



On the Cutting Edge of GIST: Novel Surgical Approaches

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HEALTH SYSTEM

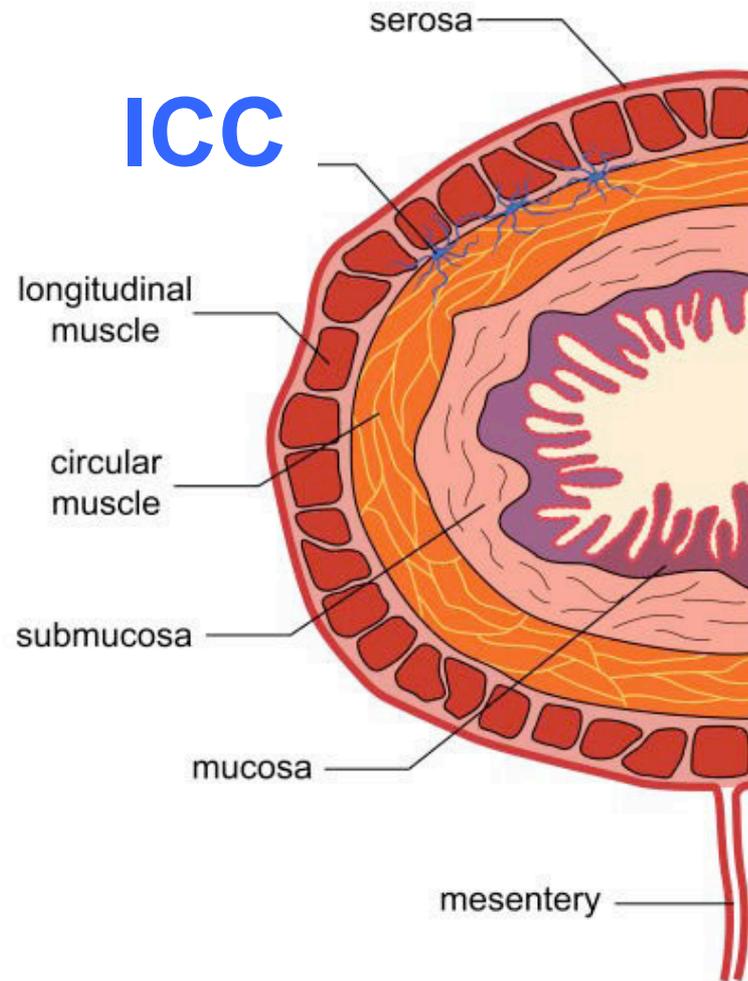


Where discoveries are delivered.SM

Disclosures

- Investigator-initiated Trial Sponsored by Novartis Pharmaceuticals (2013 – present)
- Investigator-initiated Trial Sponsored by Foundation Medicine (2015 – present)
- Consultant, Sirtex (2015)
- Consultant, Grand Rounds (2015 - present)
- Research funding, Blueprint Medicines (2015)
- Consultant, CARsgen Therapeutics (2017)

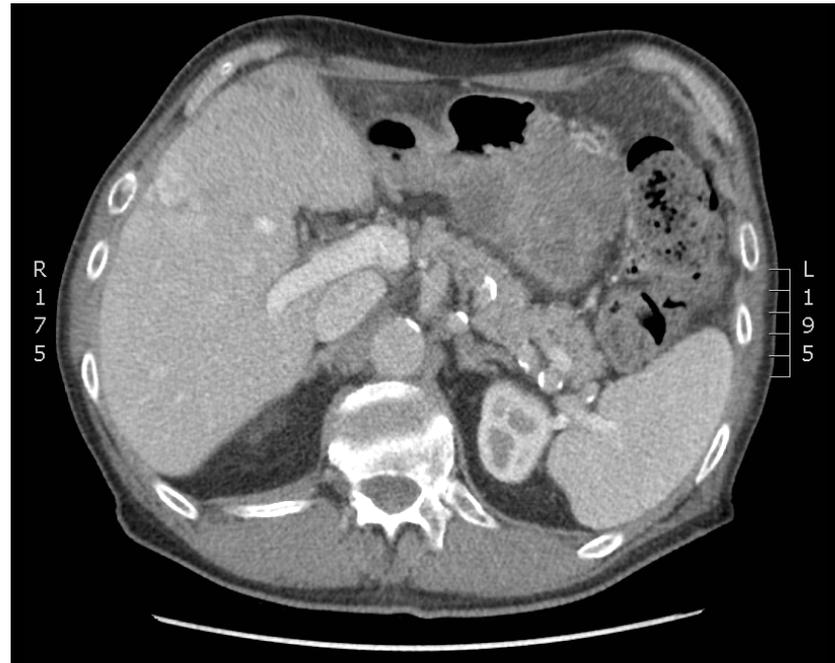
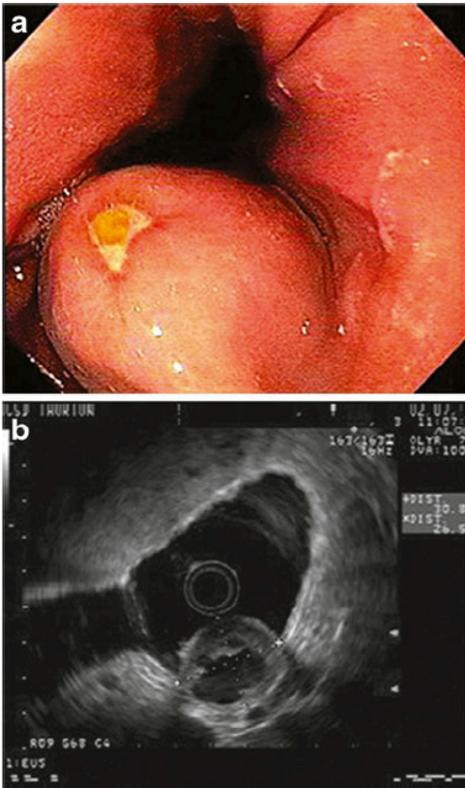
ICCs are Submucosal Cells



Submucosal Tumor (SMT) Growth Pattern

Endophytic

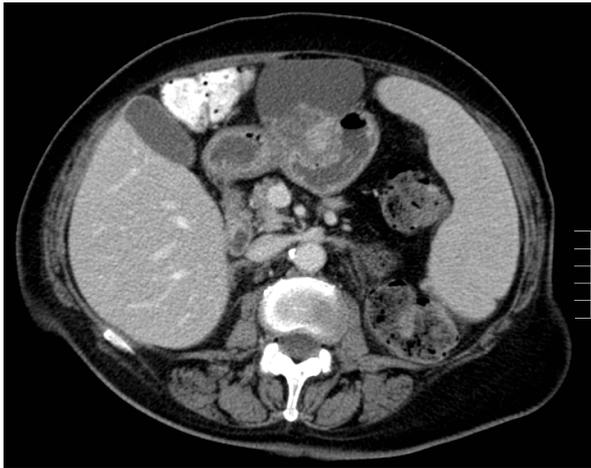
Exophytic



SMT Ddx: leiomyoma, leiomyosarcoma, schwannoma, pancreatic heterotopia, gastric cavernous hemangioma

Spectrum of Clinical Presentation

Asymptomatic



- Incidentally discovered (median size 3 cm)

