

Advances in the Surgical Management of GI Stromal Tumors

GIST Summit
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Cancer Center

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Agenda

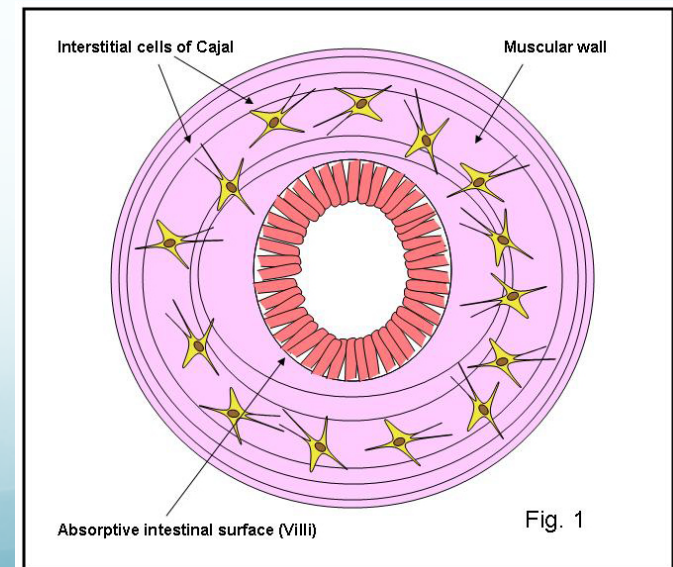
- Advances in diagnosis and treatment
- Surgical management of GISTs by anatomic site
- Neoadjuvant therapy
- Laparoscopic resection
- Surgical management of metastatic disease

Gastrointestinal Stromal Tumors

- GISTs are rare neoplasms requiring multidisciplinary management
- Management has been revolutionized with the introduction of tyrosine kinase inhibitors
- Rapid progress from bench to bedside
- Rigorous clinical investigation redefining the standards of care

Background

- Approximately 6000 new cases of GIST diagnosed in US each year
- Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumor of the GI tract
- Thought to originate from the interstitial cells of Cajal
- Males and females affected equally
- Mean age of 63 years at diagnosis

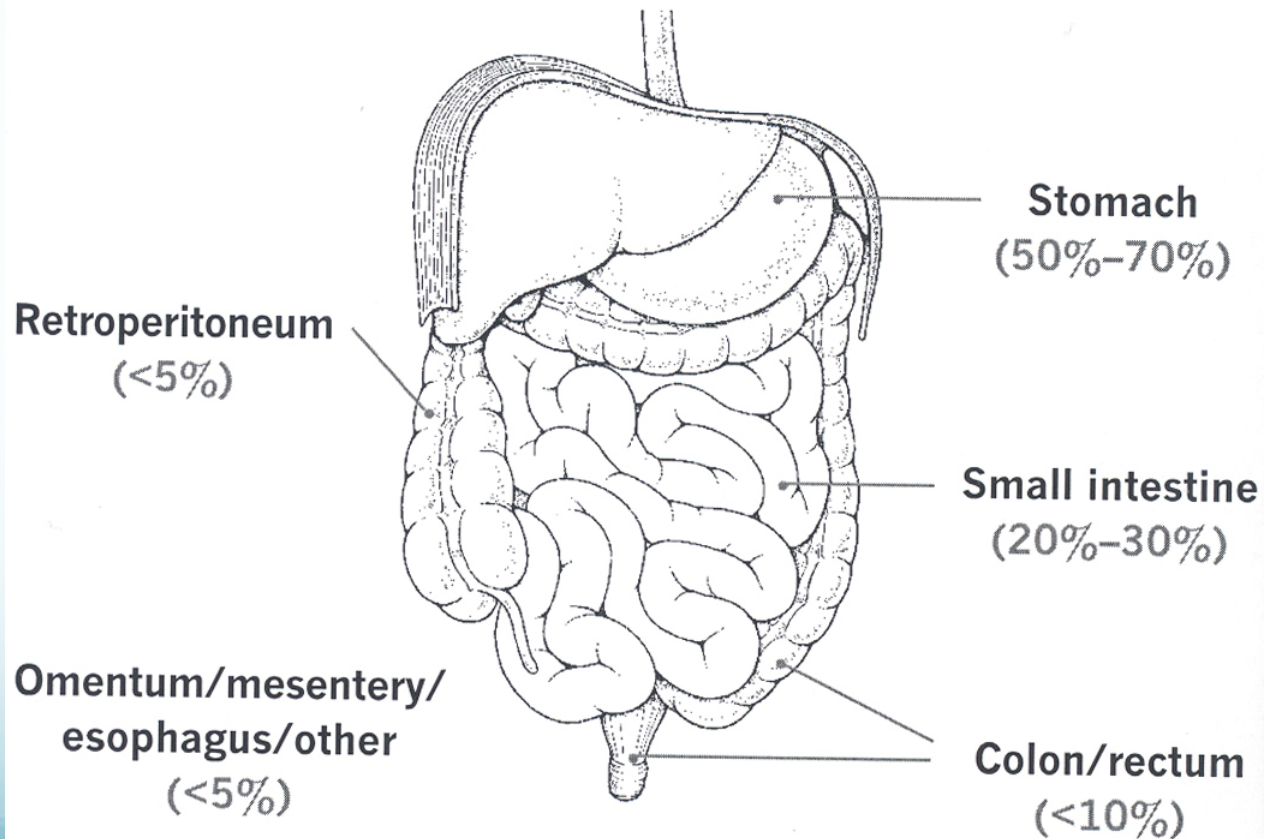


Diagnostic Criteria

- Anatomic Site: GI-tract, mesentery, omentum, retroperitoneum
- Appropriate histologic appearance
- CD117 (KIT receptor) immuno-reactivity

Distribution of GIST in the GI Tract

Most common anatomic locations of GISTs.^{4,5,7,8}



Gastrointestinal Stromal Tumors

Clinical Presentation

Signs/symptoms related to location of tumor

- GI hemorrhage
- Abdominal mass
- Vague GI pain / discomfort
- Anorexia, weight loss, nausea, anemia
- Surgical emergencies – perforation, bleeding

Often asymptomatic, incidental finding

Establishing Diagnosis

- History and Physical Exam
- Pathologic Assessment
 - About 95% of GISTs are positive for KIT (CD117)
- Radiologic Assessment

CT imaging

- è Mass
- è Absence regional lymph node metastases
- è Metastases: liver, implants

Prognostic Factors

Good prognosis

Tumor < 5 cm

Low mitotic rate
(< 2 /10 HPF)

Low proliferation index

Absence of necrosis

Gastric tumor

Age < 40 years

Poor prognosis

Tumor > 10 cm

High mitotic rate
(>5–10 /10 HPF)

Tumor rupture

High proliferation index

Necrosis

Extraintestinal tumor

Male gender

Surgical Principles

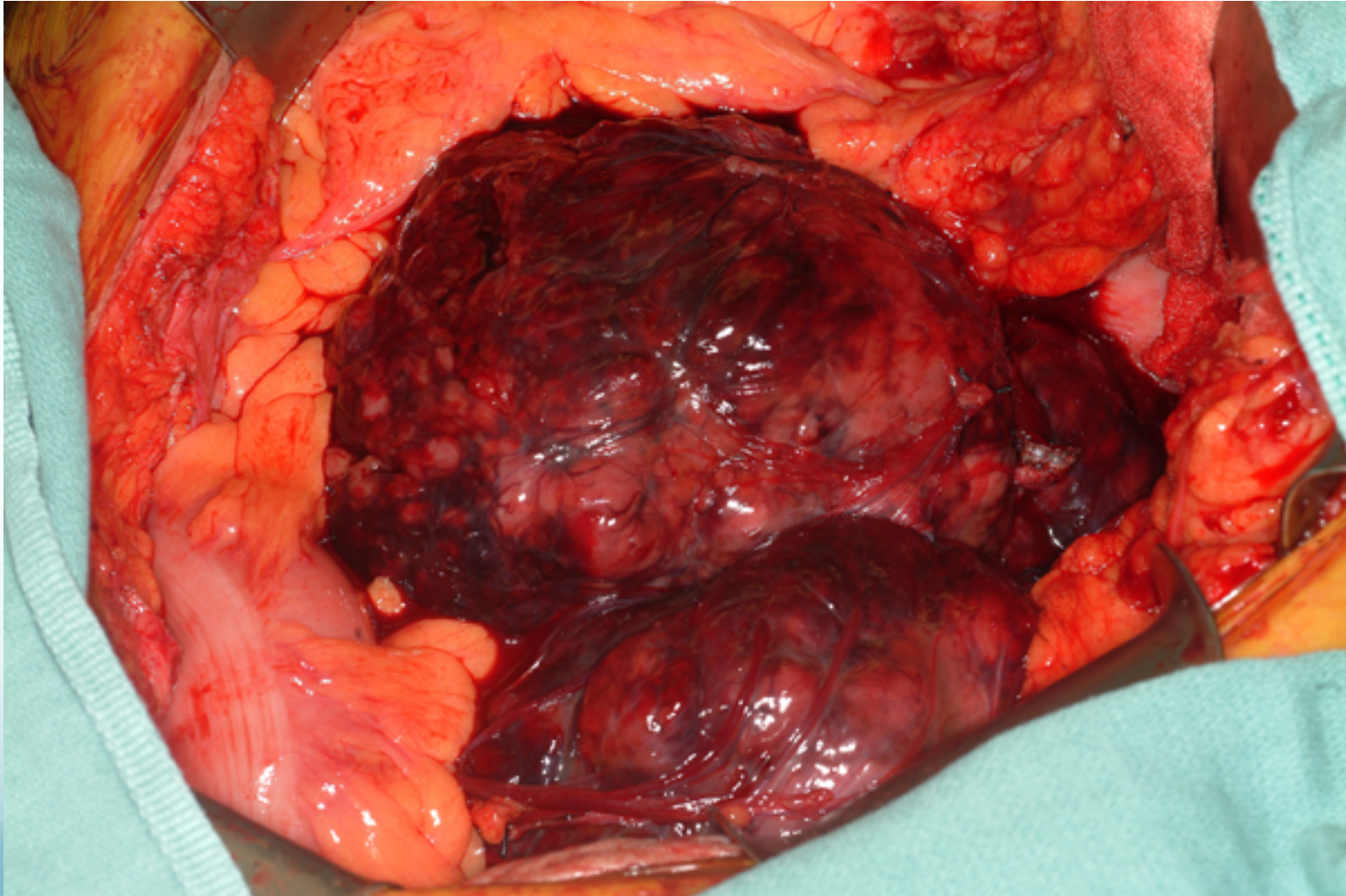
- Surgical resection is standard practice for localized GIST
 - Generally no role for radiation
 - GISTs are mostly refractory to standard chemotherapy
- Most recurrences distant rather than local
 - Liver or widespread intra-abdominal disease
 - Recurrence rates are about 50% at 5 years
- Goal of surgery: Achieve complete resection

