The Role of Surgery in GIST Treatment

Neoadjuvant and Adjuvant Therapy

Jason Sicklick, MD, FACS

Professor of Surgery | Division of Surgical Oncology

Adjunct Professor | Department of Pharmacology

Executive Vice Chair of Research | Department of Surgery

Co-Leader, Sarcoma Disease Team | Moores Cancer Center

jsicklick@health.ucsd.edu

@JasonSicklick

UC San Diego
MOORES CANCER CENTER

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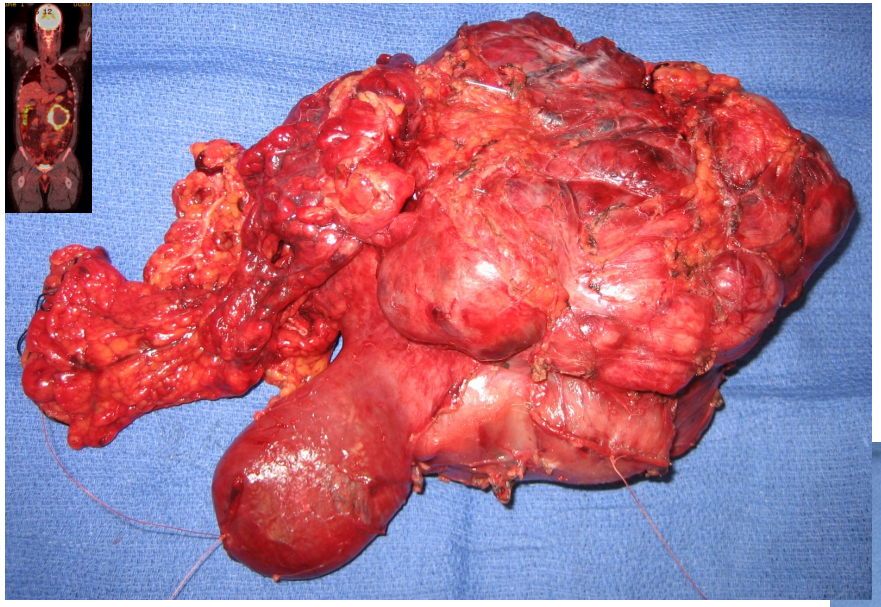
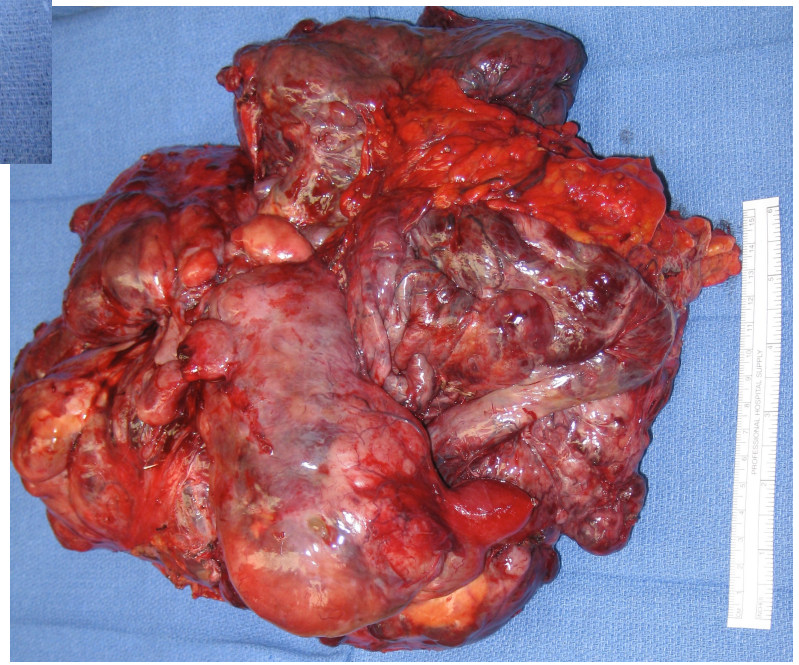
Surgical Resection May Be Curative…