Spectrum of Clinical Presentation



Non-specific Symptoms

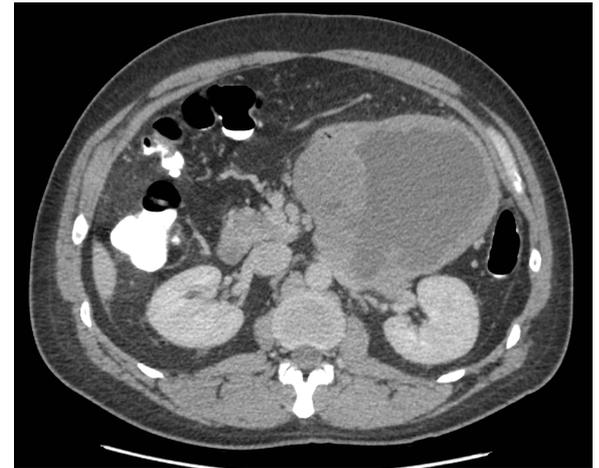
1. Nausea/vomiting
2. Abdominal pain
3. Abdominal distension
4. Early satiety

Spectrum of Clinical Presentation



- Slow bleeding
 - Anemia
 - Melena
- Acute bleeding
 - Intraluminal erosion
 - Intra-peritoneal rupture

Spectrum of Clinical Presentation

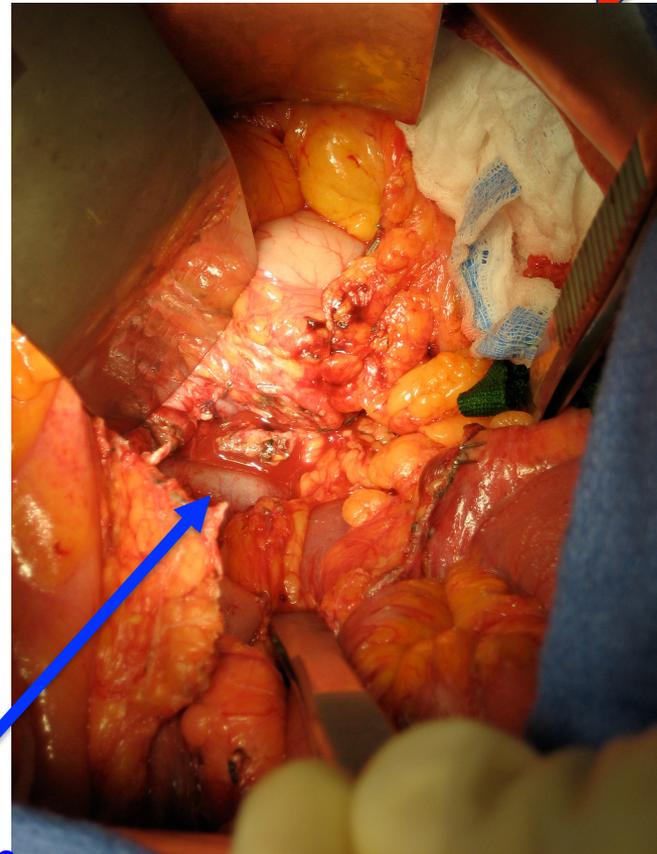
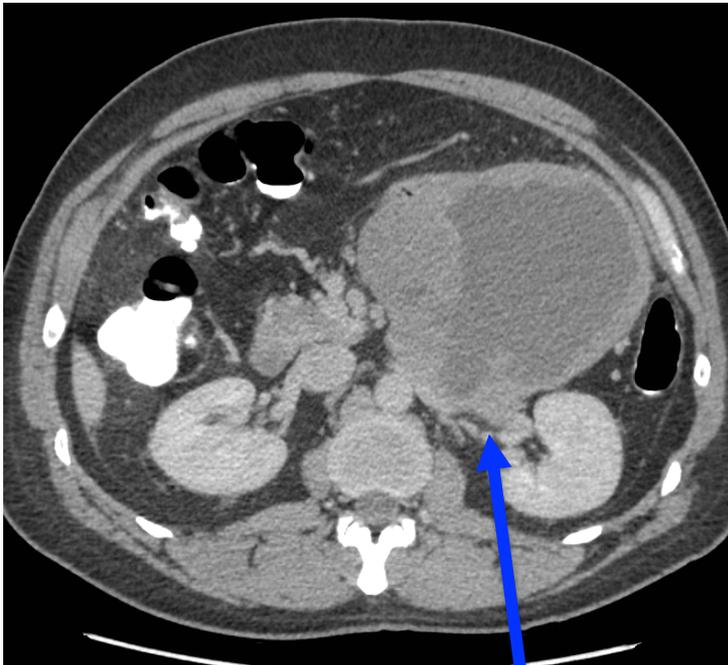


- Acute onset pain
- Fever
- Leukocytosis

Tumor Biology

Push

Rarely Invade

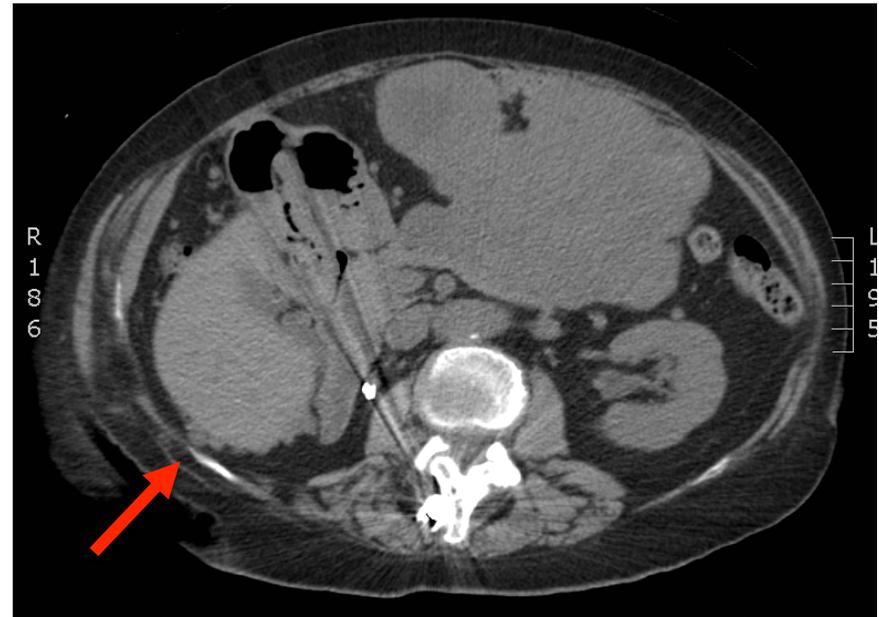
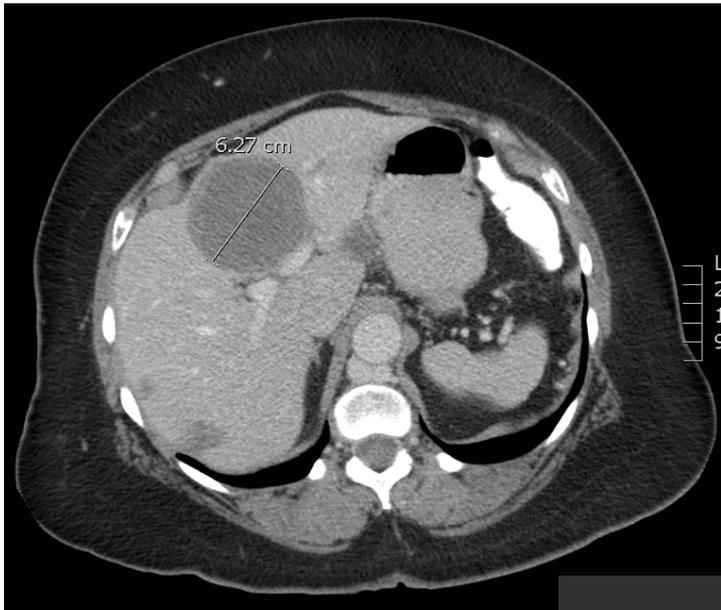


