



Not all Surgeries are the Same: Neoadjuvant Therapy

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HEALTH SYSTEM

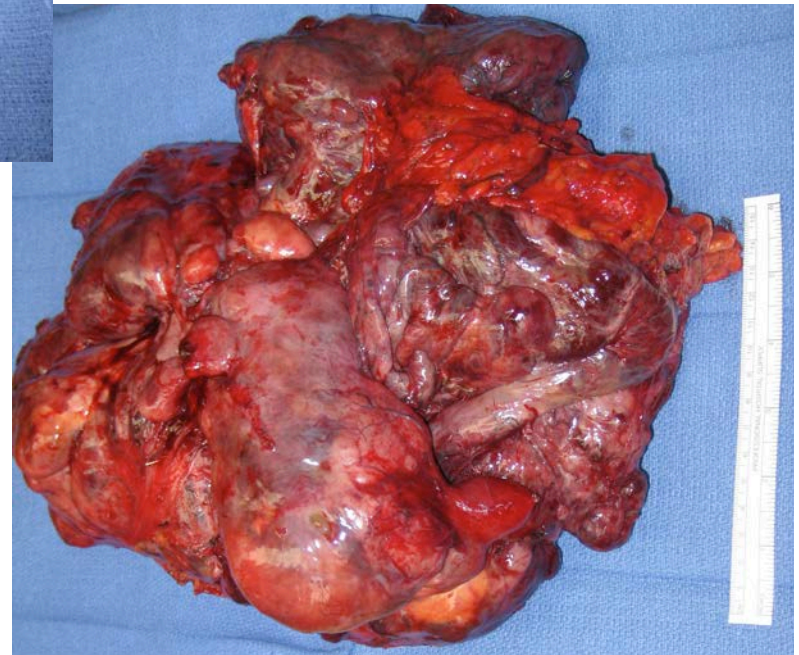
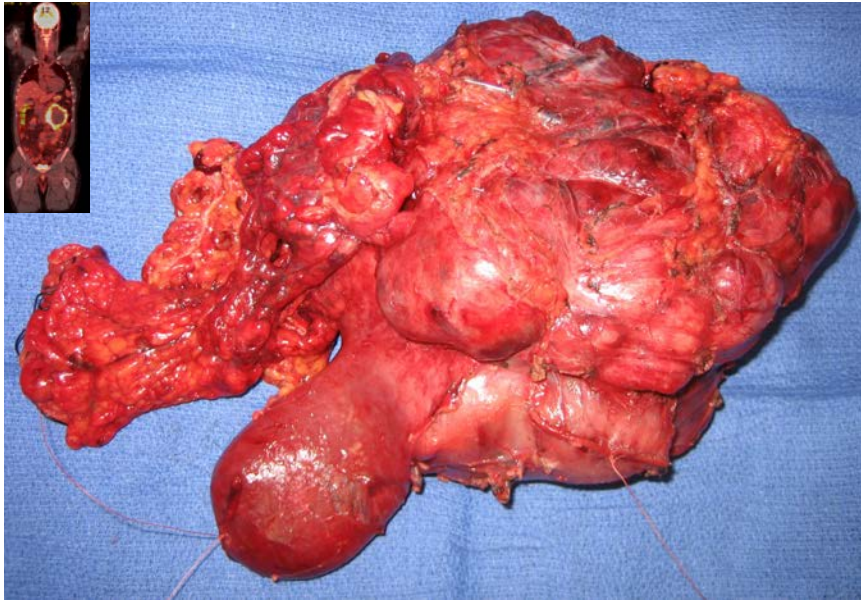
Where discoveries are delivered.SM

Goals of Operation

- Total gross resection
- Negative microscopic margins
- Avoid tumor rupture



Surgery is Only Potentially Curative Therapy



Complete Resection

Not Always Possible



Is there a role for
neoadjuvant (preoperative)
therapy before surgical
resection?

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	<i>N</i> = 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	<i>N</i> = 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
Apollon CST1571 BDE43 Phase II, open label trial ⁵⁵	400 mg/d for 4–6 mo	<i>N</i> = 40 (target)	Primary endpoint: overall tumor response	NA

Eisenberg and Trent. Adjuvant and neoadjuvant imatinib therapy: current role in the management of gastrointestinal stromal tumors. *Int J Cancer*. 2011.