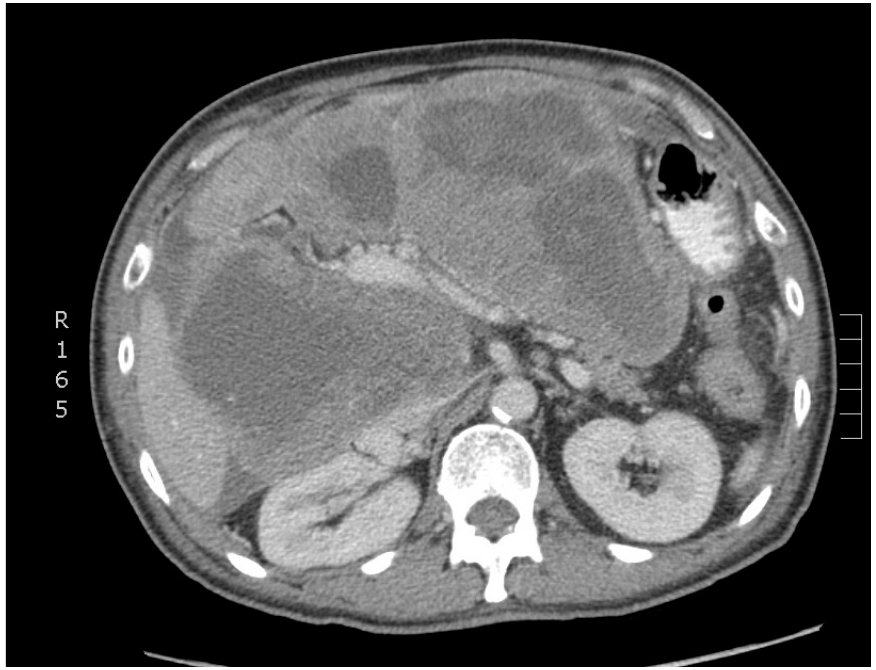


Goals of Resection in GIST > 2 cm

- Total gross resection without tumor rupture (including disruption of tumor capsule)
- Negative microscopic margins (R0)
- Lymphadenectomy is not generally indicated because LN metastases are uncommon outside SDH-def GIST and gene fusion GIST

Complete Resection

Not Always Possible



Fanta, Sicklick, et al. *JCO*, March 2014.

Factors to Consider

		Location & Anatomy	
		Good	***Bad***
Biology	***Good***	Good Location Good Biology	Bad Location Good Biology
	Bad	Good Location Bad Biology	Bad Location Bad Biology

Neoadjuvant Therapy?

Definitions

Neoadjuvant Therapy

Operation

OPEN PROCEDURE

LAPAROSCOPIC PROCEDURE

Adjuvant Therapy

NCCN & ESMO Recommendations

Neoadjuvant Treatment

1. Marginally resectable disease (i.e., locally advanced or large tumors) where total gross resection may not be feasible
2. Likely positive margins
3. Potential for adjacent organ sparing
4. Opportunity for less extensive operation
5. Potential for safer operation (e.g., less bleeding or lower risk of tumor rupture)

