Surgery: The Primary Treatment for GIST

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Disclosure

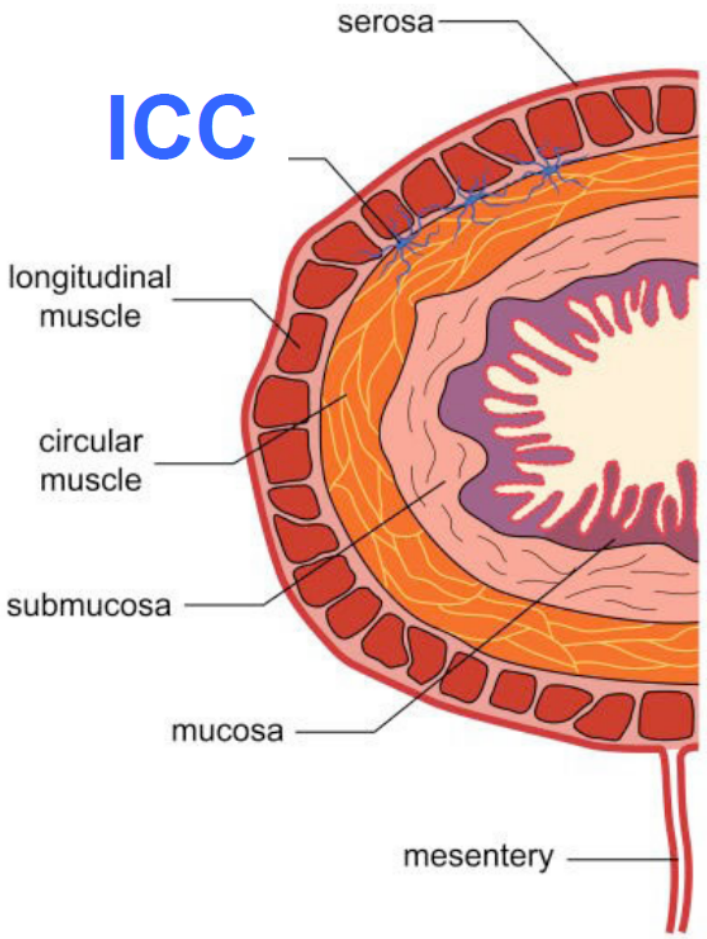
- Investigator-Initiated Trial sponsored by Bristol-Myers Squibb (2017-present)