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)

Summary of Recommendations

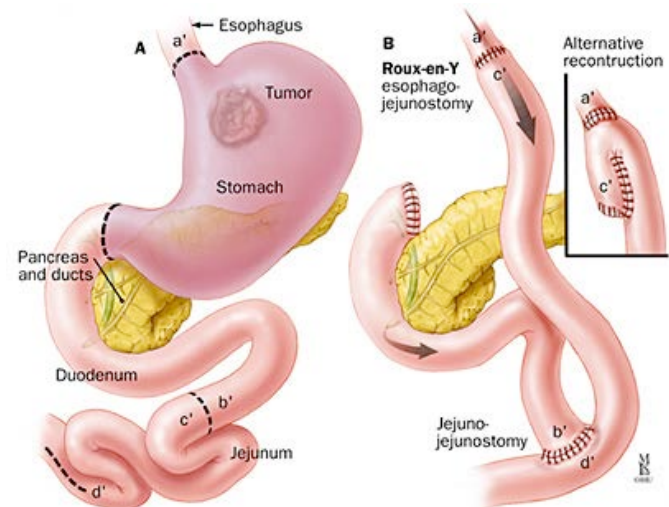
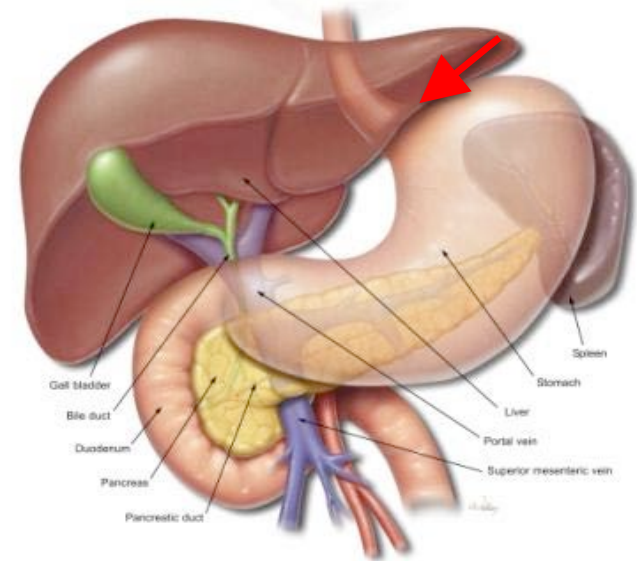
Factors to Consider:

1. Location / Anatomy
2. Biology
3. Both

		Location	
		Good	Bad
Biology	Good	Good Location Good Biology	Bad Location Good Biology
	Bad	Good Location Bad Biology	Bad Location Bad Biology

“Bad” Location

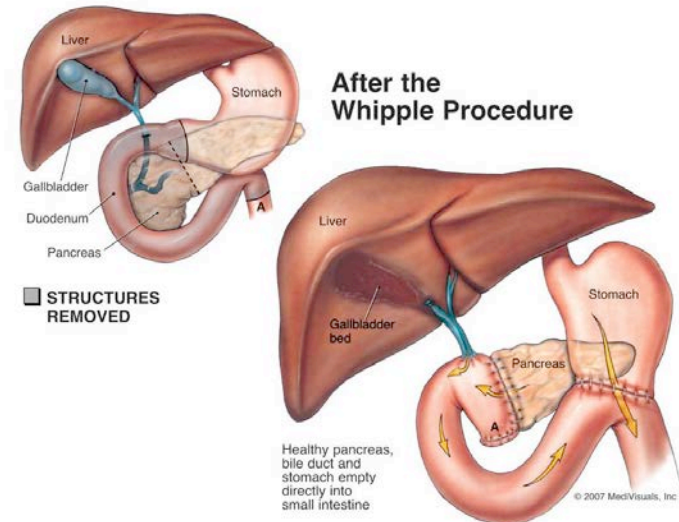
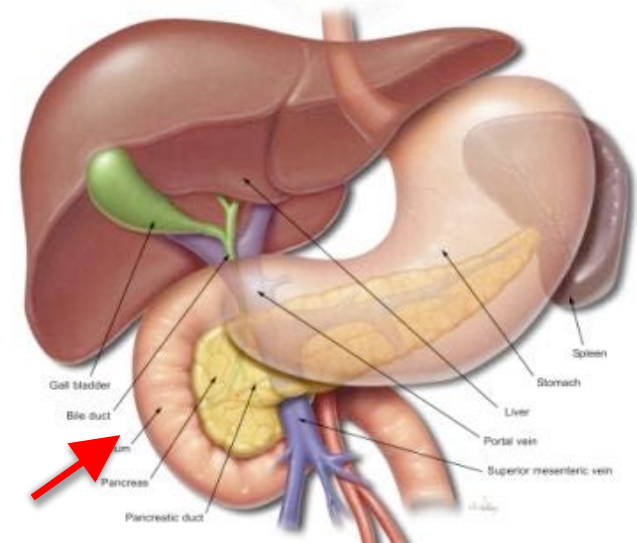
- Gastroesophageal junction