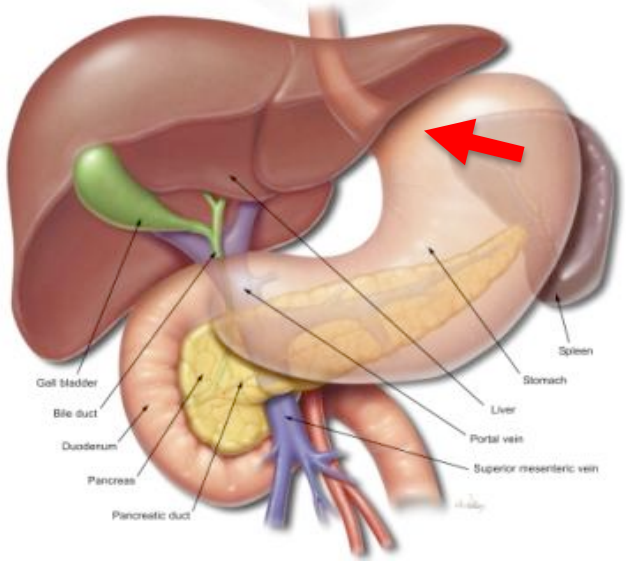
Studies to Support Safety and Efficacy

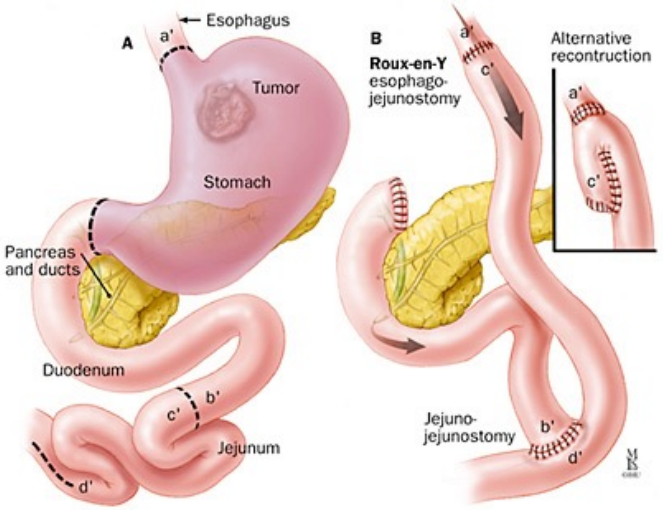
Trial (phase)	Imatinib dosage and duration	Patients	Outcomes	Safety
RTOG S032/ ACRIN 6665[49] Phase II, nonrandomized, prospective trial	Neoadjuvant: 600 mg/d for 8–12 wk Adjuvant: 400 mg/d for 2 yrs Follow-up: 3 yr	*N* = 63 (52 analyzable): 30 with primary GIST; 22 with recurrent/ metastatic	Primary GIST: 7% PR; 83% SD; 10% unknown Recurrent GIST: 4.5% PR; 91% SD; 4.5% PD 2-yr PFS: 83% for primary; 77% for recurrent 2-yr OS: 93% for primary; 91% for recurrent	Post-operative toxicities: 29% Gr 3; 16% Gr 4; 4% Gr 5
BFR14 substudy[59] Phase III, BFR14 database sub-analysis (retrospective)	Median treatment duration prior to surgery: 7.3 mo	*N* = 25 (9 patients underwent resection) locally advanced GIST without metastases	Median PFS: not reached for resected vs 29.4 mos for non-resected Median OS: Median not reached for resected vs 42.2* months for non-resected	NA

Eisenberg and Trent. *Int J Cancer*. 2011.

“Bad” Location

- **Gastroesophageal junction**
  - Avoid total gastrectomy





- Tielen R, Verhoef C, van Coevorden F, Gelderblom H, Sleijfer S, Hartgrink HH, Bonenkamp JJ, van der Graaf WT, de Wilt JH. Surgical treatment of locally advanced, non-metastatic, gastrointestinalstromal tumours after treatment with imatinib. Eur J Surg Oncol 2013;39:150-155.
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“Bad” Location

- **Gastroesophageal junction**
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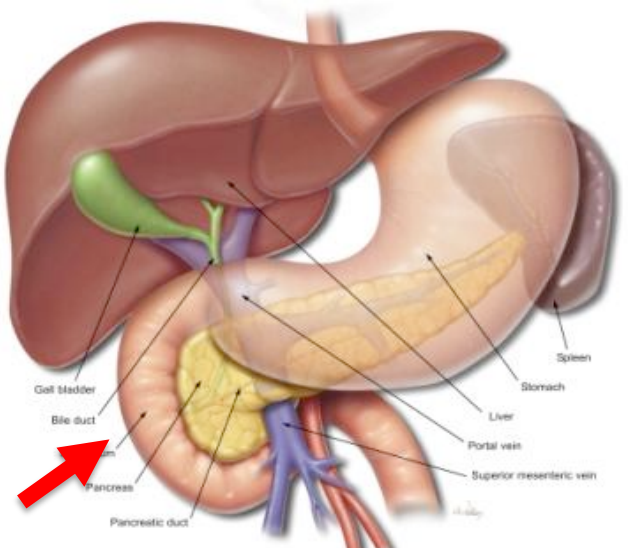
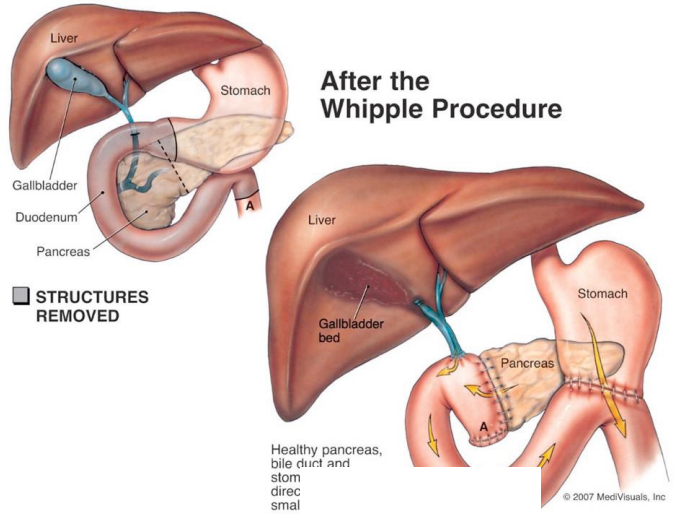
- **Duodenum**
  - Avoid Whipple(s) operation (pancreaticoduodenectomy)