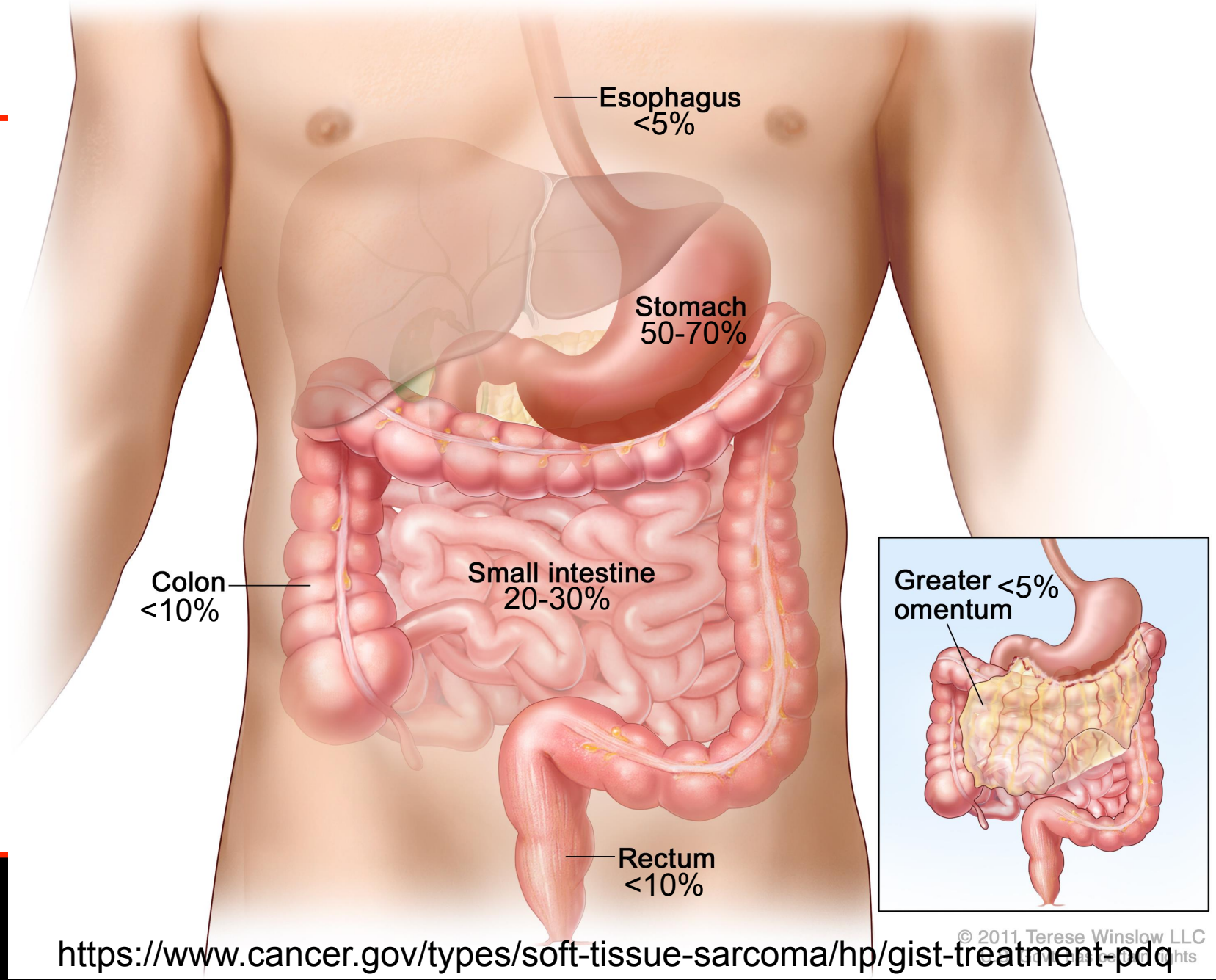
Principles of Surgery for GIST

1. Multidisciplinary Management
2. No Tumor Rupture
3. 1-2 cm margin
4. Complete Resection:
   - Including adjacent involved organs

Gastrointestinal Stromal Tumors

- Historically classified as:
  - leiomyoma
  - leiomyosarcoma
  - leiomyoblastomas
- 1998: Hirota and colleagues:
  - Interstitial Cells of Cajal
  - Pacemaker cells throughout intestine
  - cKIT+