Surgical Principles

- Aim is to resect the tumor with negative margins
 - Small bowel 2-3 cm segmental resection
 - Stomach 1-2 cm wedge resection
- The pseudocapsule of the tumor should not be violated

Warning:
Slides contain photographs of surgical specimens

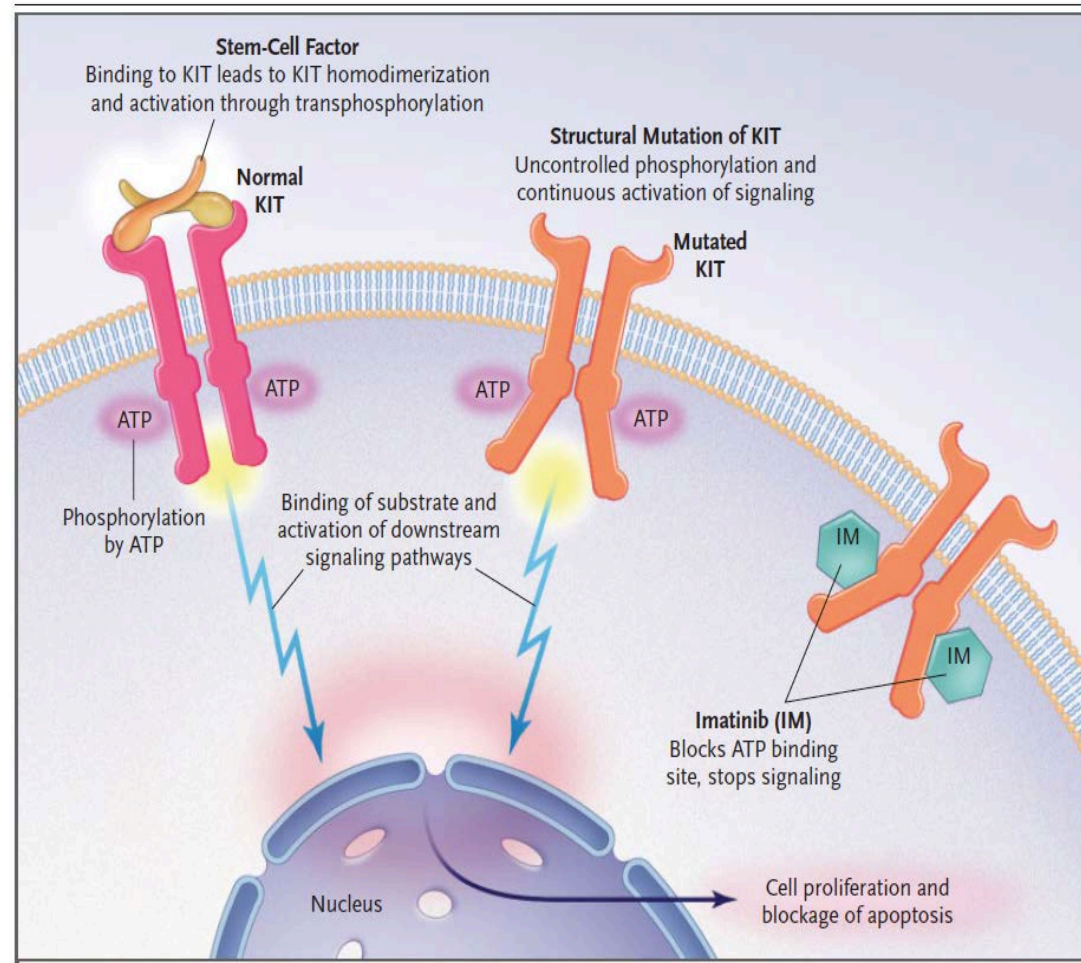
Small bowel GIST



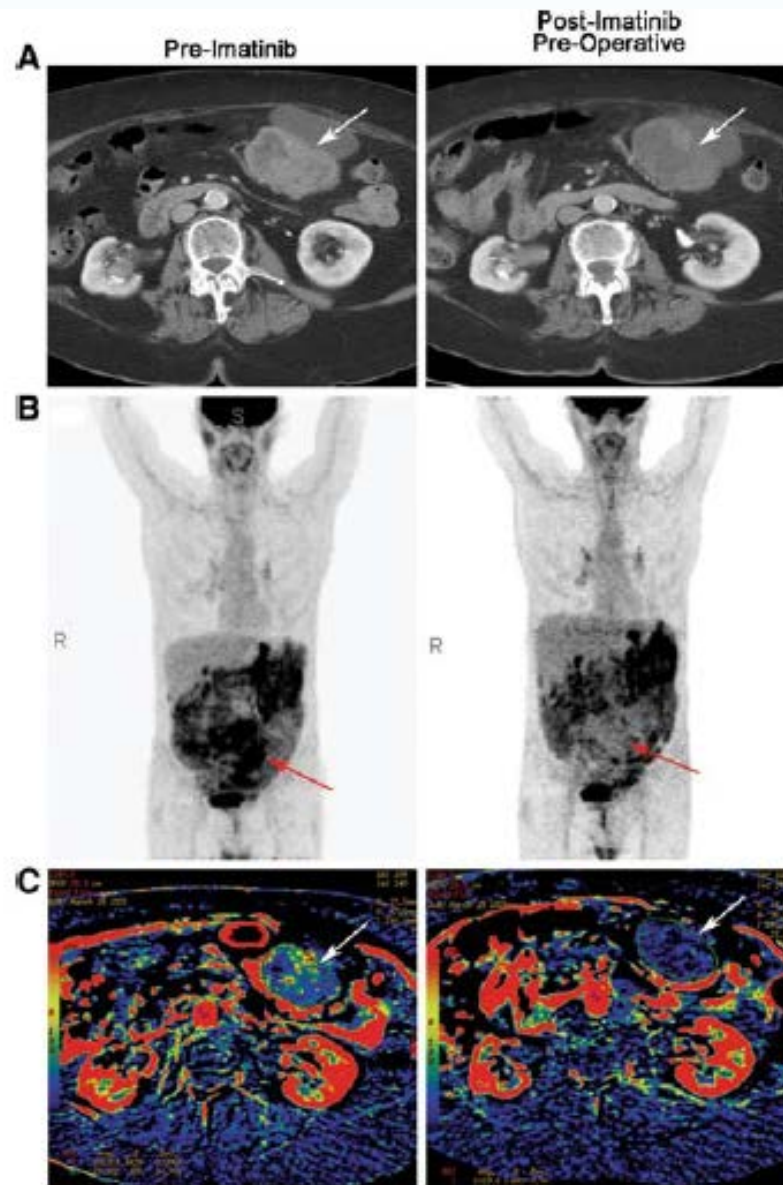
Tyrosine kinase inhibitors

- Effective in reducing recurrence after surgery and against metastases
- Considered for treating tumors before surgery (neoadjuvant) when tumors are large or in anatomic sites that could benefit from reduction in tumor size before resection

Demetri G et al., N Engl J Med, 2004



GIST Patient Treated With Imatinib:



CT Scan Results: Decrease in Tumor Volume

June 27

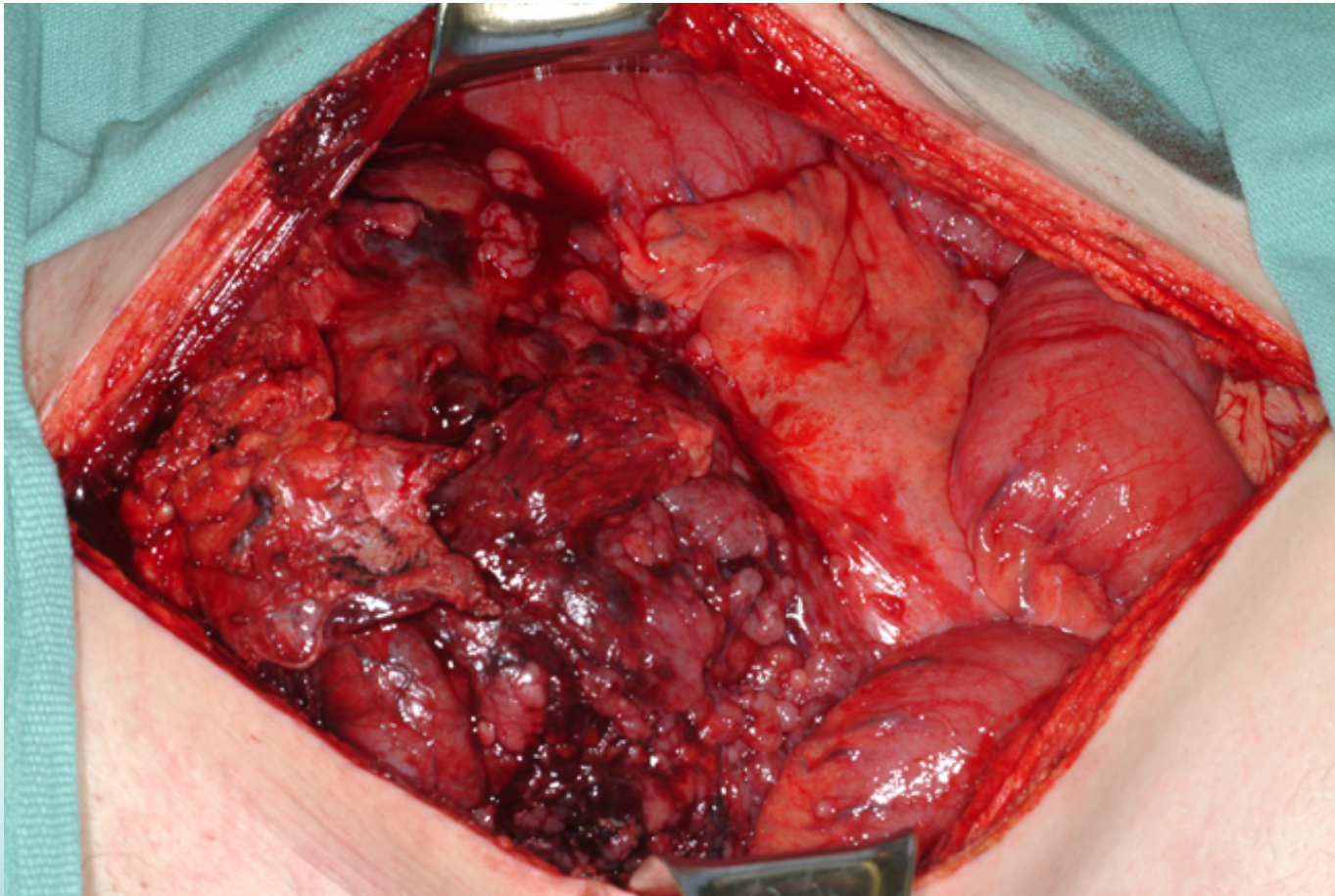
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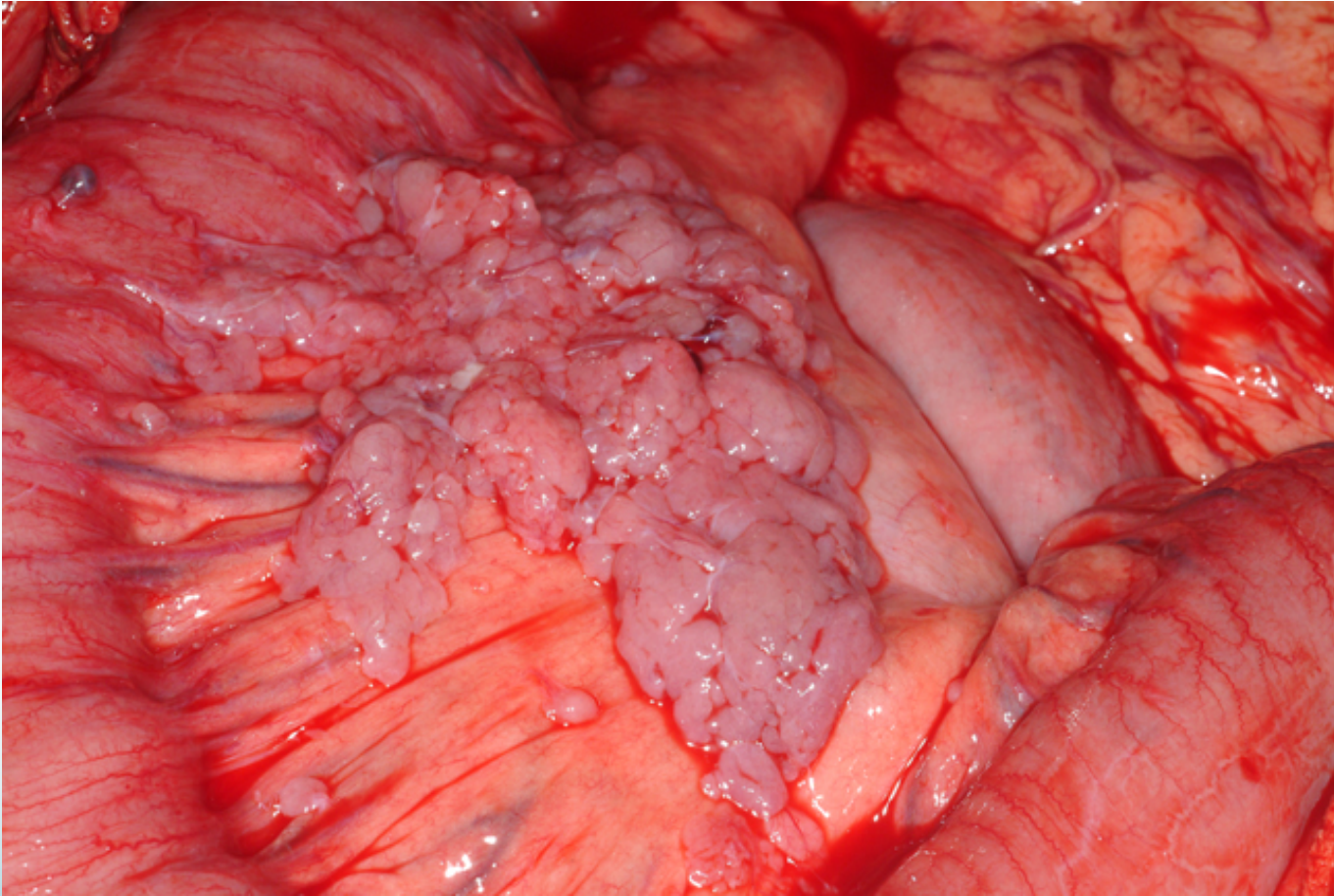
Before Therapy

After Therapy

GIST Prior to Therapy



GIST After Therapy



Treatment of GIST

- **Localized Resectable Disease**

 - Surgical Resection**

 - Extent of resection dependent on anatomic site**

- **Locally Advanced Unresectable Disease**

 - Gleevec (Imatinib mesylate)

 - Surgical resection of residual disease (if downstaged)

 - (little prospective data to support survival benefit)

- **Metastatic Disease**

 - Gleevec - FDA approved 2002

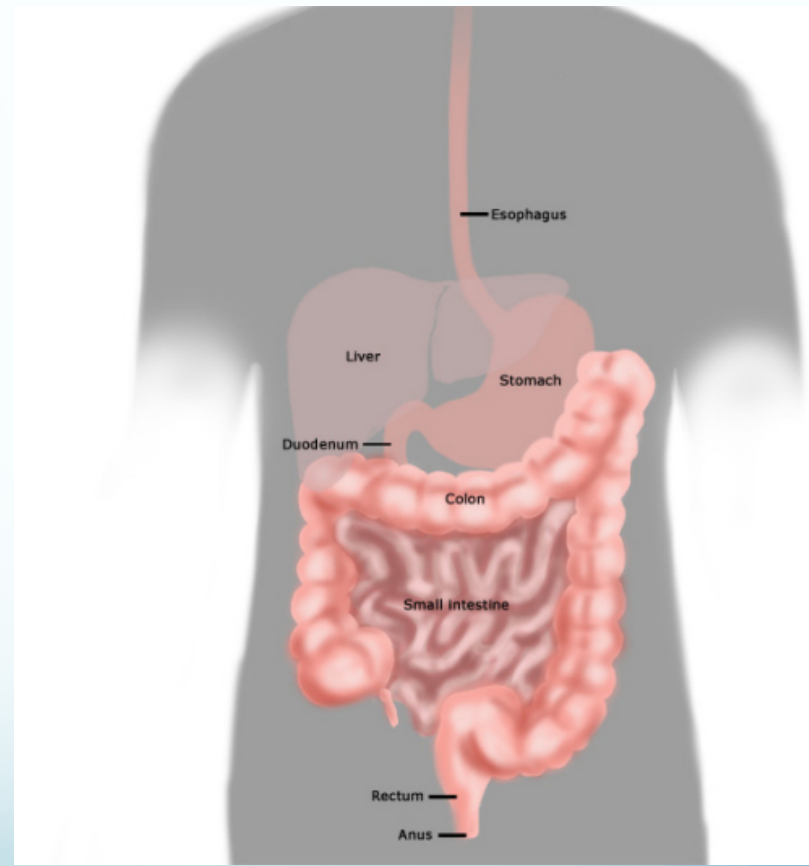
 - Possible surgical resection of residual disease
(if response)

 - Secondary resistance (median 24 months)

 - dose escalation, sunitinib or other trials

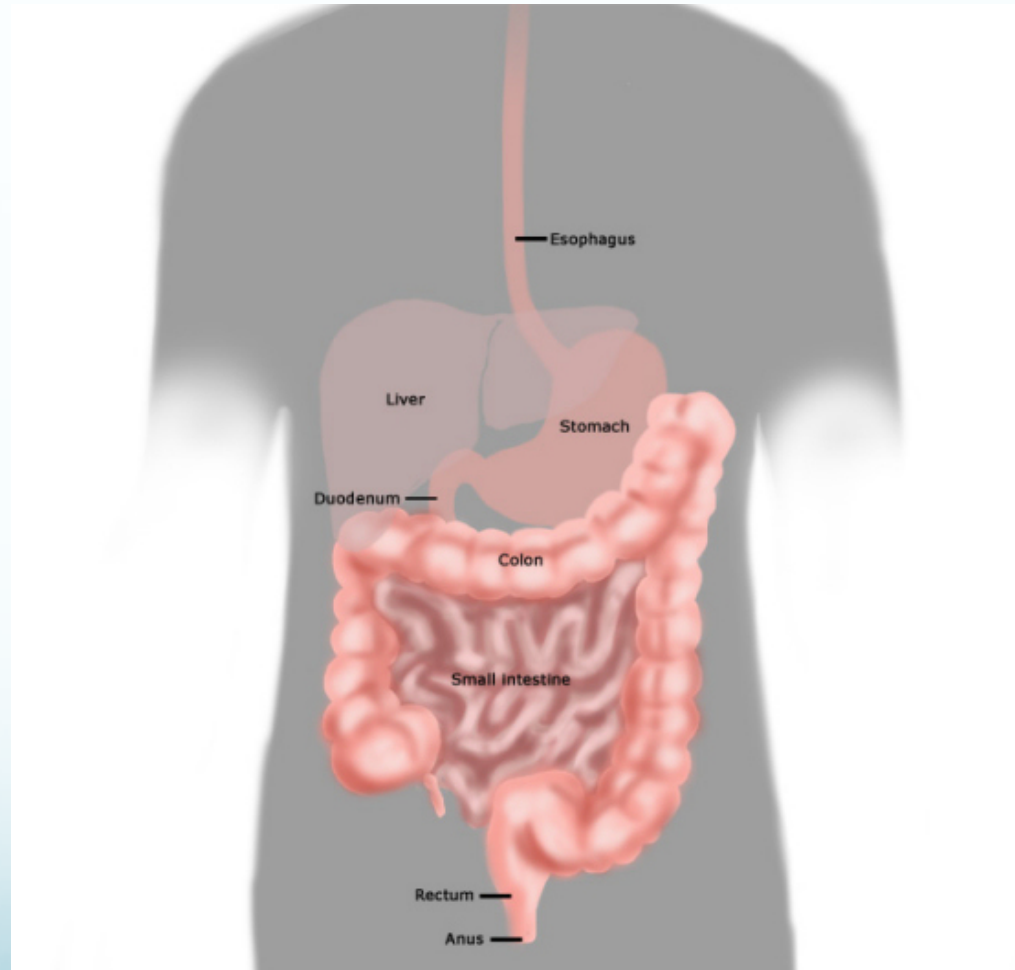
Esophageal GIST

- Tumors < 2cm that don't involve adjacent structures can be resected
- Tumors > 2cm and those close to juncture of stomach may require esophagectomy (through left abdominothoracic incision)
- Large tumors that involve other structures (such as diaphragm) may require imatinib treatment before surgery (neoadjuvant) to reduce the size of the tumor first.