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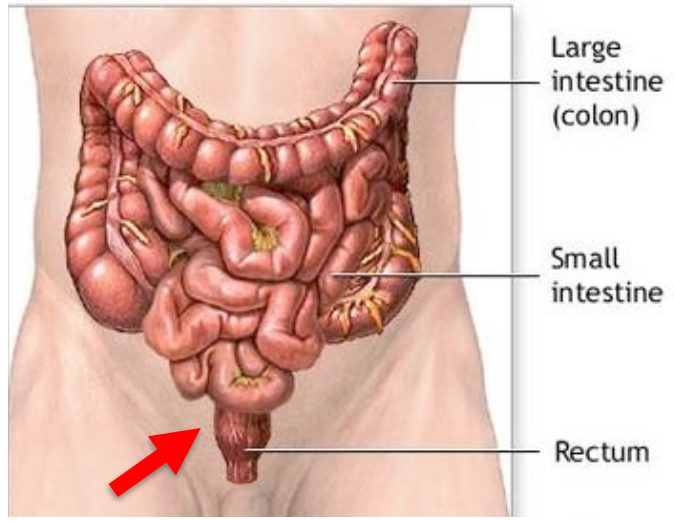
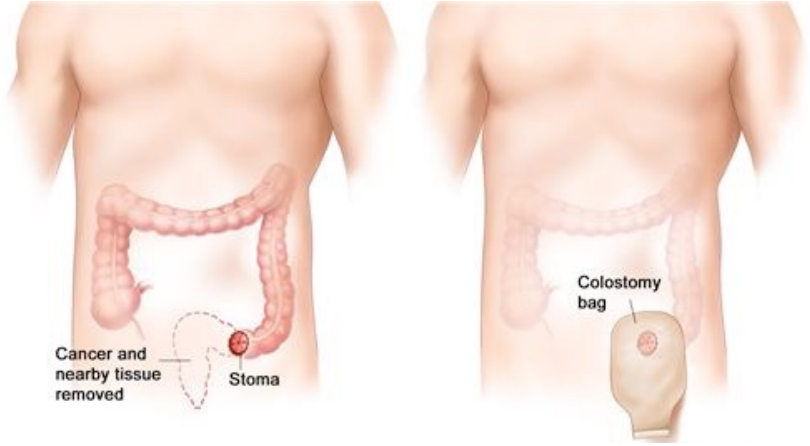
“Bad” Location

- **Gastroesophageal junction**
  - Avoid total gastrectomy
- **Duodenum**
  - Avoid Whipple(s) operation (pancreaticoduodenectomy)
- **Rectum**
  - Avoid Low Anterior Resection (LAR)
  - Avoid Abdominoperineal Resection (APR)





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Bad Location + Bad Biology

Fanta, Sicklick, et al. *JCO*. 2015.