Left Renal Vein

Hematogenous (Not Lymphatic) Spread

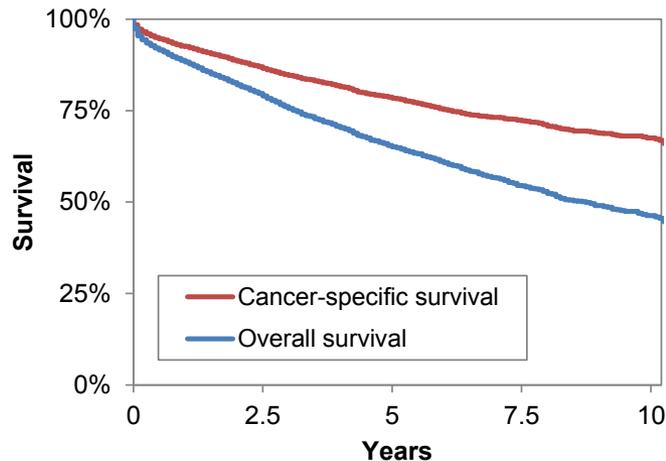
Liver Metastases

Peritoneal Metastases



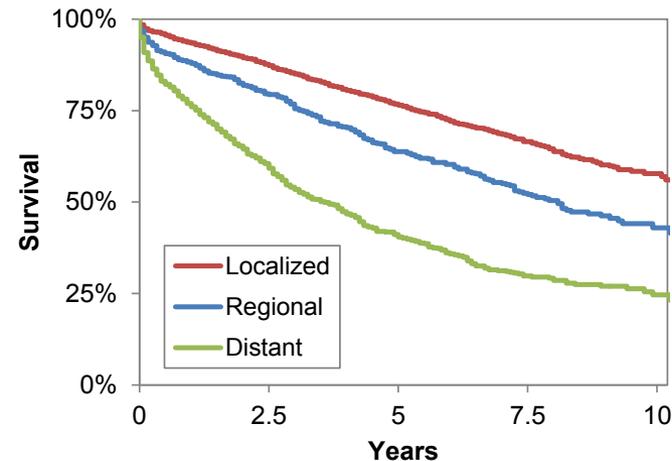
*< 1/3 patients have both types of metastases
Nodal and other metastases are rare*

Survival in the Era of TKIs



Entire GIST cohort

- 5-year DSS: 79%
- 5-year OS: 65%

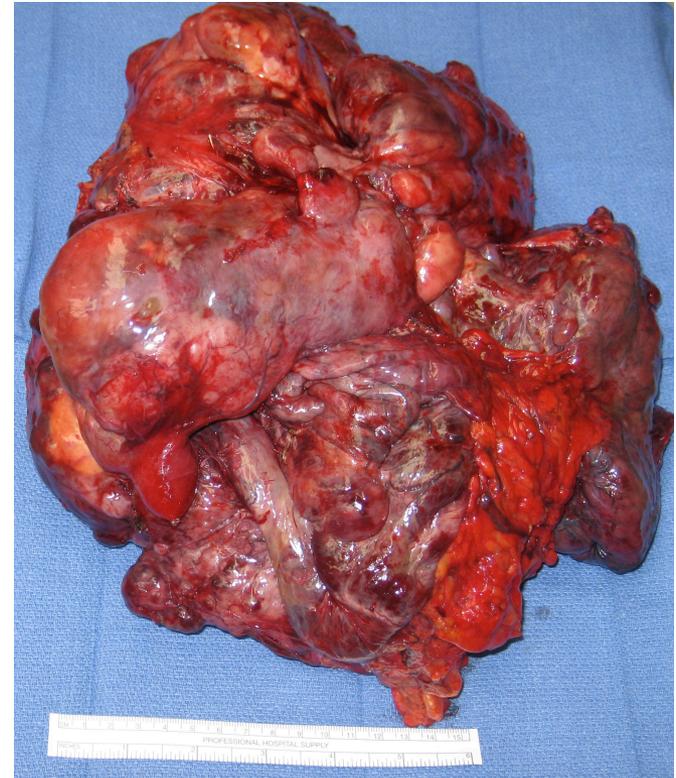
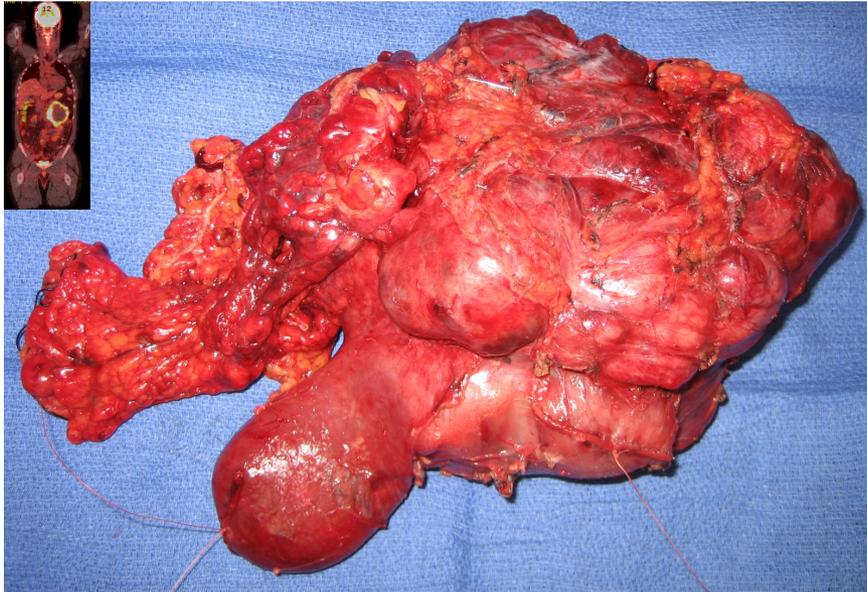


5-year OS by Stage

- Localized disease: 77%
- Regional disease: 64%
- Distant metastases: 41%

Surgery is the Primary Treatment

Potentially Curative



Goals of Surgical Treatment

- Total gross resection
- Negative microscopic margins
- Intact pseudocapsule without tumor rupture
- Because LN metastases are uncommon, lymphadenectomy is not generally indicated



Surgical Margins, Not the Technique, Dictate Prognosis

Table 1 Clinicopathological parameters and recurrence-free survival/disease-specific survival of Gastrointestinal Stromal Tumor (GIST) patients

Parameters	RFS					DSS				
	<i>n</i> (%)	Events (<i>n</i>)	HR	95% CI ^b	<i>p</i> Value	<i>n</i> (%)	Events (<i>n</i>)	HR	95% CI ^b	<i>p</i> Value
Type of surgery										
Wedge/segmental resection	53 (55)	6	NA		NA	56 (54)	7	NA		NA
Enucleation	21 (22)	2	NA		NA	22 (21)	0	NA		NA
Total/subtotal organ resection	20 (21)	4	NA		NA	22 (21)	4	NA		NA
En bloc resection	2 (2)	0	NA		NA	4 (4)	2	NA		NA