https://www.cancer.gov/types/soft-tissue-sarcoma/hp/gist-treatment-pdq

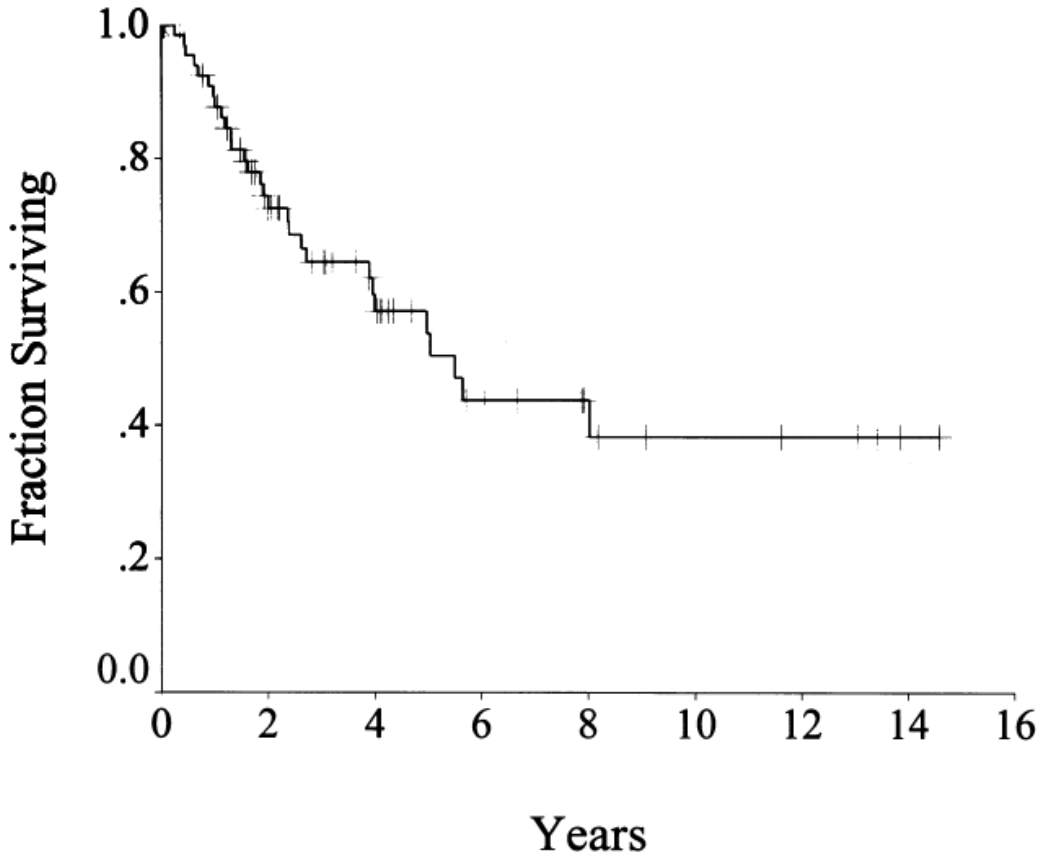
What do Surgeon's think about when evaluating a patient with GIST?

1. Where is the tumor located?
2. Additional organs involved?
3. Bad Biology?
4. Would preoperative imatinib (Gleevec) help?
5. Approach?
   - Role for laparoscopy
   - ? Role for Observation

GISTs-Historical Outcomes

Table 2. PATIENT PRESENTATION IN 200 PATIENTS WITH GASTROINTESTINAL STROMAL TUMOR

Presentation	n	Median Survival (months)	Complete Resection	
			n	% of Row Total
Primary	93	60	80	86
Metastatic	94	19	28	30
Metastasis only	51	22	16	31
Primary tumor + metastasis	26	23	8	31
Local recurrence + metastasis	17	9	4	24
Locally recurrent	13	12	6	46



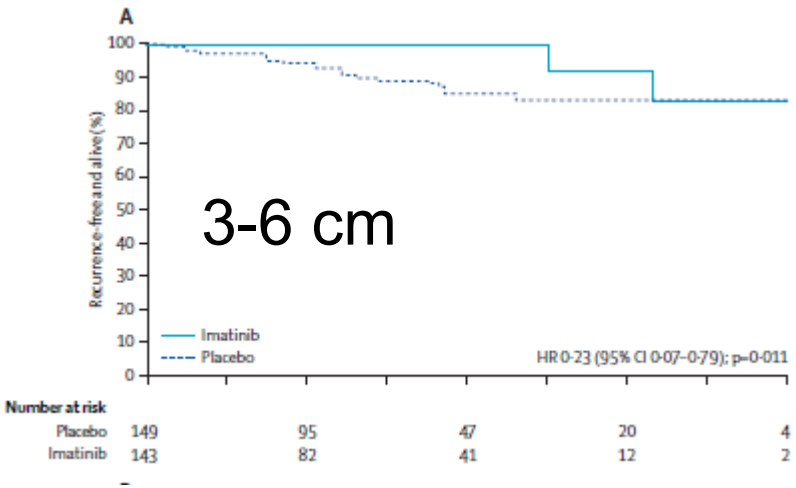
DeMatteo et al, *Ann Surg* 2000: 231(1); 51-8.