- 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, gastrointestinal stromal tumours after treatment with imatinib. *Eur J Surg Oncol* 2013;39:150-155.
- Doyon C, Sidéris L, Leblanc G, Leclerc YE, Boudreau D, Dubé P. Prolonged therapy with imatinib mesylate before surgery for advanced gastrointestinal stromal tumor results of a phase II trial. *Int J Surg Oncol* 2012;2012:761576.
- Koontz MZ, Visser BM, Kunz PL. Neoadjuvant imatinib for borderline resectable GIST. *J Natl Compr Canc Netw* 2012;10:1477-1482.

“Bad” Location

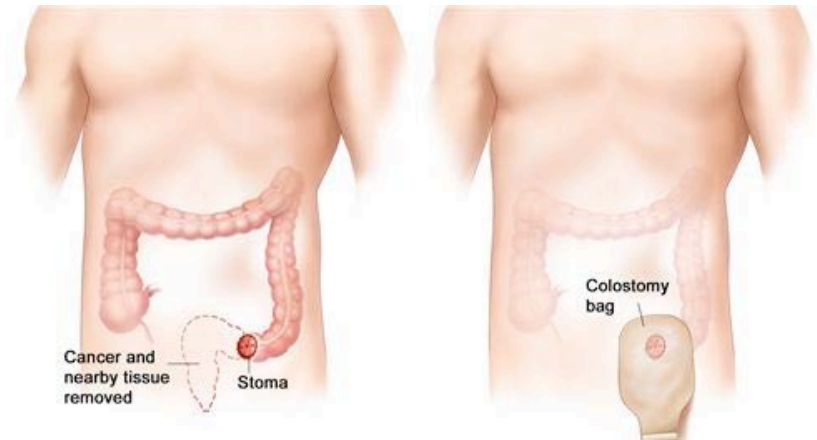
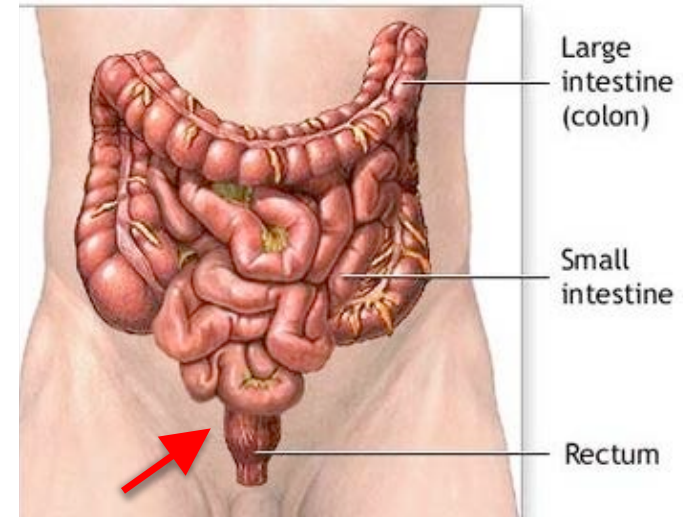
- Gastroesophageal junction
- Duodenum