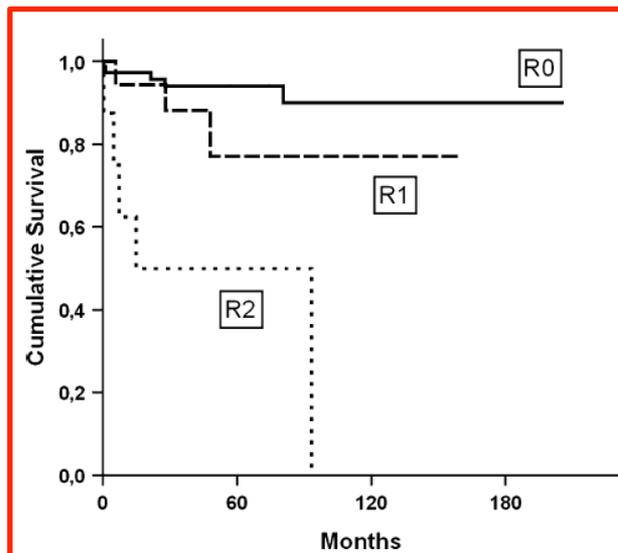


Table 2 Multivariate analysis of prognostic factors of disease-specific survival of GIST patients

Parameter	HR	95% CI ^a	<i>p</i>
Margin status			
R0	1.00		
R1	1.54	0.34–7.08	0.57
R2	5.72	1.44–22.71	0.013

^a 95% confidence interval for HR

Tumor Rupture is a Poor Prognostic Factor

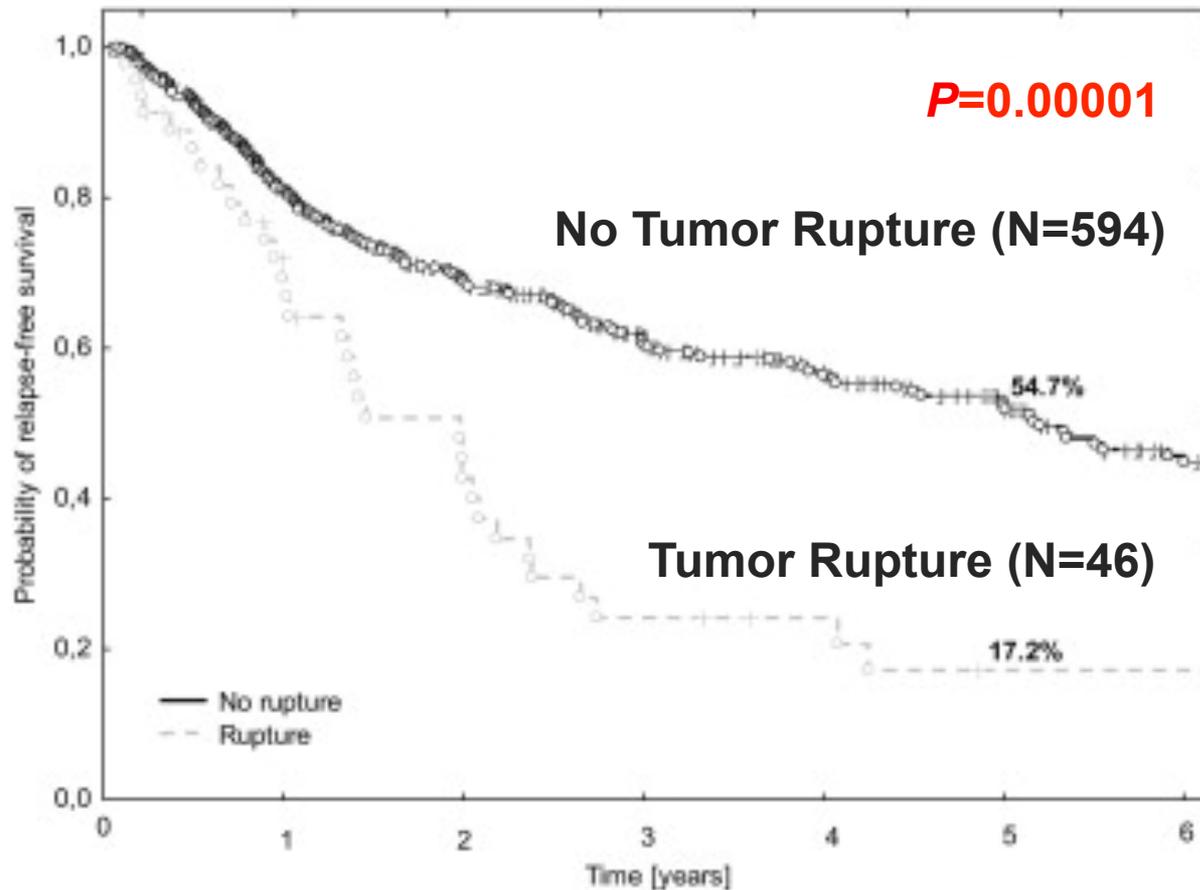
Risk of Recurrence: Modified NIH (Joensuu)

Joensuu proposed modification of NIH consensus classification^{6,15}

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

Joensuu H. Risk stratification of patients diagnosed with gastrointestinal stromal tumor. *Hum Pathol.* 39(10):1411-1414 (2008).

Tumor Rupture Influences Recurrence-free Survival



P. Rutkowski, et al., **Validation of the Joensuu risk criteria for primary resectable gastrointestinal stromal tumour – The impact of tumour rupture on patient outcomes.** European Journal of Surgical Oncology (EJSO), Volume 37, Issue 10, 2011, 890 - 896

Balancing Operative Approach



Operative Approach: Means to an End



OPEN PROCEDURE



LAPAROSCOPIC PROCEDURE

Laparoscopic Approach

ADVANTAGES

1. Shorter incision length with lower hernia risk
2. Less pain
3. Shorter length of stay
4. Lower blood loss
5. Decreased ICU admissions
6. No oncologic disadvantages in experienced centers with experience surgeons (i.e., pancreas, liver, gastric, colon cancers)

Lap vs. Open Gastric Resections for GIST

No Difference in Oncologic Outcomes

Variables	Surgery type			P value
	All (N = 80)	Lap (N = 40)	Open (N = 40)	
Chemotherapy				.91
None	74	37 (93%)	37 (93%)	
Adjuvant (imatinib)	5	3 (60%)	2 (40%)	
Neoadjuvant and adjuvant	1	0 (0%)	1 (100%)	
Margins				—
Gross –micro	79	39 (49%)	40 (50%)	
Gross +micro	0	0	0	
Gross close (<0.1 cm) micro	1	1 (1%)	0	
Recurrences, metastatic	2	1	1	—
Survival status				—
Alive and recurrence free	72	36	36	
Alive with disease	2	1	1	
Died of other causes	4	2	2	
Died of unknown causes	2	1	1	

Operative Approach: Questions to Ask

Tumor Factors

- Can total gross resection be achieved safely (for either local, regional or metastatic disease)?
- Is the tumor small enough to be manipulated laparoscopically?
- Is the tumor invading adjacent structures?
- Even if a laparoscopic resection is feasible, how large will the incision be to remove the tumor?

Operative Approach: Questions to Ask

Tumor Factors

- Is tumor rupture a significant concern?
- Is this a primary tumor or a recurrence...will the surgical bed be “stuck”?
- Is there concern for multi-focal disease?
- With preoperative (neoadjuvant) therapy, could tumor shrinkage change the resection, make it safer, or make it easier?

Operative Approach: Questions to Ask

Patient Factors

- Is the patient an appropriate operative candidate... other medical problems?
- Has the patient had prior abdominal operations- laparoscopic or open?