GIST discovery: right place, right time

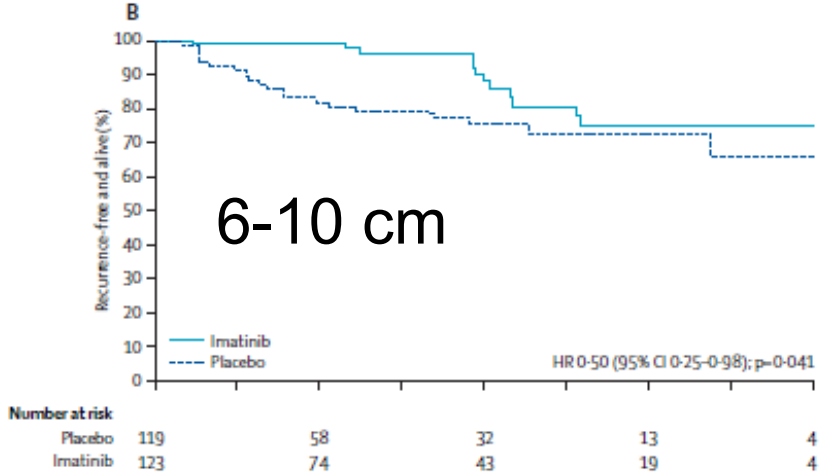
- Hirota et al :1998
- Clinical trial in leukemia
- Imatinib (Gleevec)

- Tyrosine kinase inhibitor (TKI)
  - Bcr-Abl
  - **cKIT**
  - PDGF-R

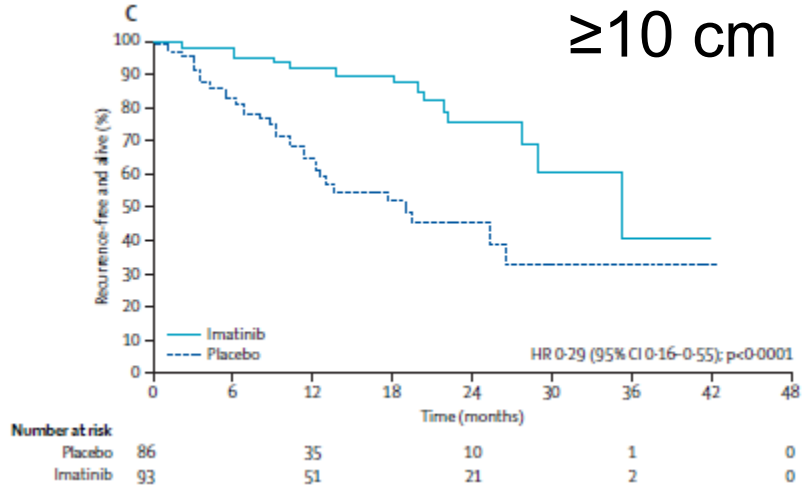
Imatinib reduces recurrence after surgery



3-6 cm



6-10 cm



≥10 cm

DeMatteo et al, *Lancet* 2009: 373; 1097-1104.

Who should get Imatinib after surgery? Prognostic Factors-Recurrence

Parameter	Low Risk	High Risk
Location	Stomach	Small/large intestine
Size	≤ 5 cm	> 5 cm
Mitotic index	≤ 5/50 HPF	> 5/50 HPF
Mutation	PDGFRA	WT
KIT mutation	Exon 11 duplication/ insertion	Exon 11 deletion, Exon 9
Surgery	R0 resection	R1, tumor rupture

Gastric vs. non-gastric GIST: Different outcomes

PREDICTORS OF GIST BIOLOGIC BEHAVIOR

Table 1: Gastric GISTs: Proposed Guidelines for Assessing the Malignant Potential[1,2]

Tumor Size	Mitotic Rate	Predicted Biologic Behavior
≤2 cm	≤5 mitoses/50 HPFs	Metastasis rate: 0%
	>5 mitoses/50 HPFs	Metastasis rate: 0%*
>2 cm ≤5 cm	≤5 mitoses/50 HPFs	Metastasis rate: 1.9%
	>5 mitoses/50 HPFs	Metastasis rate: 16%
>5 cm ≤10 cm	≤5 mitoses/50 HPFs	Metastasis rate: 3.6%
	>5 mitoses/50 HPFs	Metastasis rate: 55%
>10 cm	≤5 mitoses/50 HPFs	Metastasis rate: 12%
	>5 mitoses/50 HPFs	Metastasis rate: 86%