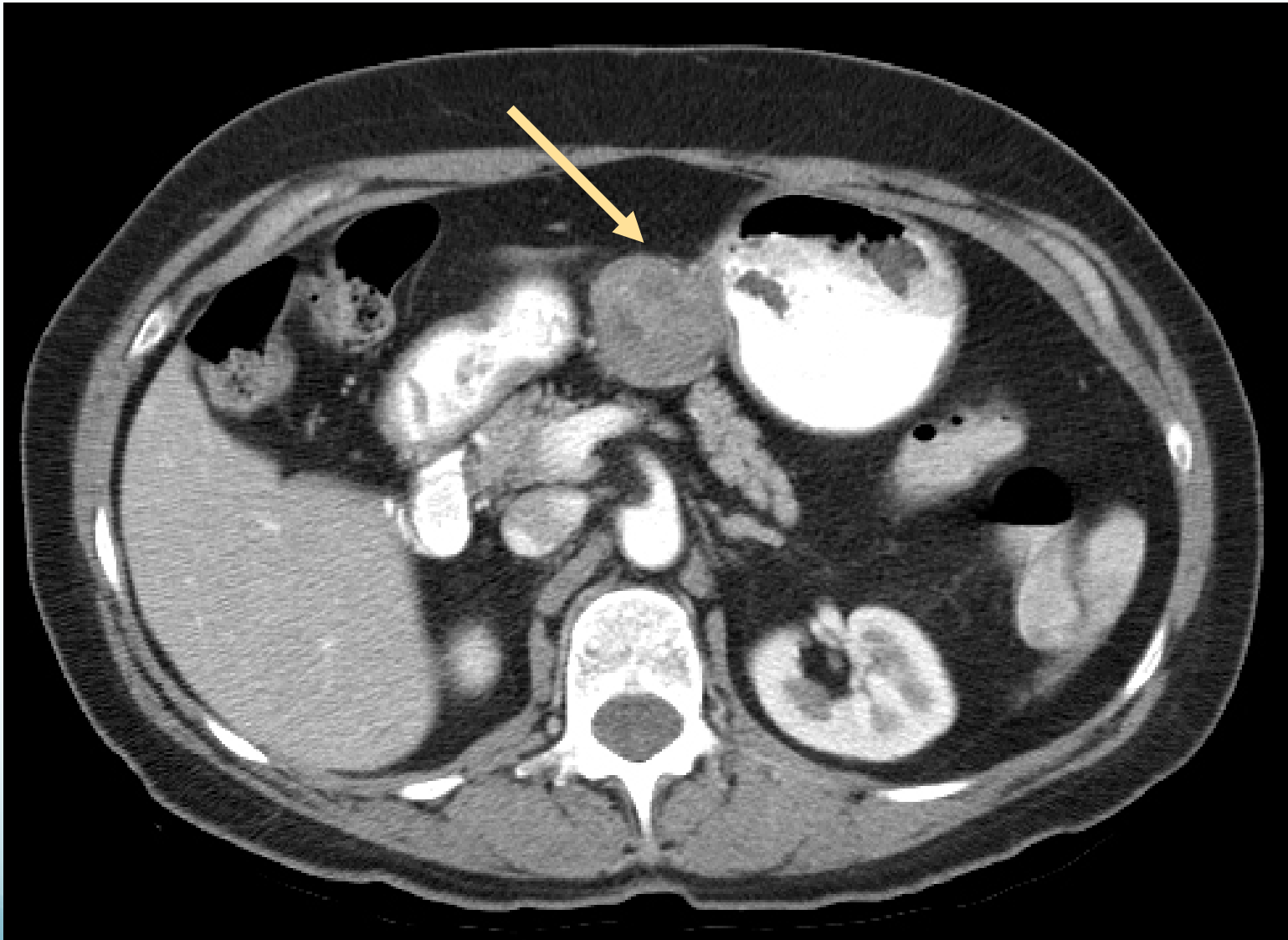


Gastric GIST

- < 2cm tumors may be managed nonoperatively
 - Endoscopic surveillance to monitor growth
- Tumors near esophagus may be surgically removed to avoid more extensive resection
- Tumors > 3cm or with chance of invading other organs such as liver or diaphragm should be considered for neoadjuvant imatinib
- Tumors in mid-body of stomach could be resected laproscopically