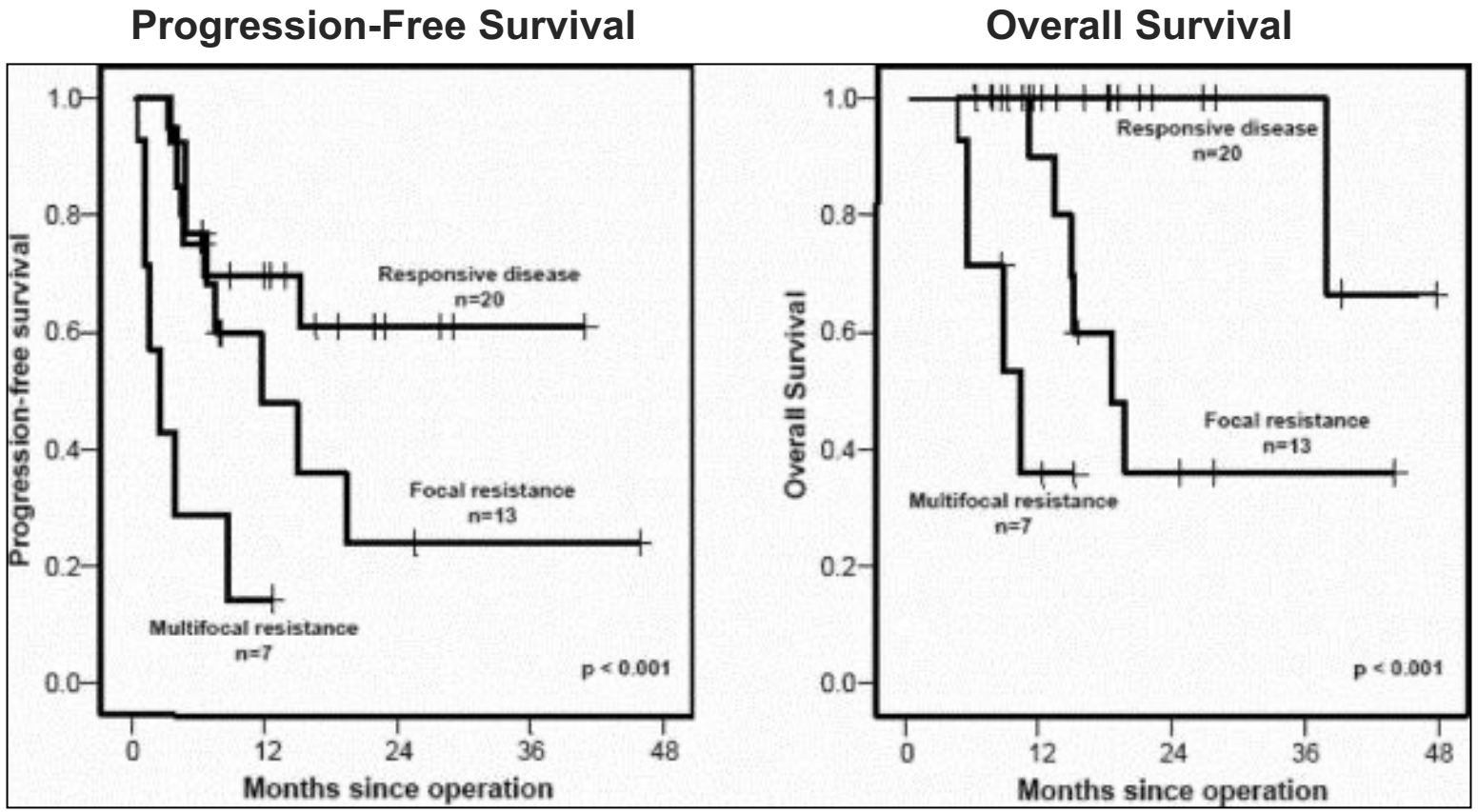
Pre-imatinib

2.5 months

4 months

Biology Beats Technique

If Tumors Respond…*Patients Do Better.*



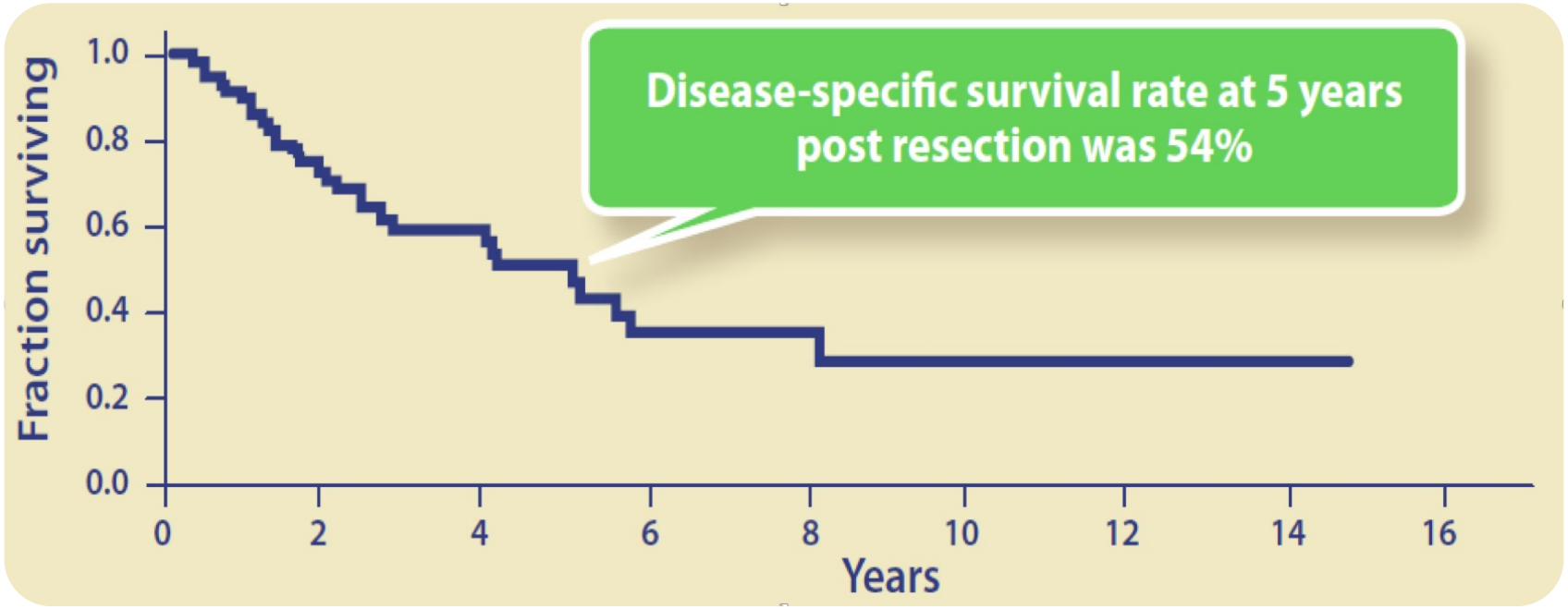
DeMatteo, et al.. *Annals of Surgery*. 2007.

