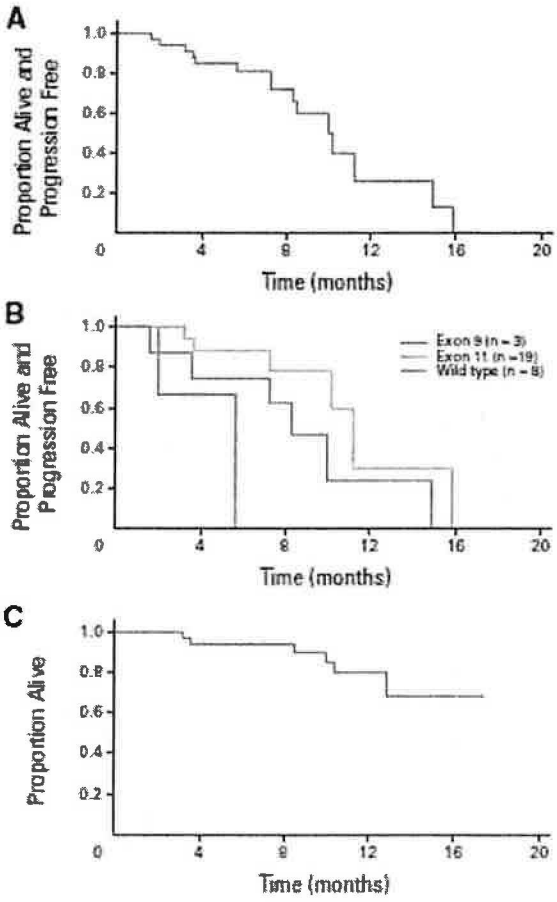


Figure14. Kaplan-Meier estimates of (A) progression-free survival (PFS) for the entire cohort (n 33); (B) PFS by genotype for patients with exon 9 *KIT* mutations (n 3), exon 11 *KIT* mutations (n 19), and wild type for both *KIT* and *PDGFRA* (n 8); and (C) overall survival (OS) for the entire cohort (n 33). Median PFS for the entire cohort was 10.0 months (95% CI, 8.3 to 14.9 months); median OS has not yet been reached.

Regorafenib since has been evaluated in a phase III trial. A total of 234 patients were screened and 199 were randomized with 133 patients on Regorafenib arm and 66 patients to placebo. Median PFS was 4.8 months for Regorafenib versus 0.9 months for placebo.[54]

Regorafenib is currently under evaluation for FDA approval.

Other TKIs including Nilotinib, Dasatinib, MLN518, Vatalanib, OSI-930, AZD2171, Amuvatinib, TKI 258, Pazopanib, Masitinib, Crenolanib, DCC-2618; HSP90 inhibitors; mTOR inhibitors are in different phase of development.

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