- 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, gastrointestinal stromal tumours after treatment with imatinib. *Eur J Surg Oncol* 2013;39:150-155.
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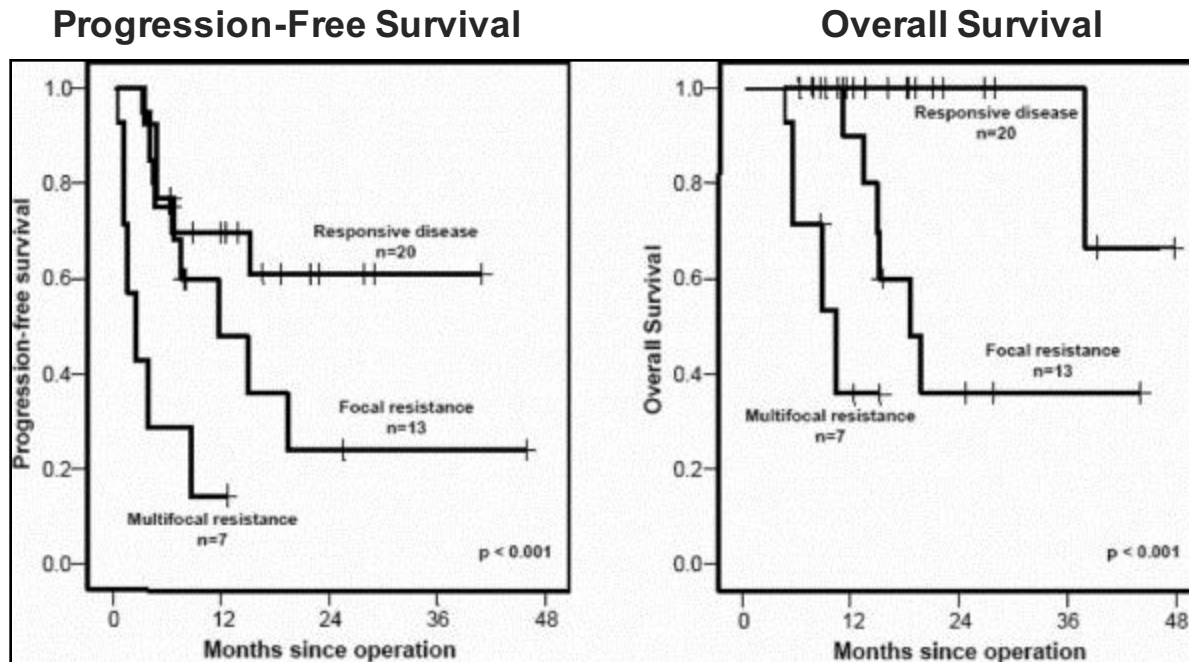
- Gastroesophageal junction
- Duodenum
- Rectum



- 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, gastrointestinal stromal tumours after treatment with imatinib. *Eur J Surg Oncol* 2013;39:150-155.
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Biology