Operative Approach: Questions to Ask

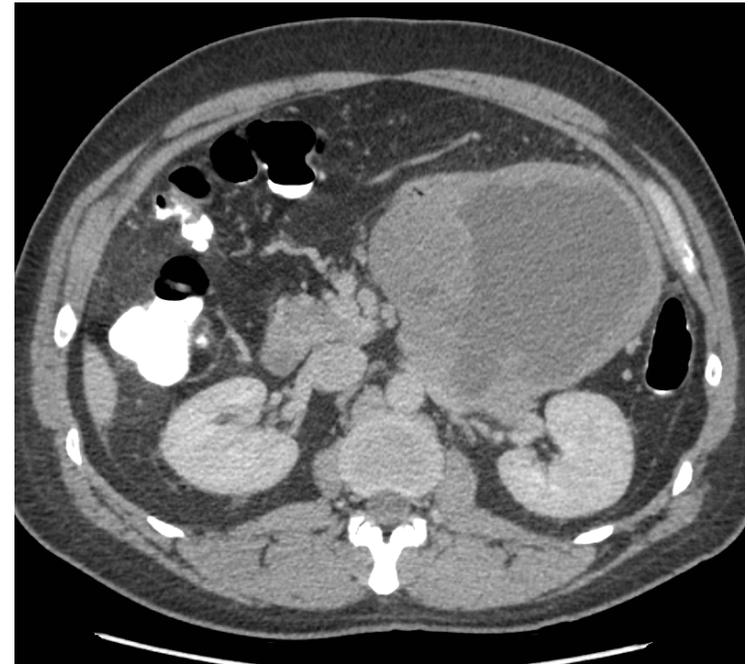
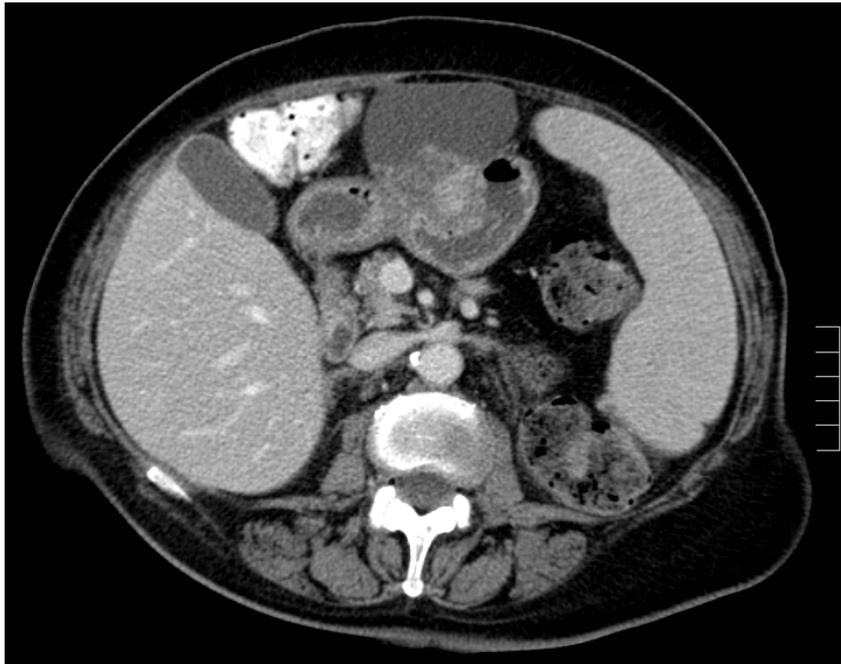
Surgeon Factors

- Is the surgeon skilled at a laparoscopic approach?
- Best approach is what the surgeon is most comfortable with.

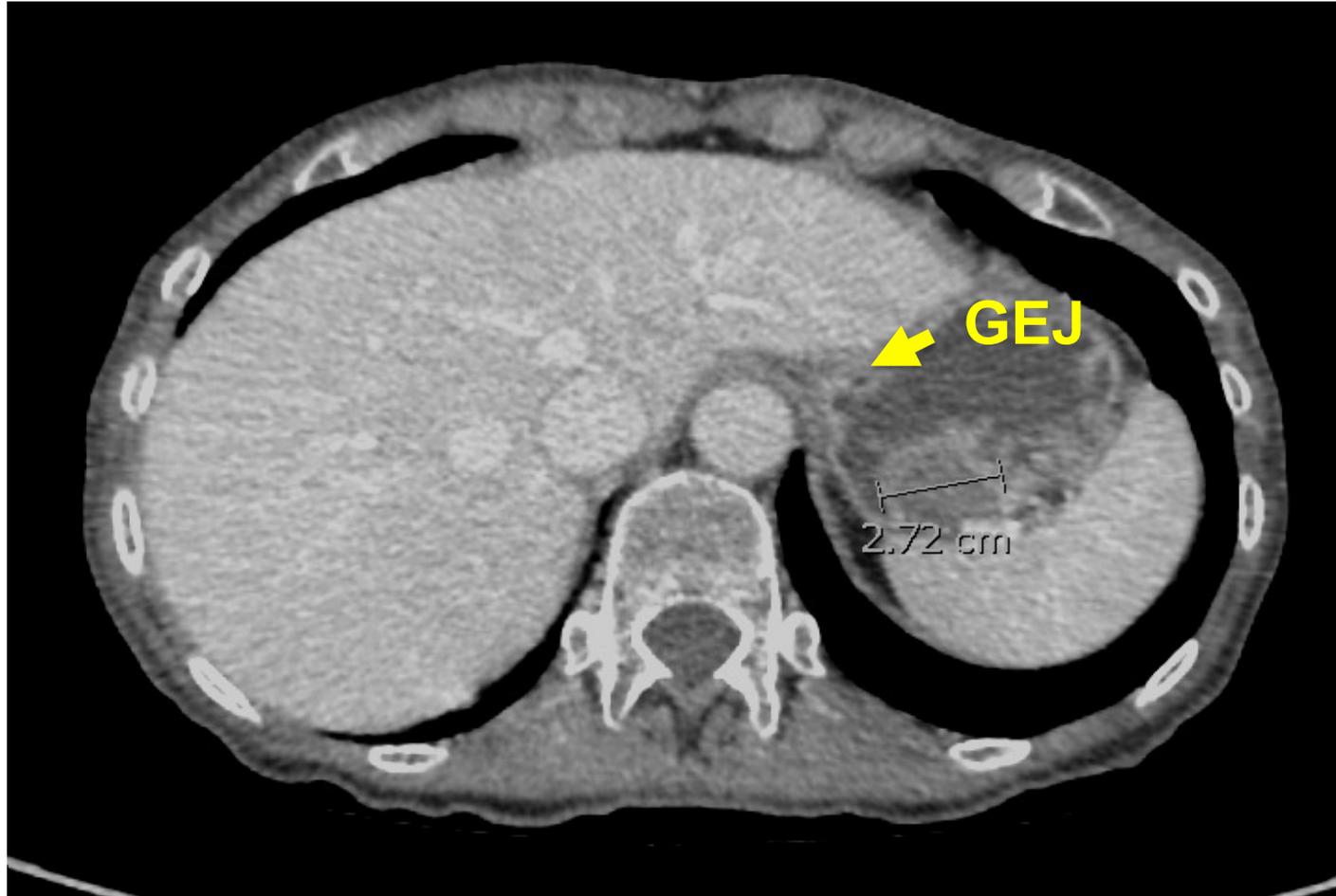
Operative Approaches in GIST

Surgical Technique	Advantages	Limitations (Evidence)	Tumor location	Disadvantages
Laparoscopy	Full-thickness resection of stomach wall; negative margins; minimal risk of dissemination; shorter hospital stay	Small studies (N=4–61)	Stomach; small bowel	Can be technically challenges with larger tumors > 10 cm
Laparotomy	Better visualization and mobilization of larger tumors or those in technically challenging locations	Small case series; retrospective studies	Any	Longer hospital stay; More blood loss; Longer operation time Reflect a selection bias because large tumors may not be resectable by laparoscopic approach

What Approach is Appropriate?