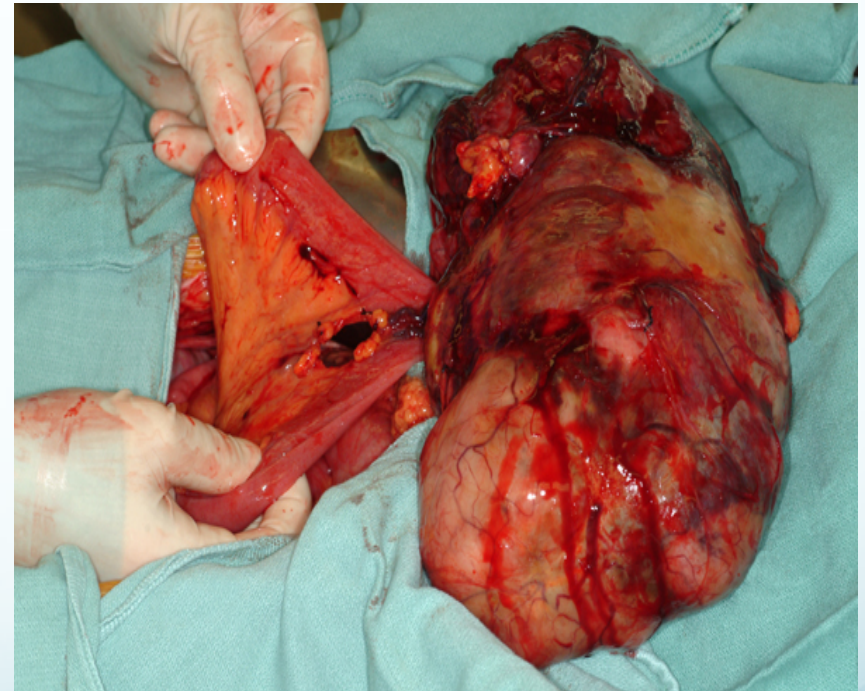


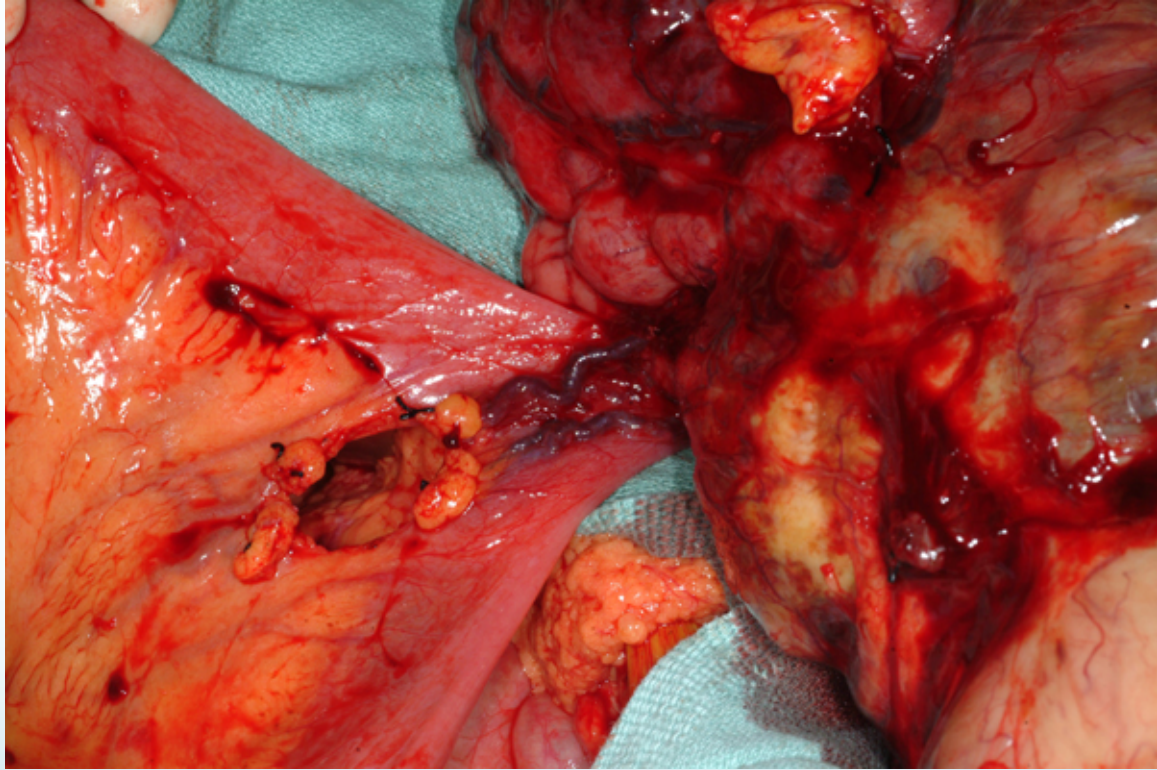
Gastric GIST



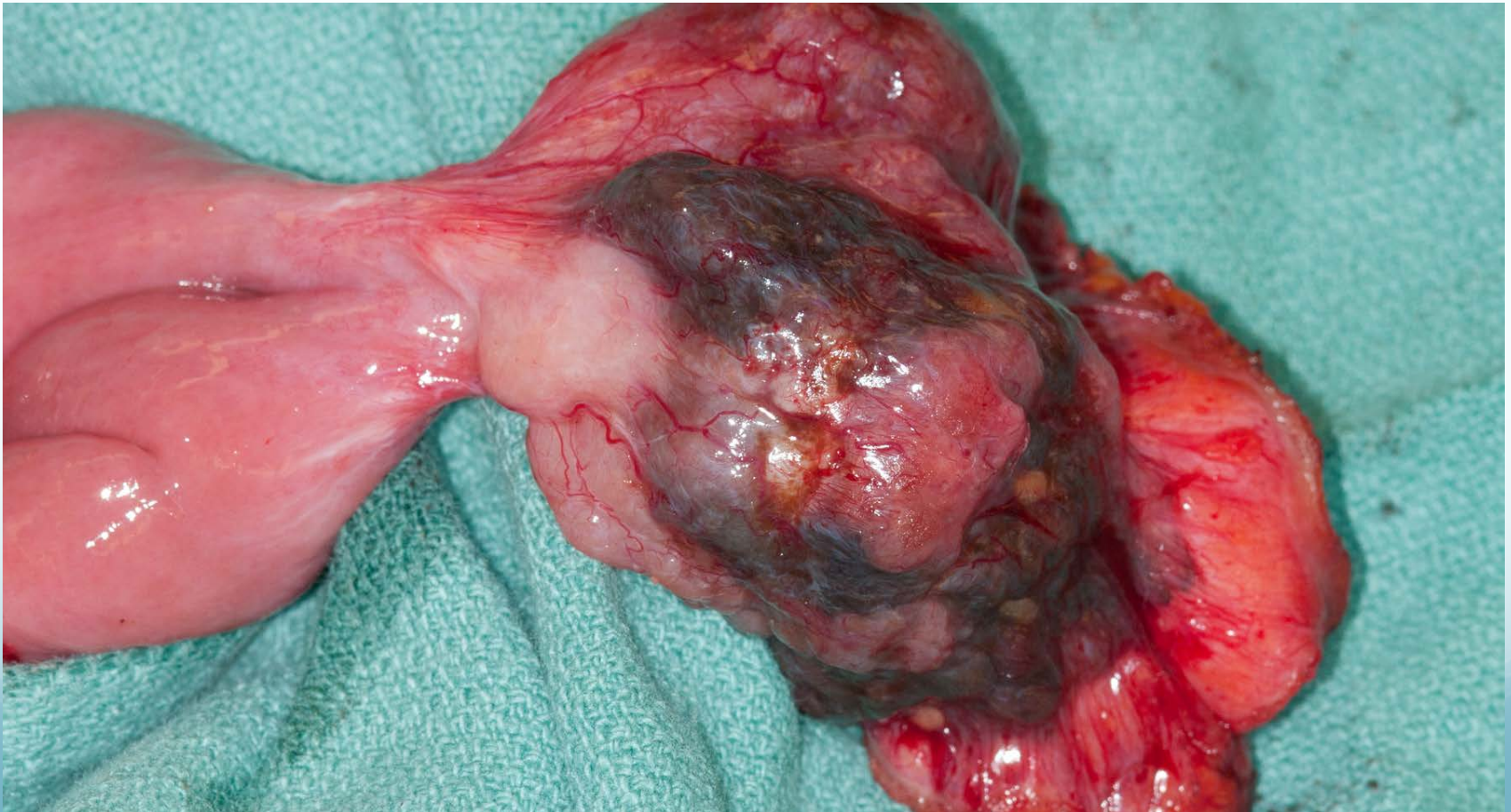
GIST of small intestine

- Neoadjuvant imatinib may be considered for duodenal GIST because of proximity to pancreas
- Tumors in jejunum and ileum are often relatively large because of later diagnosis
 - <5 cm possible laparoscopic resection
 - Other organs may be involved and could benefit from neoadjuvant imatinib