GISTs: Gastrointestinal stromal tumors; HPFs: High-power fields; *predicted rate based on tumor category with very small numbers

Table 2: Non-Gastric GISTs: Proposed Guidelines for Assessing the Malignant Potential[1,2]

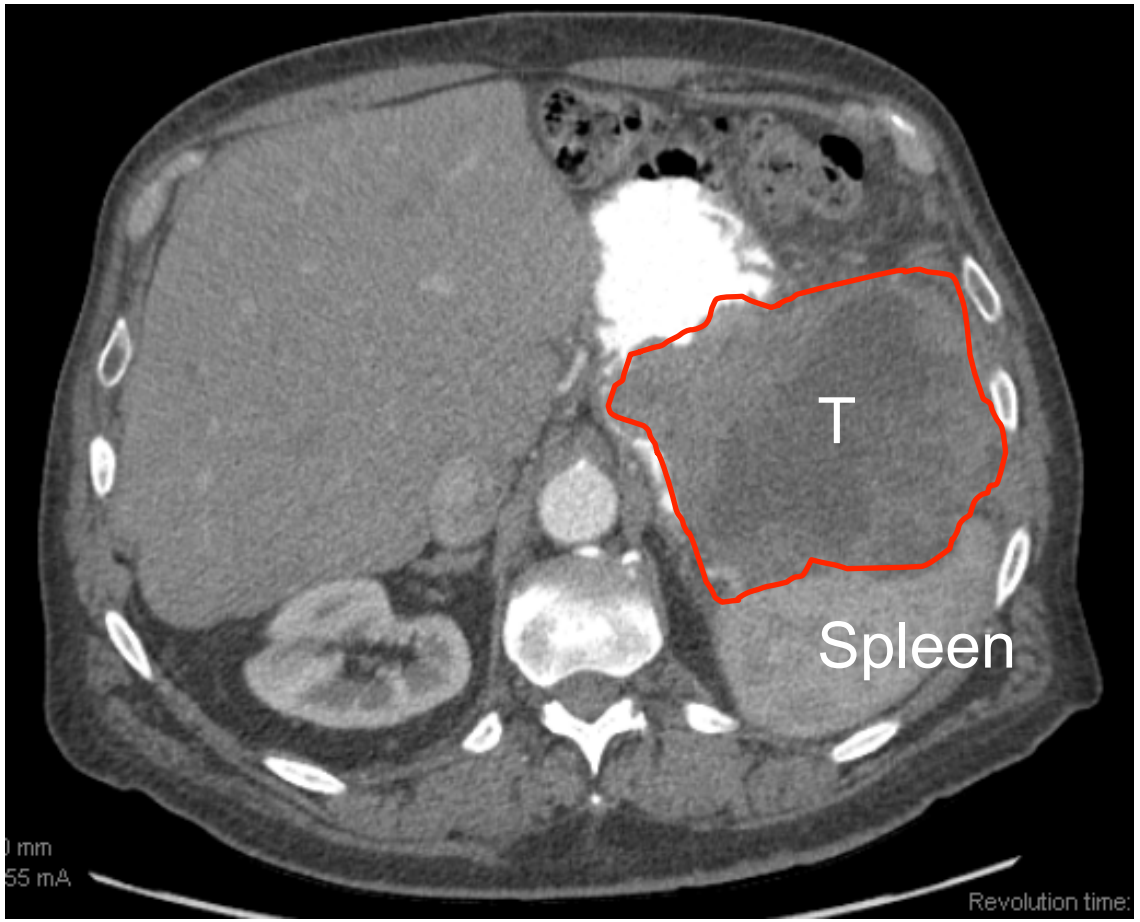
Tumor Size	Mitotic Rate	Predicted Biologic Behavior
≤2 cm	≤5 mitoses/50 HPFs	Metastasis rate: 0%
	>5 mitoses/50 HPFs	Metastasis rate: 50%–54%
>2 cm ≤5 cm	≤5 mitoses/50 HPFs	Metastasis rate: 1.9%–8.5%
	>5 mitoses/50 HPFs	Metastasis rate: 50%–73%
>5 cm ≤10 cm	≤5 mitoses/50 HPFs	Metastasis rate: 24%
	>5 mitoses/50 HPFs	Metastasis rate: 85%
>10 cm	≤5 mitoses/50 HPFs	Metastasis rate: 34%–52%
	>5 mitoses/50 HPFs	Metastasis rate: 71%–90%