How should one approach resecting a GIST close to the GEJ...Open vs. Laparoscopic?

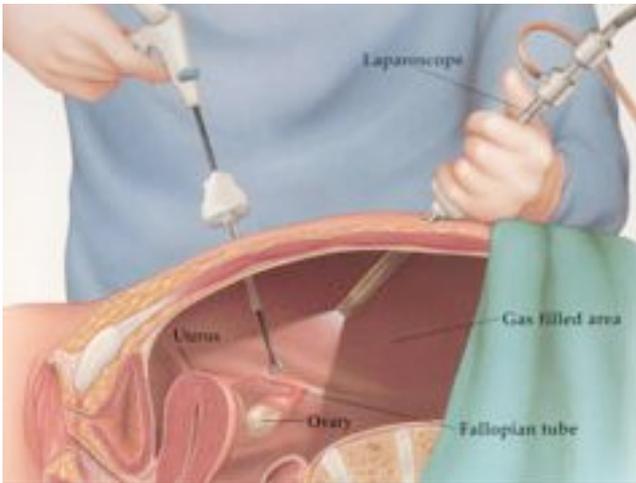


Operative Approaches in GIST

Surgical Technique	Advantages	Limitations (Evidence)	Tumor location	Disadvantages
Endoscopy	Minimally invasive; potentially shorter operation time	Small series; retrospective study Limited data on long-term outcomes	Esophagus; stomach; rectum for small lesions (1-3 cm)	Often leaves positive margins with capsular invasion and/or tumor rupture Complications: perforation, pneumothorax (9.4%), and GI bleeding (5%)

Emerging Surgical Approach

Laparoscopy



+

Endoscopy



Laparo-Endoscopy

Operative Approaches in GIST

Surgical Technique	Advantages	Limitations (Evidence)	Tumor location	Disadvantages
Laparo-endoscopy	Monitor endoscopic resection; repair injury/perforation	Case reports and series	Stomach; duodenum	Technically demanding

Surg Endosc
DOI 10.1007/s00464-014-3910-2



Laparo-endoscopic transgastric resection of gastric submucosal tumors

Juan S. Barajas-Gamboa · Geylor Acosta · Thomas J. Savides · Jason K. Sicklick · Syed M. Abbas Fehmi · Alisa M. Coker · Shannon Green · Ryan Broderick · Diego F. Nino · Cristina R. Harnsberger · Martin A. Berducci · Bryan J. Sandler · Mark A. Talamini · Garth R. Jacobsen · Santiago Horgan

Sicklick and Lopez, Journal of GI Surgery. 2013.

Laparo-Endoscopic Surgical (LES) Approach

ADVANTAGES

1. Extra working port via the endoscope in order to minimize instrument changes while decreasing the clutter/clashing of additional trocars/instruments
2. Improved ability to visualize remote locations in the abdomen given the endoscope's flexibility
3. Superior ergonomics when compared to single access laparoscopic surgery

Lessons Learned

- Takes a team approach with coordination between surgeons and gastroenterologists
- Approach reduces the number of trocars
- Avoids large gastric resections for proximal gastric tumors
- Oral extraction is generally safe and feasible for tumors < 3-4 cm in size

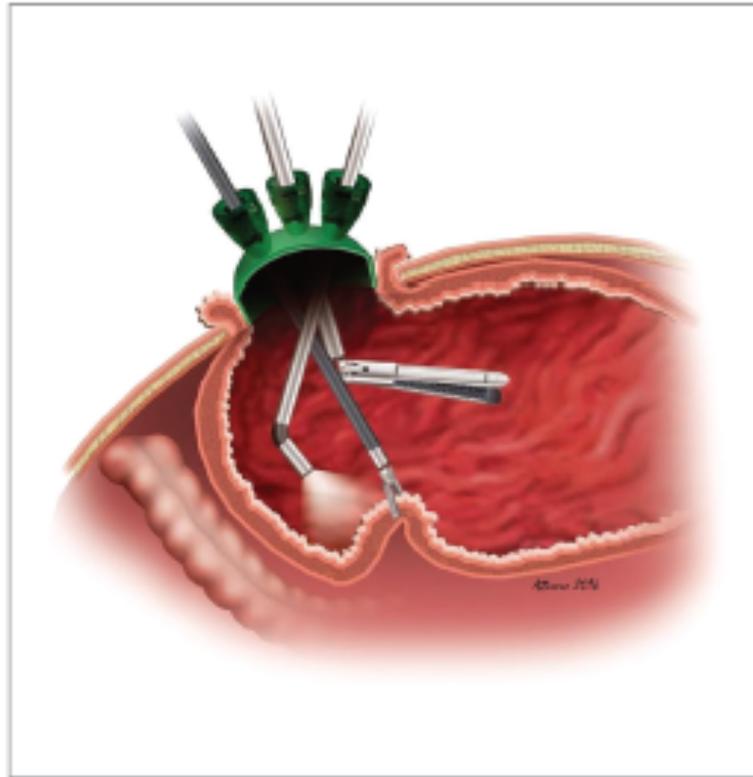
Assessment of Intra-gastric Single-Port Surgery for Gastric Tumors

Felix Krenzien, MD; Johann Pratschke, MD; Ricardo Zorron, MD, PhD

JAMA Surgery August 2017 Volume 152, Number 8

Figure. Intra-gastric Single-Port Surgery (IGS)

A Schematic of IGS



B Anterior wall of the stomach



C GIST at the cardia

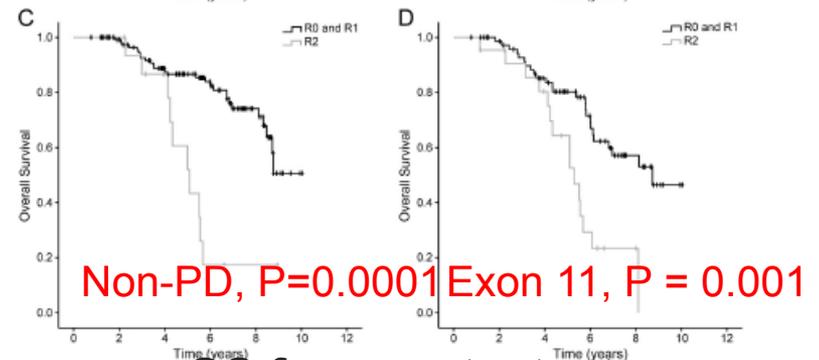
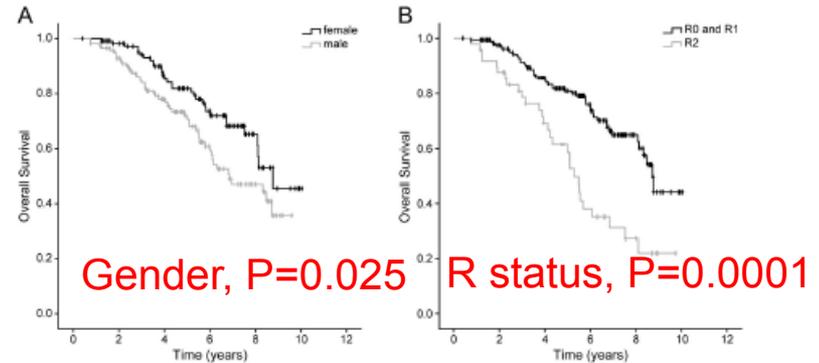


Limited Metastatic Disease

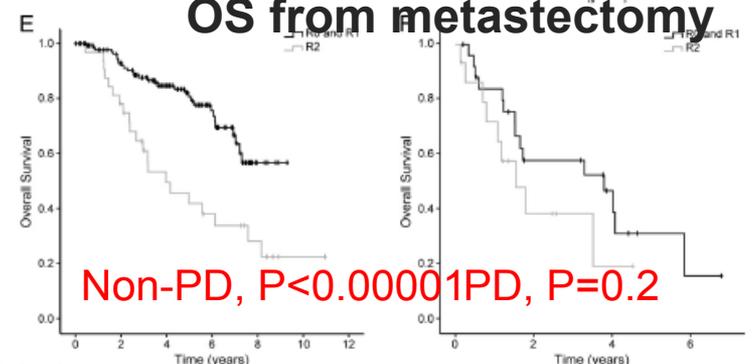
Long-term follow-up of patients with GIST undergoing metastasectomy in the era of imatinib – Analysis of prognostic factors (EORTC-STBSG collaborative study)★

- Long-term survival in patients in whom surgical complete remission can be achieved.
- Incomplete resection, including debulking surgery does not seem to prolong survival.