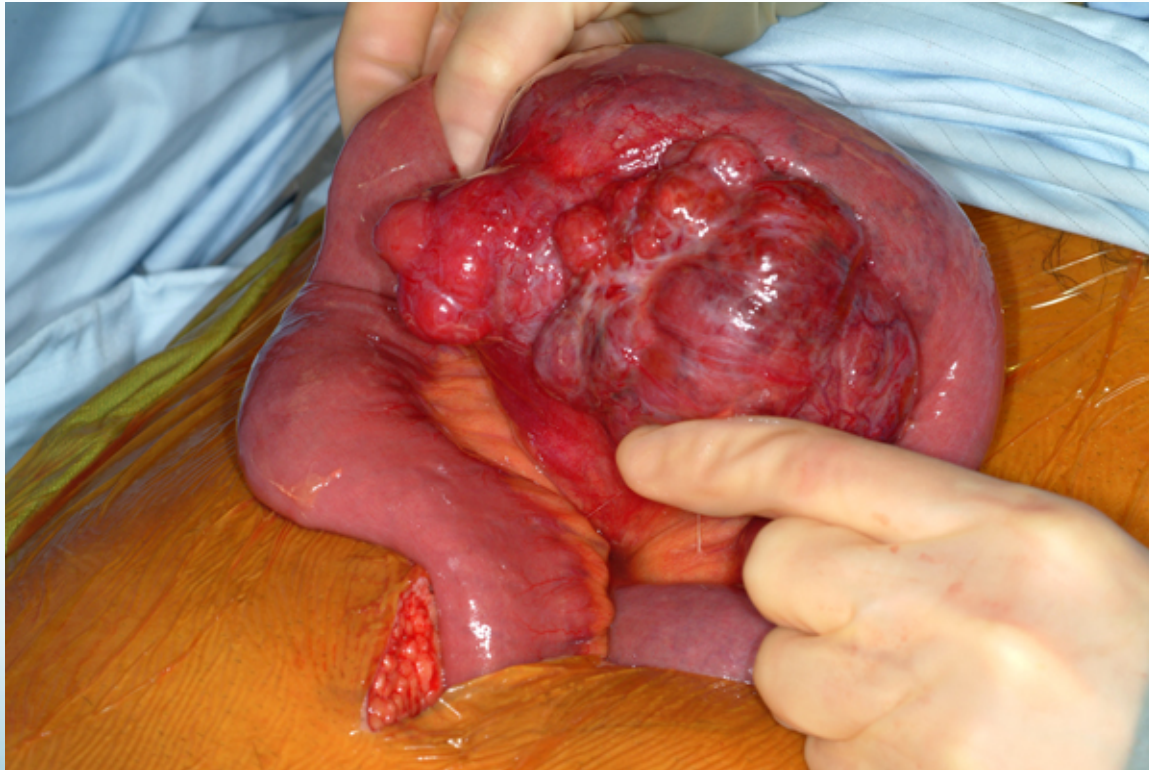




Small bowel GIST after therapy

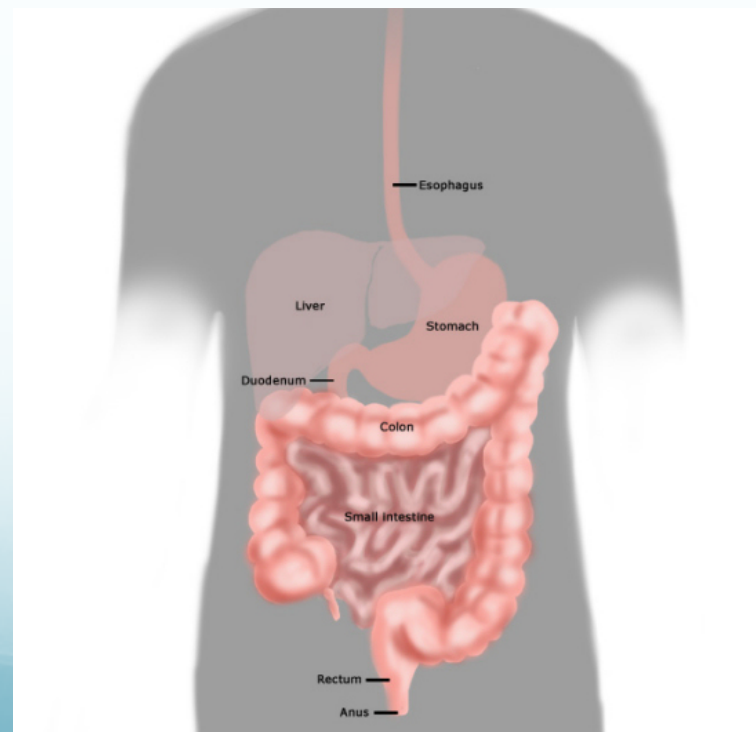


Small bowel GIST involving the mesentery

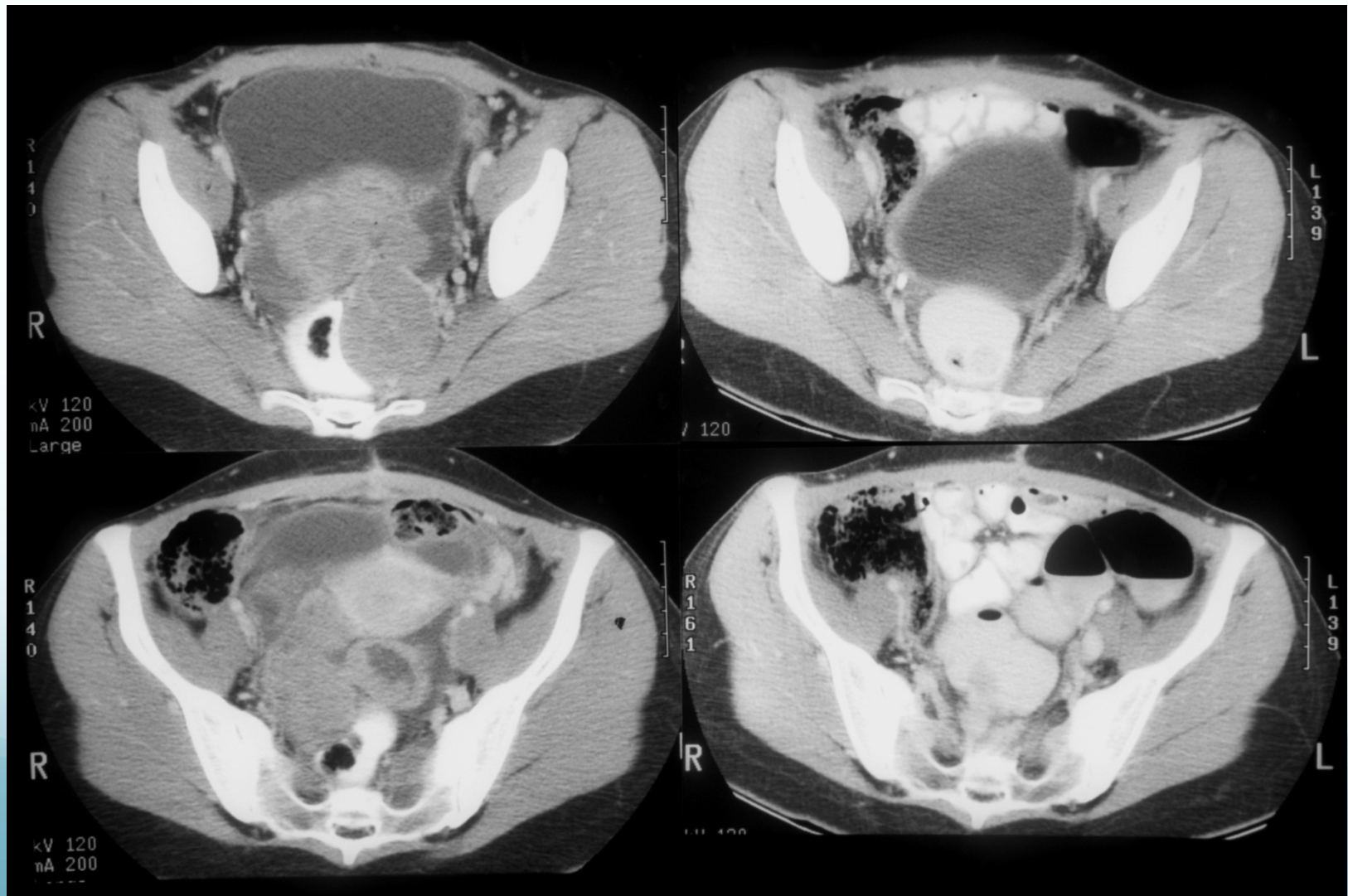


GIST of colon or rectum

- Tumors < 3cm can be considered for resection
- Tumors that may involve sphincters or other organs could be considered for neoadjuvant imatinib to reduce need for radical resection or colostomy.



Rectal GIST before and after treatment



Neoadjuvant therapy

- Rationale:
 - Decrease the size of the tumor
 - Decrease the vascularity of the tumor
 - Diminish the extent of resection required
- For locally advanced primary GIST patients receiving neoadjuvant imatinib (Andtbacka R, et al. *Ann Surg Oncol* 2007):
 - 1% complete response, 73% partial response, 9% stable disease, 1% progressive disease
 - Responding patients had a median decrease in tumor volume of 85% (27-99%)

Neoadjuvant Therapy for GIST

Locally Advanced Primary



Metastatic/Recurrent



Potential Benefits

- *Decreased tumor size*
- *Decreased surgical complexity*
- *In situ measure of drug response*
- *Assessment of tumor biology*
- *Early treatment of microscopic distant disease*

Neoadjuvant Therapy for GIST

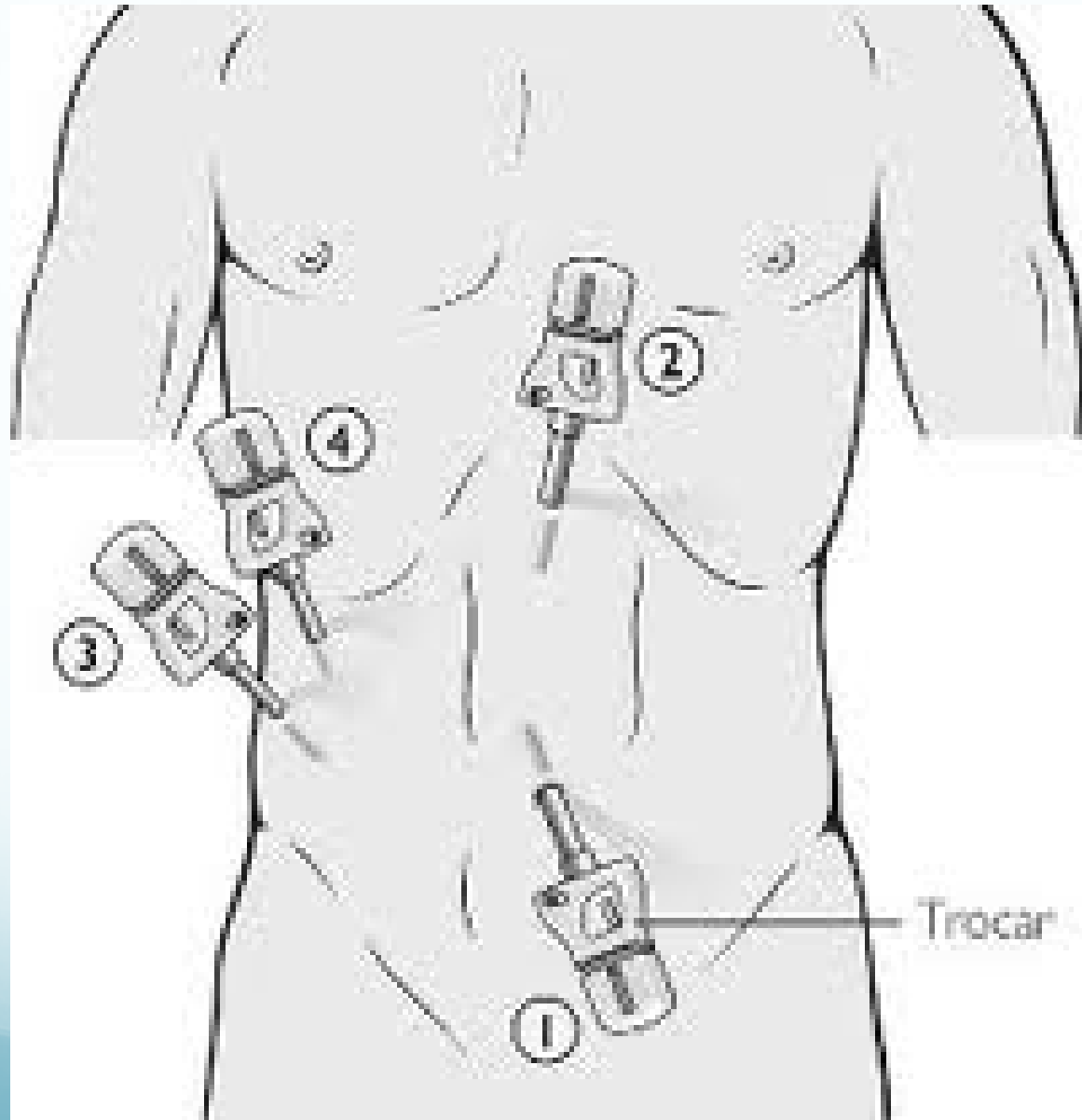
- Randomized phase II trial
 - 19 pts received neoadjuvant imatinib for 3, 5, or 7 days
 - No effects on surgical morbidity
 - Increased tumor apoptosis with increased exposure
 - 62% had evidence of radiographic response

McAuliffe et al, *Ann Surg Onc*, 2009

- RTOG 0132
 - Multi-institutional prospective trial of 53 pts
 - 2 months neoadjuvant imatinib + 2 yrs adjuvant therapy
 - No significant effects on surgical morbidity
 - 5 yr PFS: 57% in primary and 30% in metastatic/recurrent
 - 5 yr OS: 77% in primary and 68% in metastatic/recurrent

Wang et al, *Ann Surg Onc*, 2012

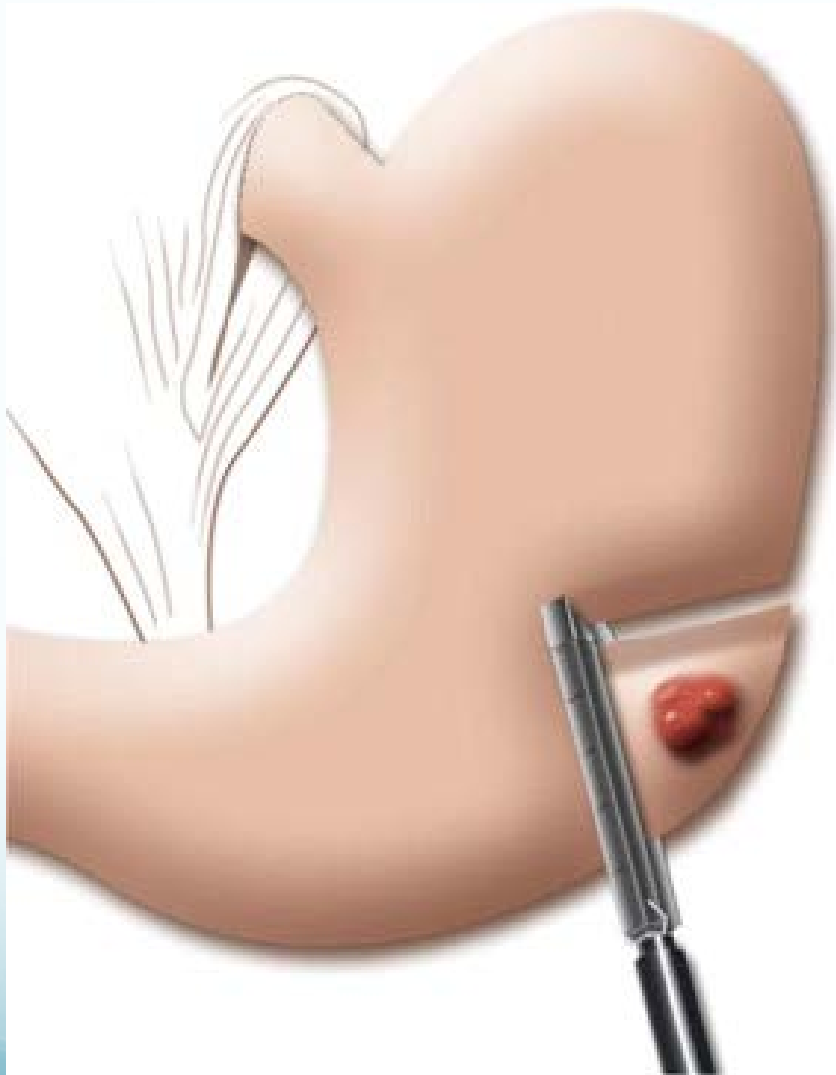
Laparoscopic Resection for GIST?