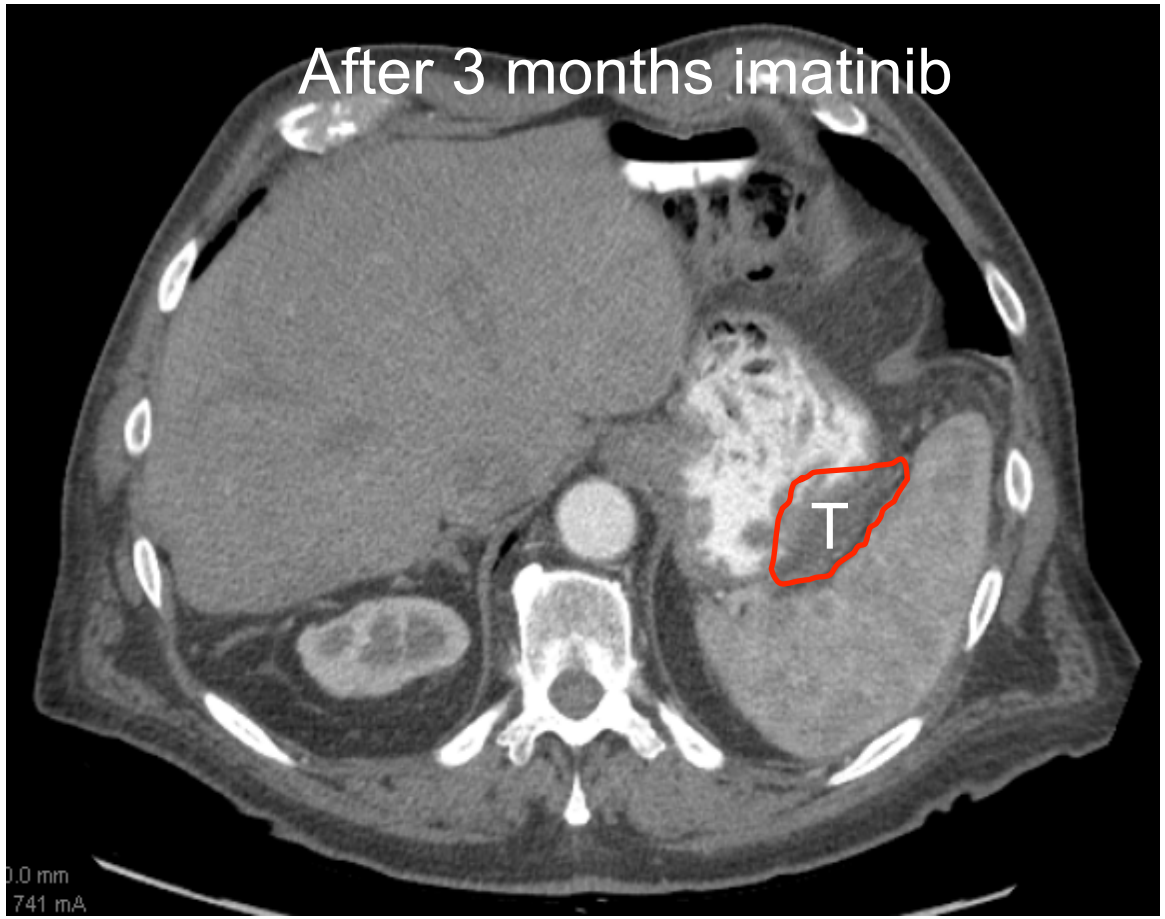
GISTs: Gastrointestinal stromal tumors; HPFs: High-power fields

What do Surgeon's think about when evaluating a patient with GIST?