OS from first imatinib



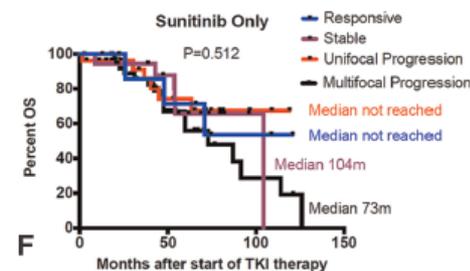
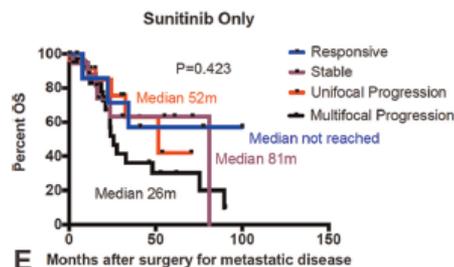
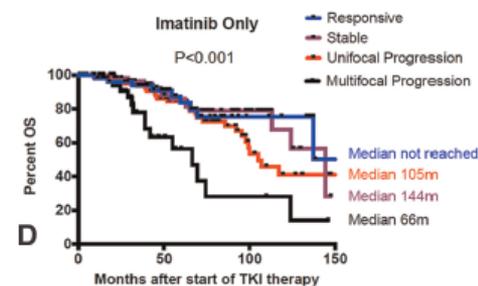
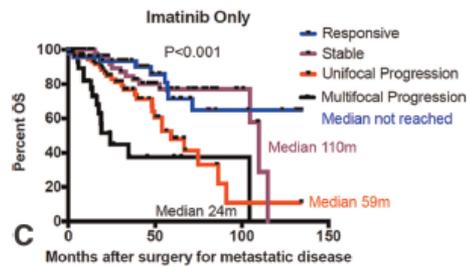
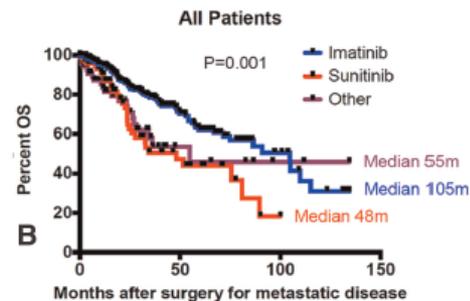
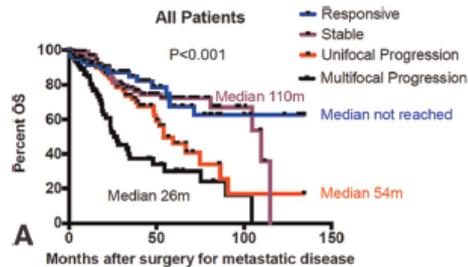
OS from metastectomy



Cytoreductive Surgery for Metastatic Gastrointestinal Stromal Tumors Treated With Tyrosine Kinase Inhibitors

A 2-institutional Analysis

Mark Fairweather, MD,*† Vinod P. Balachandran, MD,‡ George Z. Li, MD,* Monica M. Bertagnolli, MD,*†
 Cristina Antonescu, MD,§ William Tap, MD,¶|| Samuel Singer, MD,‡ Ronald P. DeMatteo, MD,‡
 and Chandrajit P. Raut, MD, MSc*†



Summary

- Although surgery remains the only potentially curative treatment, patients who undergo complete resection may still experience local recurrence or distant metastases.
- Therapeutic strategies that combine surgical resection and imatinib therapy may represent the best treatment to maximize patient outcomes.
- Selected patients with metastatic disease may be treated with a combination of preoperative imatinib and metastasectomy.
- Surgery in metastatic GIST patients in the absence of MPD on imatinib is associated with outcomes at least comparable with second-line sunitinib and may be considered in select patients.

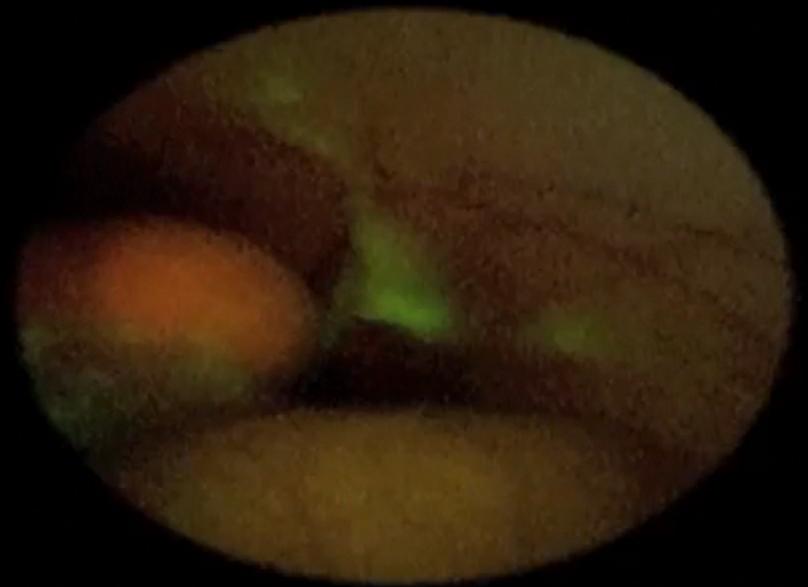
Future Directions in Surgical Management of GIST?