Neoadjuvant Therapy Summary

- Neoadjuvant imatinib therapy is generally safe for patients with GIST, but bleeding with response may occur.
- Treatment is usually recommended for 6-9 months to achieve maximal response.
- Treatment may be stopped earlier if additional response will not change conduct or safety of the operation.
- Imatinib may be stopped immediately before an operation and may be restarted once the patient has recovered.
- Tumor mutation analysis may help exclude patients with imatinib-resistant mutations (e.g., *PDGFRA* D842V) from consideration for neoadjuvant imatinib therapy
- Currently lacking established safety data for neoadjuvant avapritinib for *PDGFRA* D842V mutant GIST

Risk of Recurrence (ROR)

- Resection is the primary treatment for localized GIST
- However, it is *not* routinely curative despite complete gross resection
  - ≥50% patients will develop recurrence or metastasis
  - 5-year OS rate is ~50%[1,2]



1. NCCN Clinical Practice Guidelines in Oncology. Soft Tissue Sarcoma. V3.2012
2. DeMatteo RP, et al. Ann. Surg. 2000;231(1):51-58.

ROR Depends on 4 Prognostic Factors

Assessment Methodology	Mitotic Rate	Tumor Size	Tumor Site	Tumor Rupture	Peritoneal Dissemination	Mucosal Invasion	Mutational Status
Fletcher, et al, 2002 (NIH Guidelines)[1]	●	●					
Huang, et al, 2007[2]	●	●					
Miettinen, et al, 2006[3]	●	●	●				
Mucciarini, et al, 2007[4]	●	●	●				
Hassan, et al, 2008[5]	●	●	●				
DeMatteo, et al, 2008[6]	●	●	●				
Joensuu, 2008 (Modified NIH)[7]	●	●	●	●			
Gold, et al, 2009[8]	●	●	●				
Takahashi, et al, 2007[9]	●	●	●	●	●	●	
Singer, et al, 2002[10]	●						●
Edge, et al, 2010[11]	●	●	●				
Joensuu, et al, 2012[12]	●	●	●	●			

Modified NIH Criteria (Joensuu)

Risk category	Tumor size (cm)	Mitotic index (per 50 HPFs)	Primary tumor site
Very low risk	<2.0	≤5	Any
Low risk	2.1-5.0	≤5	Any
Intermediate risk	2.1-5.0	>5	Gastric
	<5.0	6-10	Any
	5.1-10.0	≤5	Gastric
High risk	Any	Any	Tumor rupture
	>10 cm	Any	Any
	Any	>10	Any
	>5.0	>5	Any
	2.1-5.0	>5	Nongastric
	5.1-10.0	≤5	Nongastric

Mitotic Index (MI)
Mitoses per 50 hpf (old microscopes)
Mitoses per 20 hpf (new microscopes)
Mitoses per 5 mm^2 (standardized)

Tumor rupture is a poor prognostic factor

Joensuu H. *Hum Pathol.* 2008.