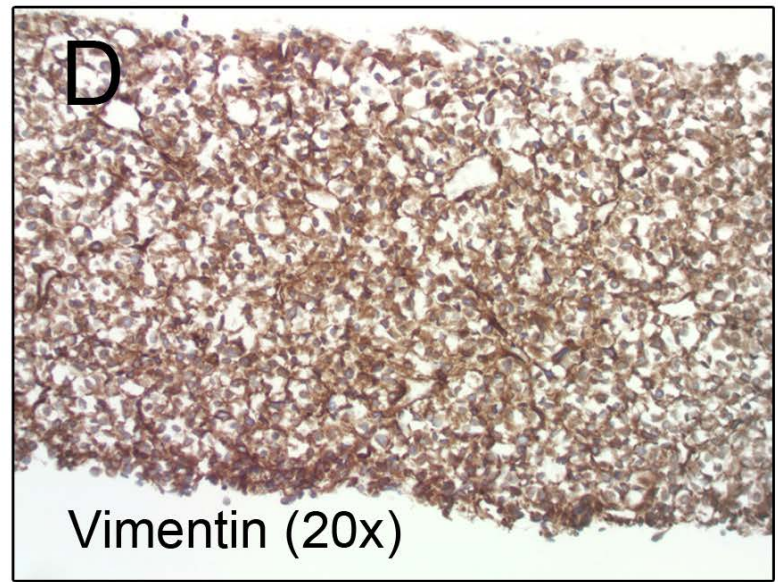
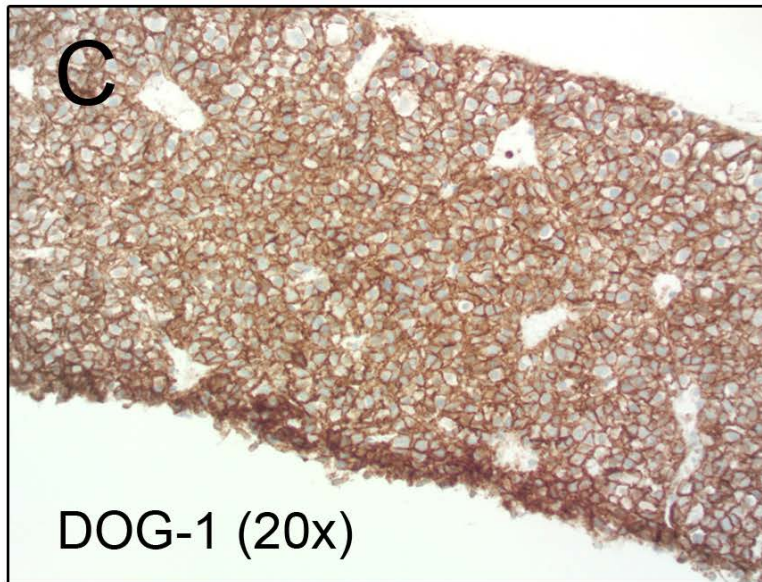
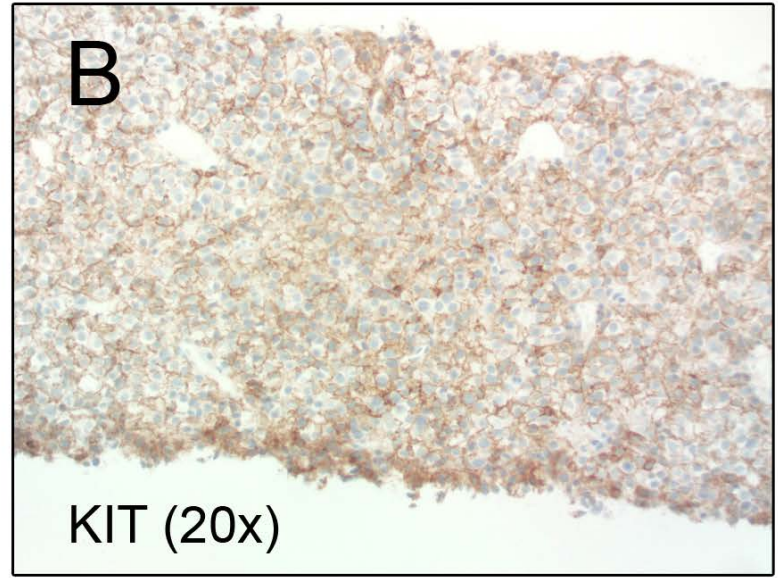
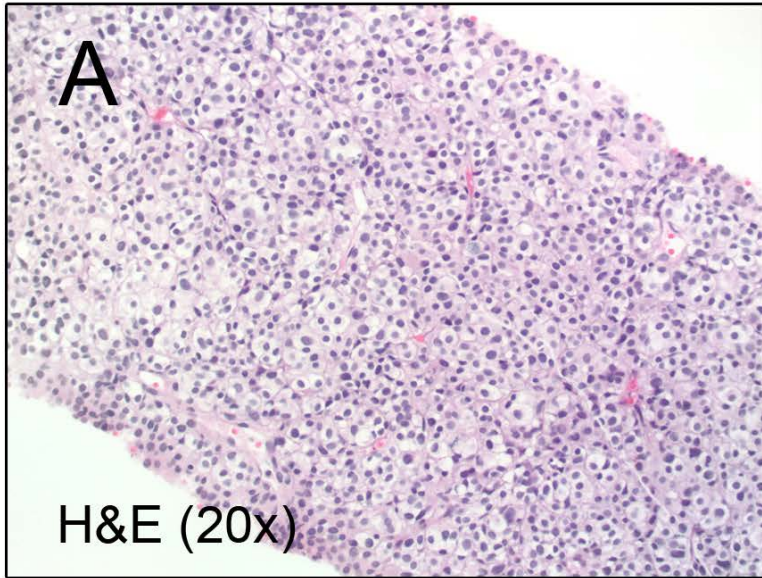
If Patients Respond... *They Do Better.*



DeMatteo, et al. Results of Tyrosine Kinase Inhibitor Therapy Followed by Surgical Resection for Metastatic Gastrointestinal Stromal Tumor. *Annals of Surgery*. 2007.