Approach Surgical Challenges in the Lab

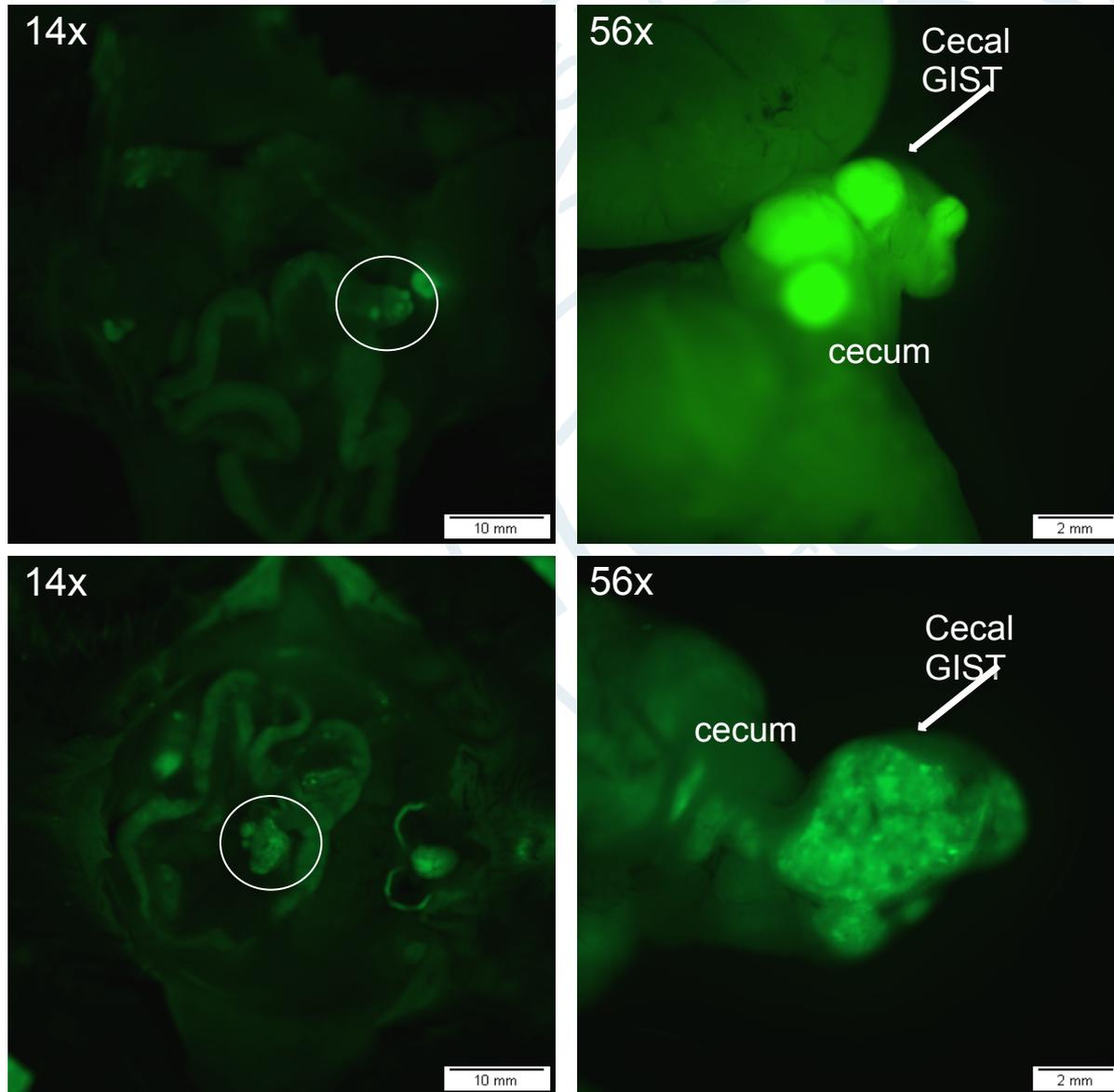
- **Diagnosis**
 - Can be mistaken for benign gastric submucosal tumors
 - Schwannoma
 - Leiomyoma
- **Surgical Treatment**
 - R0 resection
 - Cytoreduction of peritoneal and/or liver metastases in highly selected patients
- **Response to Tyrosine Kinase Inhibitor Therapy**

Approach Surgical Challenges in the Lab

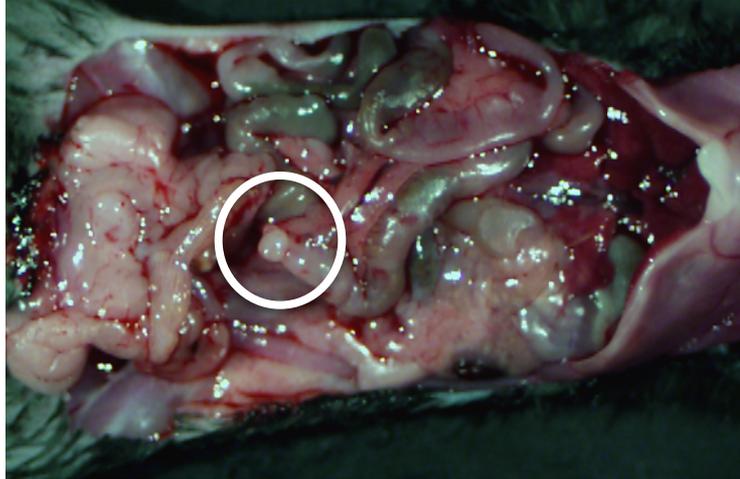
To develop a technique for using fluorophore-conjugated anti-KIT antibodies delivered intravenously to transgenic GIST-bearing mice for detection of GISTs *in vivo*.



In Vivo Fluorescent Labeling of GIST



KIT K641E^{+/-} Transgenic Mouse Model of GIST

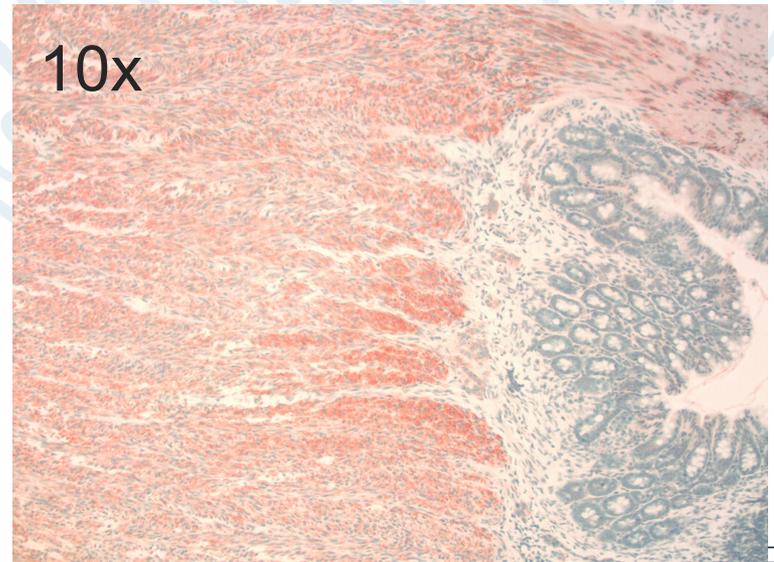
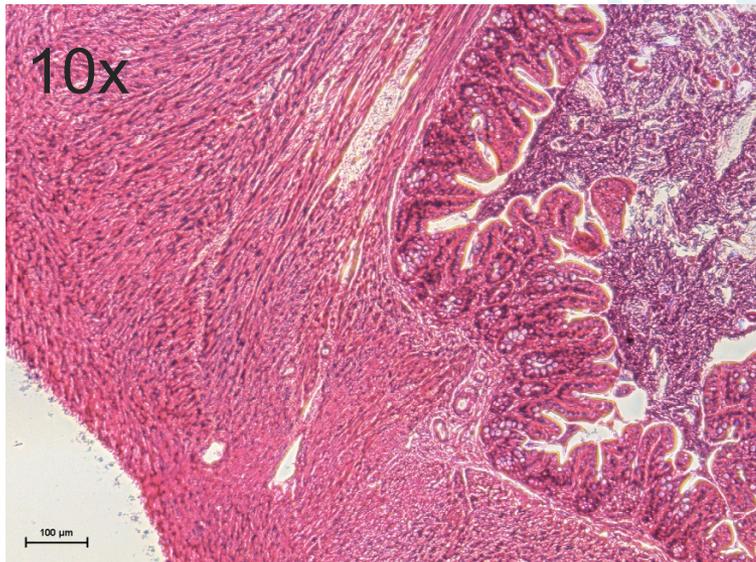


H&E



KIT

KIT K641E^{+/-}



In Vivo Fluorescent Labeling of GIST

- Multiple translatable surgical applications:
 - Laparoscopic staging
 - Assessment of margin status or residual disease