Laparoscopic ports







REVIEW ARTICLE – GASTROINTESTINAL ONCOLOGY

A Systematic Review and Meta-Analysis Comparing Laparoscopic Versus Open Gastric Resections for Gastrointestinal Stromal Tumors of the Stomach

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- A total of 11 nonrandomized studies reviewed 765 patients: 381 LR and 384 OR.
- A higher proportion of high-risk tumors and gastrectomies in the OR compared with LR.
- LR results in superior short-term postoperative outcomes without compromising oncological safety and long-term oncological outcomes compared with OR.

TABLE 1 Characteristics of included studies

Reference	Year	Recruitment period		Country	Study design	LR		OR		Conversion	Mean/median size (cm)	Inclusion/exclusion	Study quality scoring scale
						n	Tumor locations	n	Tumor locations				
Wan ¹⁶	2012	2004	2011	China	Retro	68	U: 32 M: 26 L: 10	88	U:45 M: 29 L: 14	0	3.5		8
Pucci ²⁰	2012	2002	2012	USA	Retro	57	U: 5 M: 47 L: 5	47	Combined with LR	1	3.8	No long term follow up, no tumor risk assessment	6
Karakousi ¹⁰	2011	1998	2009	USA	Retro	40	U: 7 M: 44 L: 1	40	U: 3 M: 47 L: 0	13	3.9		8
Lee ¹³	2011	2001	2008	Korea	Retro	50	U: 22 M: 19 L: 9	50	U: 21 M: 19 L: 10	1	2.9	70 % of cases GIST only	7
Goh ¹¹	2010	2001	2009	Singapore	Retro	14	U: 14 M: 21 L: 4	39	U: 4 M: 10 L: 0	1	4.0	Short follow up of the laparoscopic arm	6
Nakamori ¹⁴	2008	1998	2003	Japan	Retro	25	U: 30 M: 25 L: 1	31	Combined with LR	0	5.0	10 patients with metastatic GIST	6
Catena ¹⁵	2008	2001	2006	Italy	Retro	21	U: 1 M: 16 L: 4	25	U: 2 M: 17 A: 6	0	4.5		8
Nishimura ¹⁷	2007	1993	2004	Japan	Retro	39	U: 18 M: 16 L: 4	28	U: 11 M: 11 L: 6	1	4.0		6
Basu ²¹	2007	2000	2006	UK	Retro	15	Not stated	4	Not stated	2	6.0	6 extra gastric GISTs 4 metastatic tumors	6
Mochizuki ¹⁸	2006	2000	2004	Japan	Retro	12	U: 6 M: 5 L: 1	10	U: 8 M: 2 L: 0	0	2.7		7
Otani ⁹	2006	1993	2004	Japan	Retro	35	Not stated	25	Not stated	0	3.5	1 patient with metastatic GIST	6

Study quality based on Newcastle Ottawa Scale with maximum of 4 for selection, 3 for comparability and 2 for outcome

Tumor size impacts surgical approach





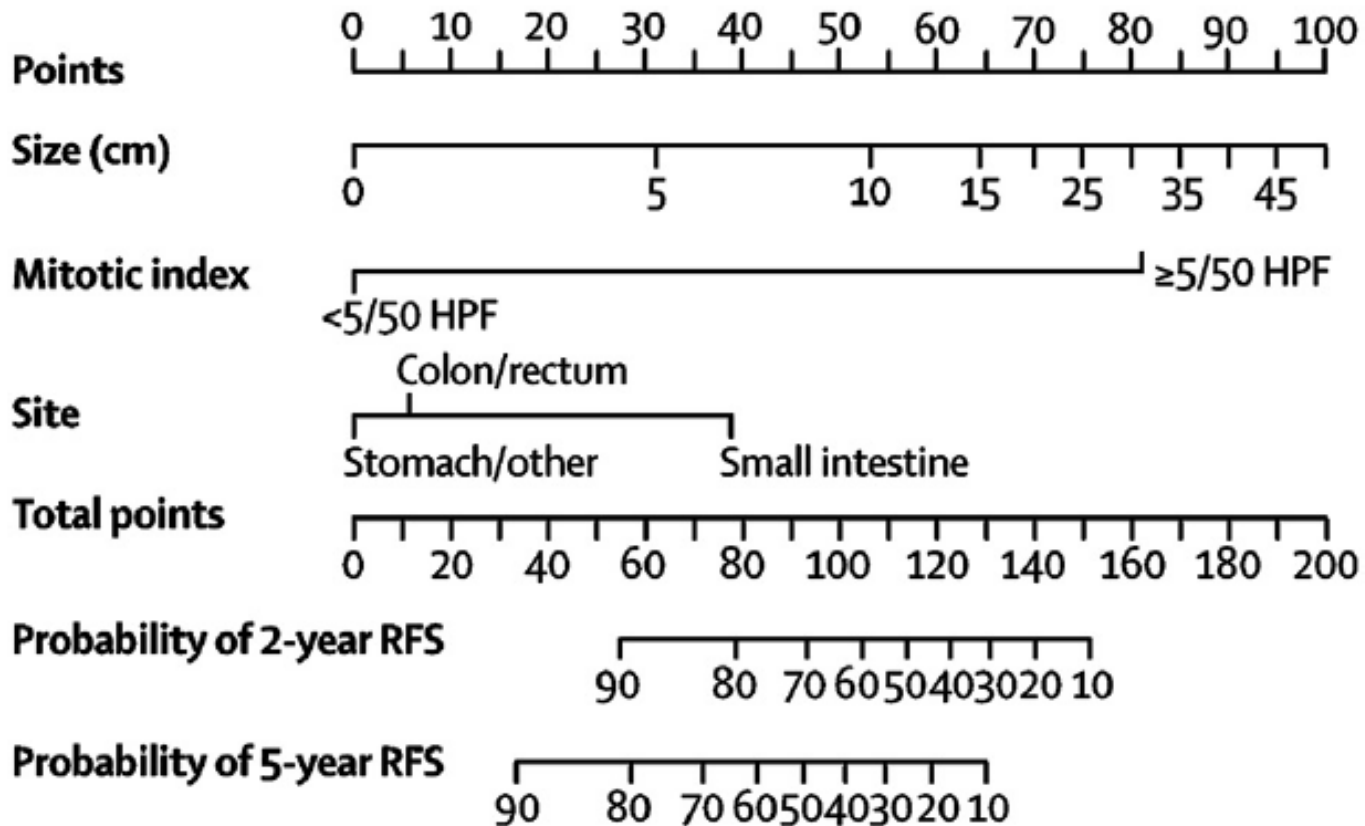
Gastric GIST



Prognostic Factors Determining Outcome after Surgical Resection

- Tumor size
- Mitotic index
- Location

Nomogram for Predicting Recurrence-Free Survival



Prognostic Factors Determining Outcome after Surgical Resection

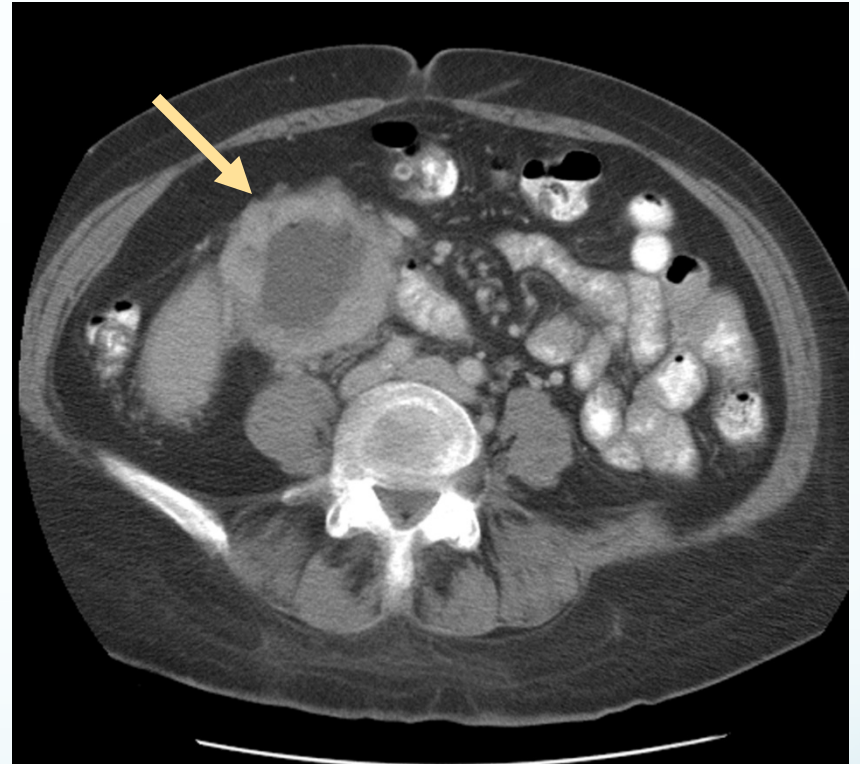
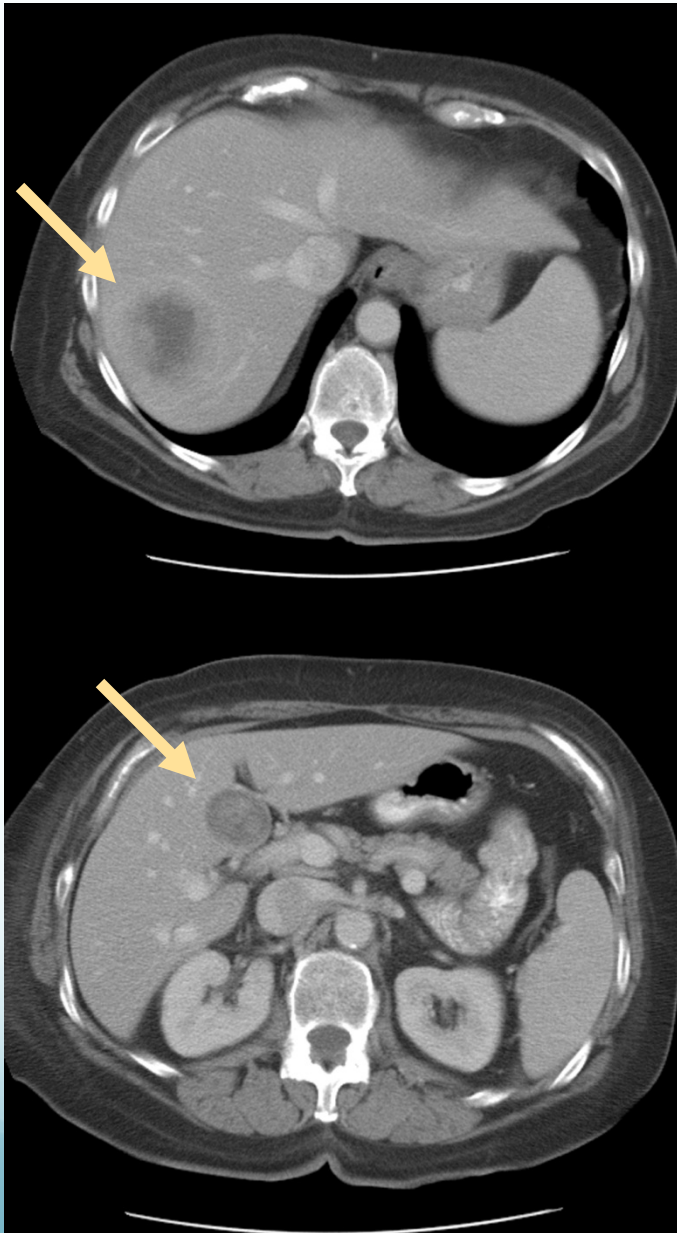
- Tumor size
- Mitotic index
- Location
- **Mutation type: deletion and insertion mutations in *KIT* exon 11 and 9**

Is there a role for surgery in patients with metastatic disease?