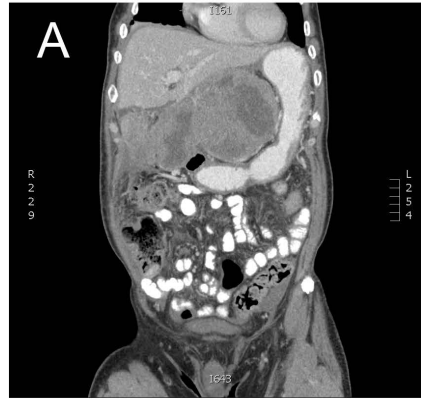
Bad Location and Bad Biology



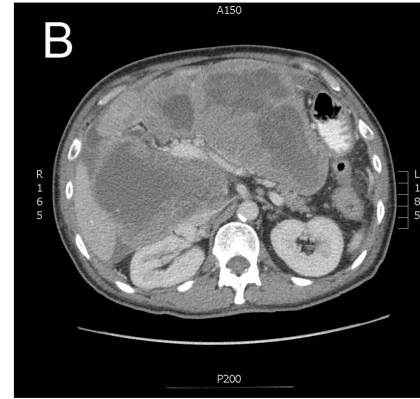


Pre-imatinib

Coronal



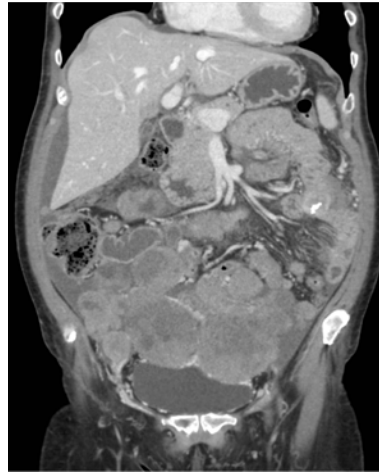
Axial



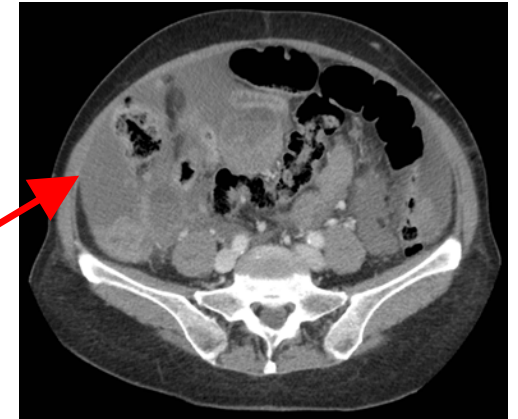
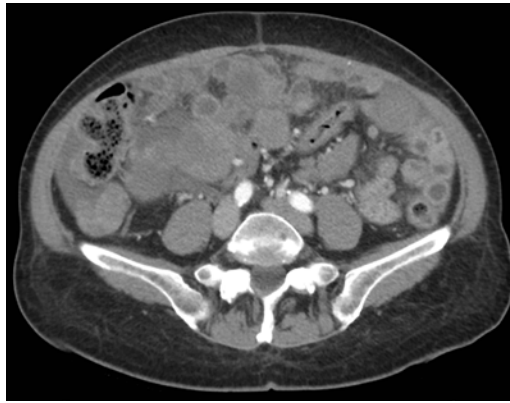
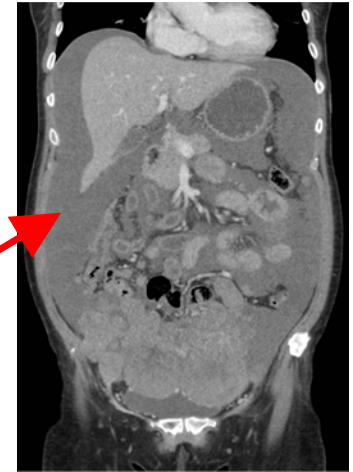
Pre-imatinib