Definitions

Neoadjuvant Therapy

Operation

OPEN PROCEDURE

LAPAROSCOPIC PROCEDURE

Adjuvant Therapy

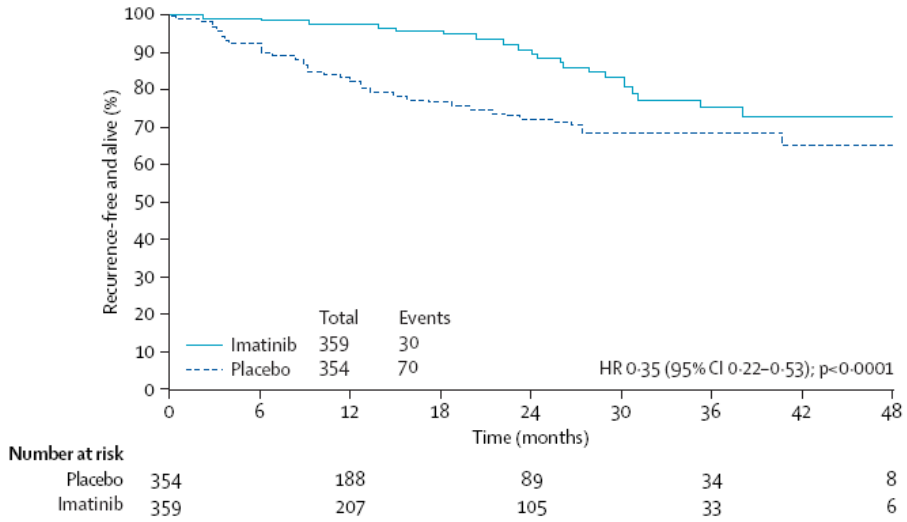
Adjuvant Imatinib Therapy

- **Total trials = 12**
  - Pilot/retrospective studies (N=2)
  - Phase II (N=7)
  - Phase III (N=3)
- **Duration of therapy**
  - Duration ≤ 1 year (N=5)
  - Duration ≥ 1 year (N=7)

2 Pivotal Trials

Phase III randomized, double-blind, placebo-controlled ACOSOG Z9001

- Multicenter
- 713 patients with KIT-positive GIST of ≥3 cm in size
- Treated with imatinib (359) or placebo (354) for 1 year
- **Estimated 1-year RFS rate was significantly higher in the imatinib arm (98%) compared with the placebo arm (83%; [HR], 0.35; *P* < 0.0001) >> early termination**
- No difference in OS at 4 years of follow-up.
- FDA Approval in 2009 for adjuvant imatinib



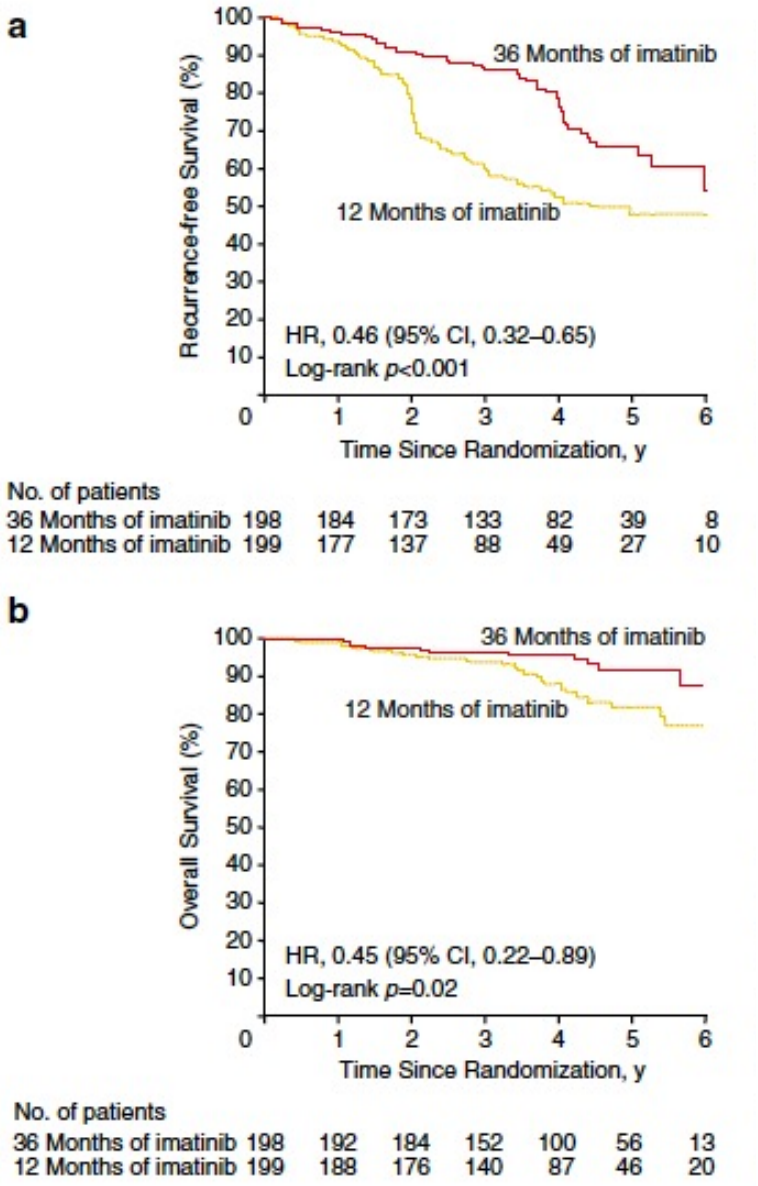
DeMatteo et al., *Lancet*, 2009.
Corless et al., *JCO*, 2010.