Favorable Prognostic Factors following GIST Recurrence

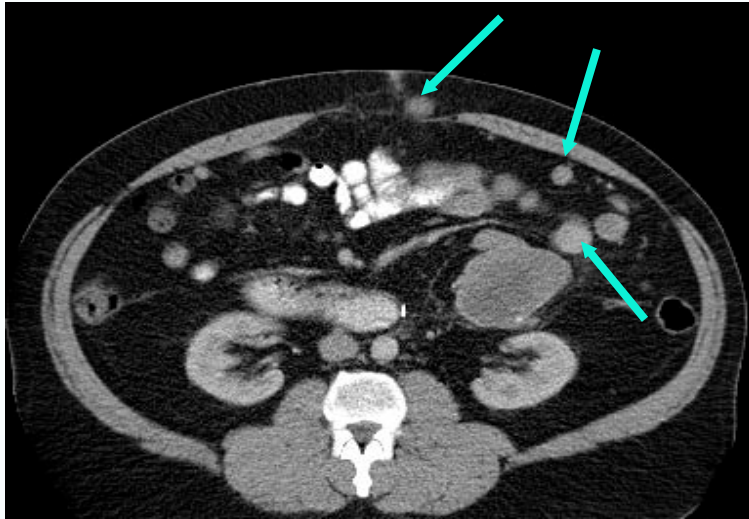
- Disease-free interval >20 months from primary tumor resection to recurrence
- Recurrence limited to *either* peritoneal cavity or liver
- Complete resection of metastatic disease

Duodenal Mass with Liver Metastases: GIST

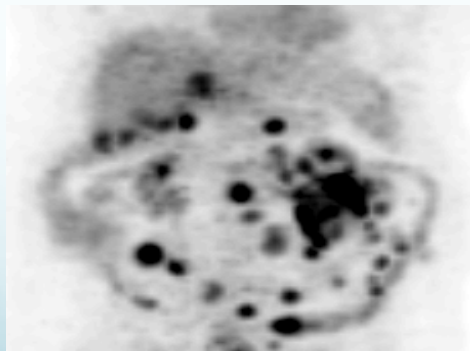
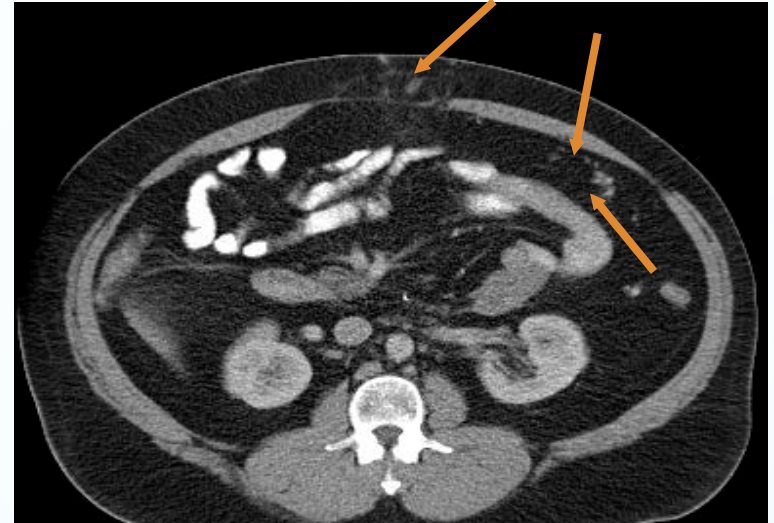


Metastatic GIST and response to therapy

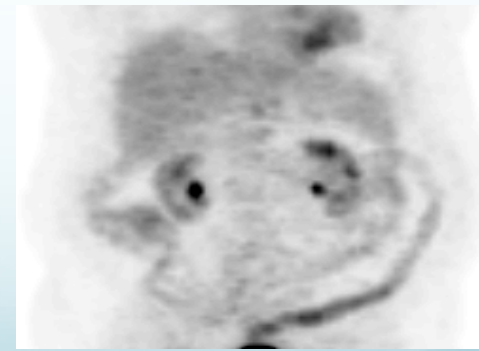
Initial



3 months



Before Gleevec



After Gleevec

Outcomes based on response

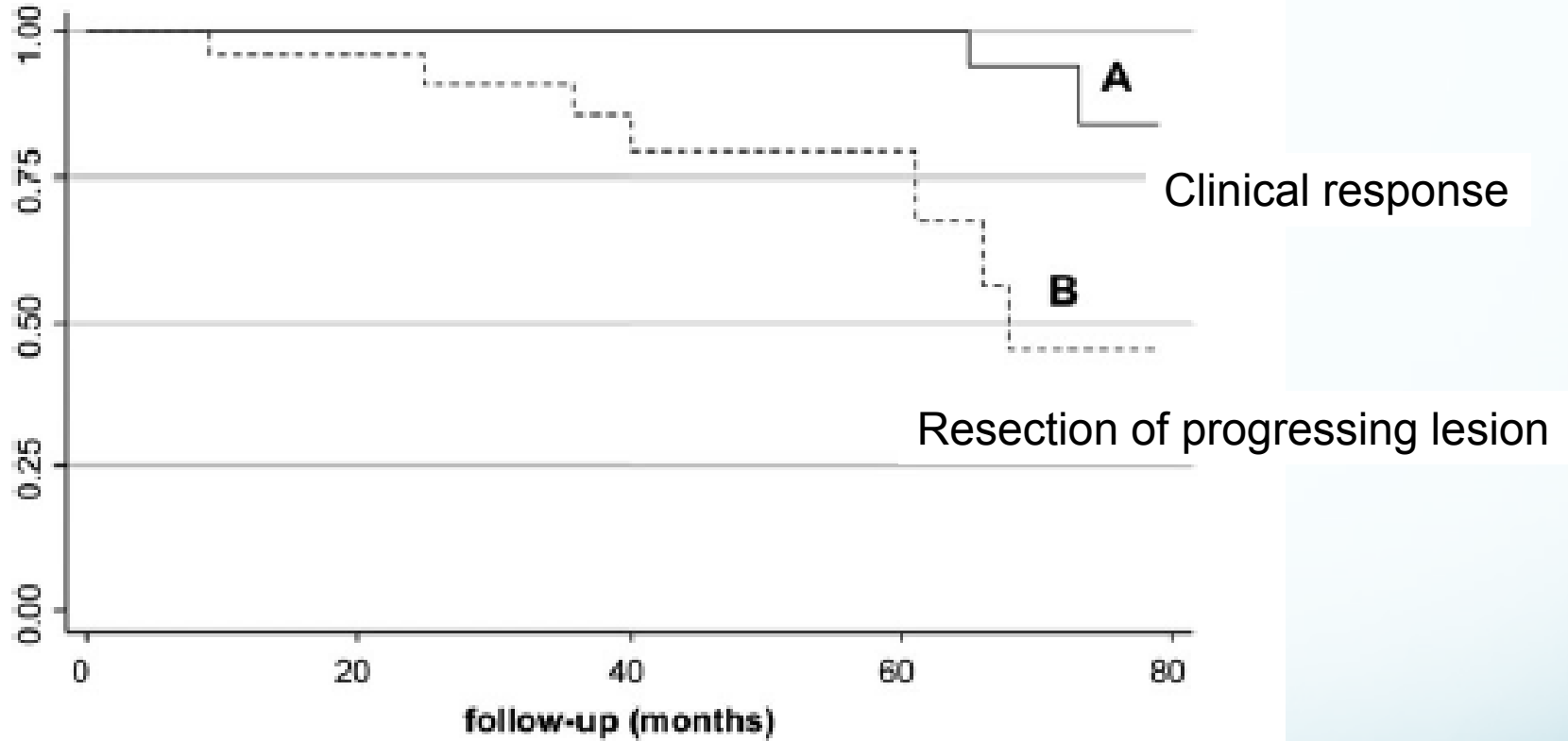


Figure 2. Kaplan-Meier curve for disease-specific survival from the time of imatinib onset according to response at the time of selection for surgery ($P < 0.01$).

Future of GIST Therapies

- Recent scientific advances have had a profound impact in patient care
- Molecular mechanisms of drug resistance
- Identification of new targets for therapy
- Development of novel agents
- Addressing subpopulations of GIST progenitor cells and stem cells

Conclusions

- Wide clinical spectrum of GISTs from benign to more malignant tumor behavior which can be predicted based on:
 - tumor size
 - mitotic activity
 - anatomic site
- High risk GISTs have high rate of recurrence requiring multidisciplinary management

Conclusions

- No standard management of recurrent/metastatic GIST
- Important prognostic factors to consider when considering surgical resection of recurrent GIST
 - prior response to Gleevec
 - disease-free interval
 - location and number of tumor(s)
 - symptomatic tumors
 - availability other targeted agents or clinical trials

Future directions

- What is optimal duration of neoadjuvant imatinib treatment?
- Need to be able to measure response
 - Functional imaging
- New prognostic systems needed for risk stratification
 - Consider mutation status and therapy
- What is the optimal duration of adjuvant treatment?



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Thank you!