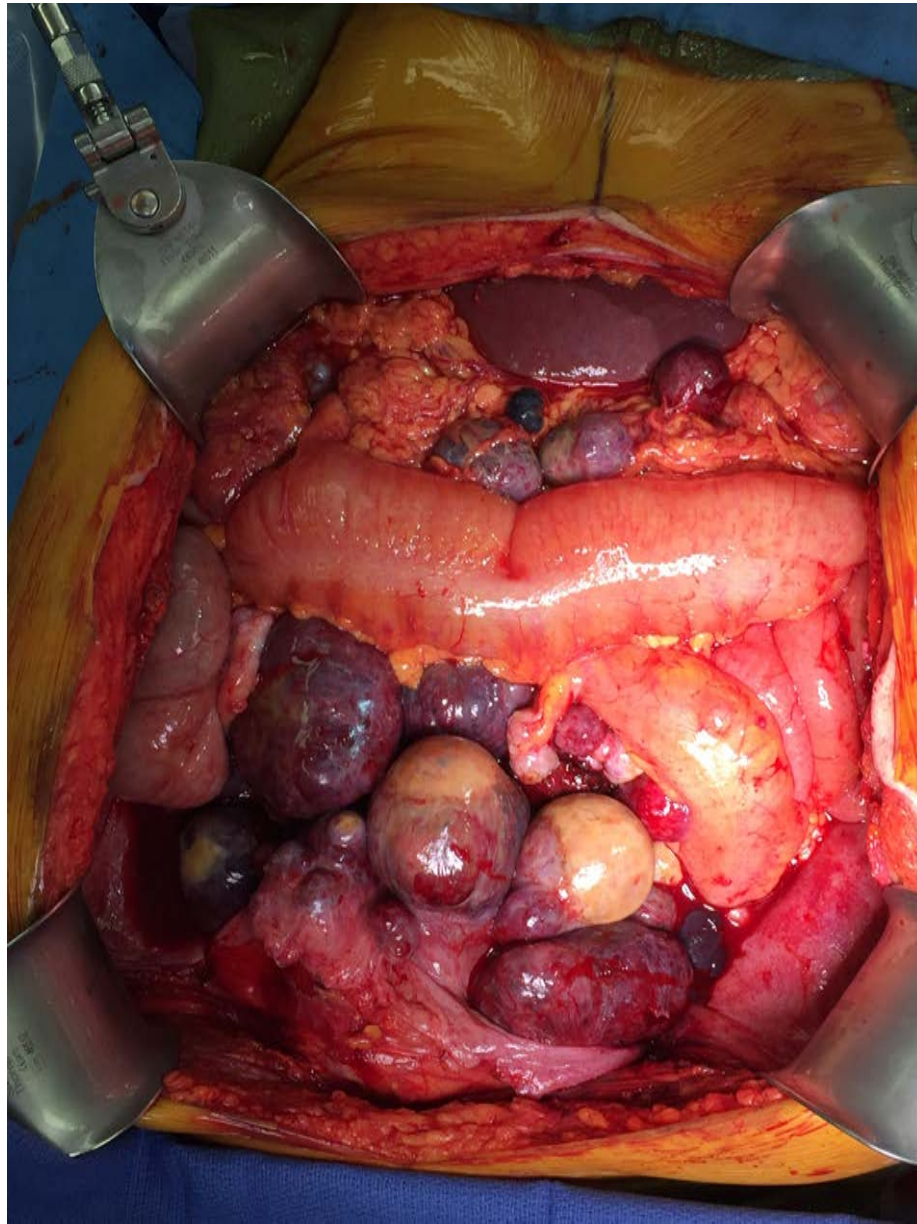


2.5 months



4 months





Summary

- Neoadjuvant imatinib therapy is generally safe for patients with GIST, but bleeding with response may occur.
- It is utilized in selected cases based upon tumor location and tumor biology.
- Treatment is usually recommended for 6-9 months in order to achieve maximal response.
- Treatment may be stopped earlier if additional response will not change 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 therapy