Adjuvant Imatinib for High ROR

- Phase III RCT
- Scandinavian Sarcoma Group (SSG) XVIII/AIO
- Patients with high risk GIST (modified NIH):

Rule of 10s

>10 cm
MI >10
>5 cm + MI >5
Tumor rupture



5-year OS

92% (3 yr)

81.7% (1 yr)

Adjuvant Imatinib for 3 years is now the gold standard for high-risk GIST

Joensuu et al. *JAMA*, 2012.

Optimal Duration of Adjuvant Therapy?

Risk category	Tumor size (cm)	Mitotic index (per 50 HPFs)	Primary tumor site
Very low risk	<2.0	≤5	Any
Low risk	2.1-5.0	≤5	Any
Intermediate risk	2.1-5.0	>5	Gastric
	<5.0	6-10	Any
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High risk	Any	Any	Tumor rupture
	>10 cm	Any	Any
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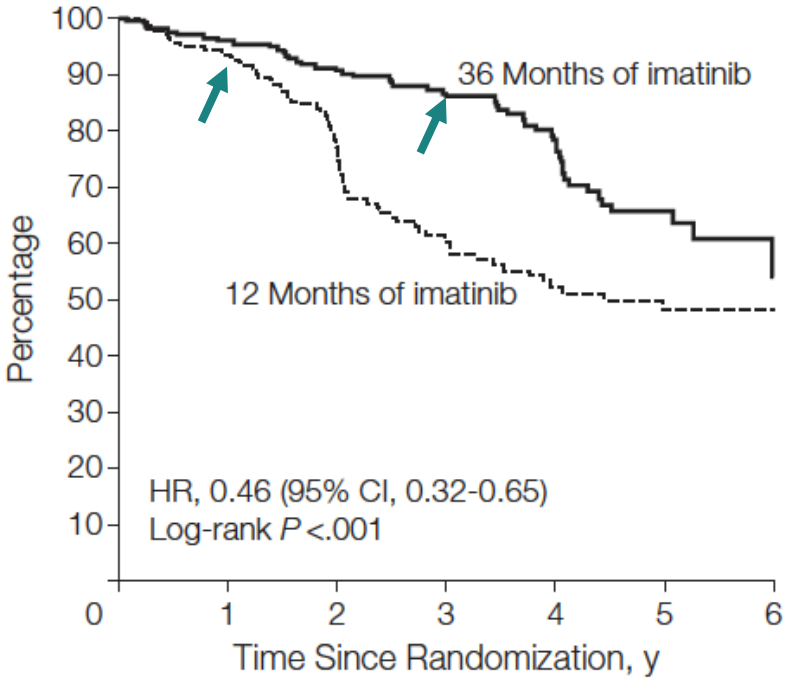

No. of patients

36 Months of imatinib	198	184	173	133	82	39	8
12 Months of imatinib	199	177	137	88	49	27	10

Recurrences begin at 8 months after stopping therapy….

Many experts will recommend indefinite imatinib or until recurrence/intolerance

Joensuu et al., *JAMA*, 2012

Adjuvant Therapy Summary

- Assessing an individual patient's risk for GIST recurrence is essential, as GIST may recur despite complete gross resection
- Risk assessment is complex, with 4 factors reported to be predictive of recurrence
- If a patient is recommended for adjuvant imatinib therapy, mutation profiling should be performed as only *KIT* and select *PDGFRA* mutations are imatinib sensitivity
- Adjuvant imatinib for ≥3 years is the gold standard for high-risk GIST (modified NIH Criteria) with consideration of 5 years (or even lifelong) therapy, although one may consider tailoring this to intermediate risk patients in select cases

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#11 GASTROENTEROLOGY & GI SURGERY

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THANK YOU!

Jason Sicklick, MD

jsicklick@health.ucsd.edu

@JasonSicklick