1. Where is the tumor located?
2. Additional organs involved? ←
3. Bad location? ←
4. Bad Biology?
5. Approach?
   - Role for laparoscopy
   - ? Role for Observation

75 yo M Diagnosed with anemia



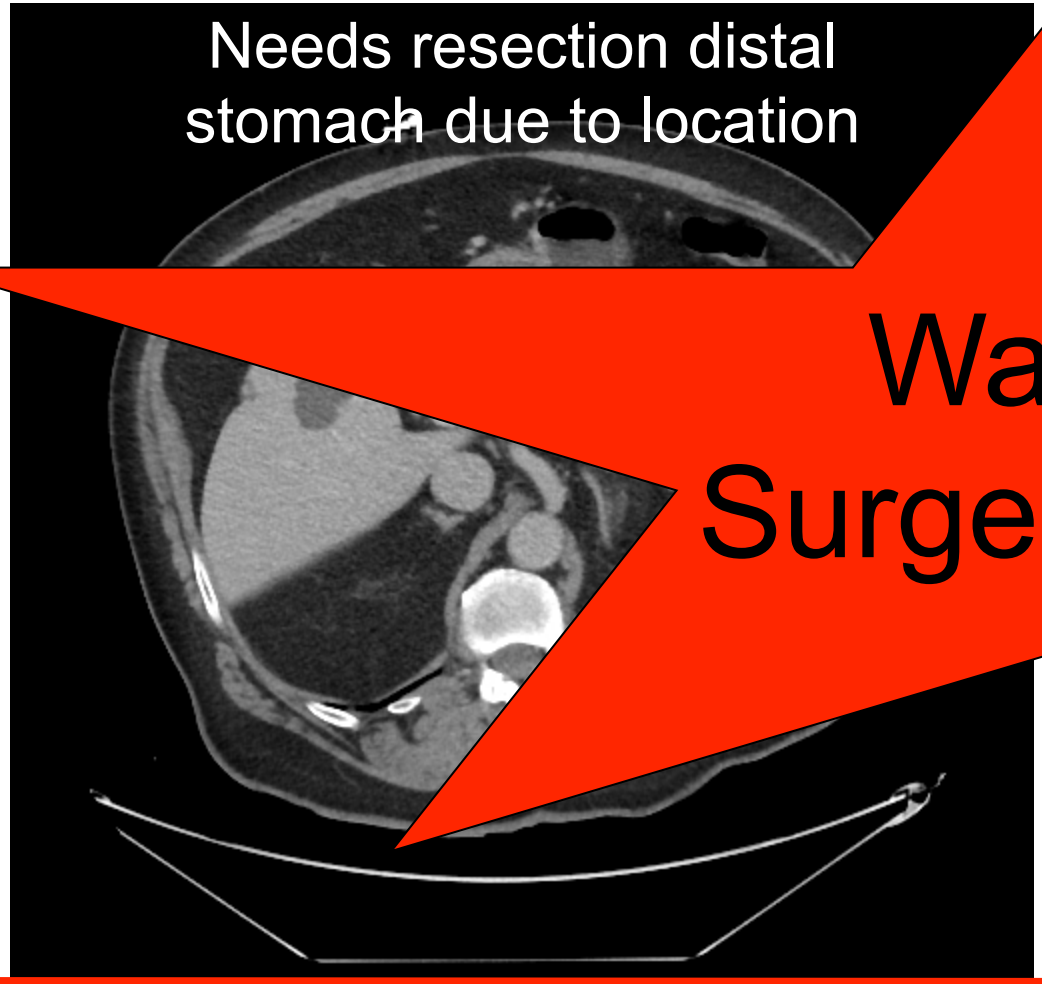


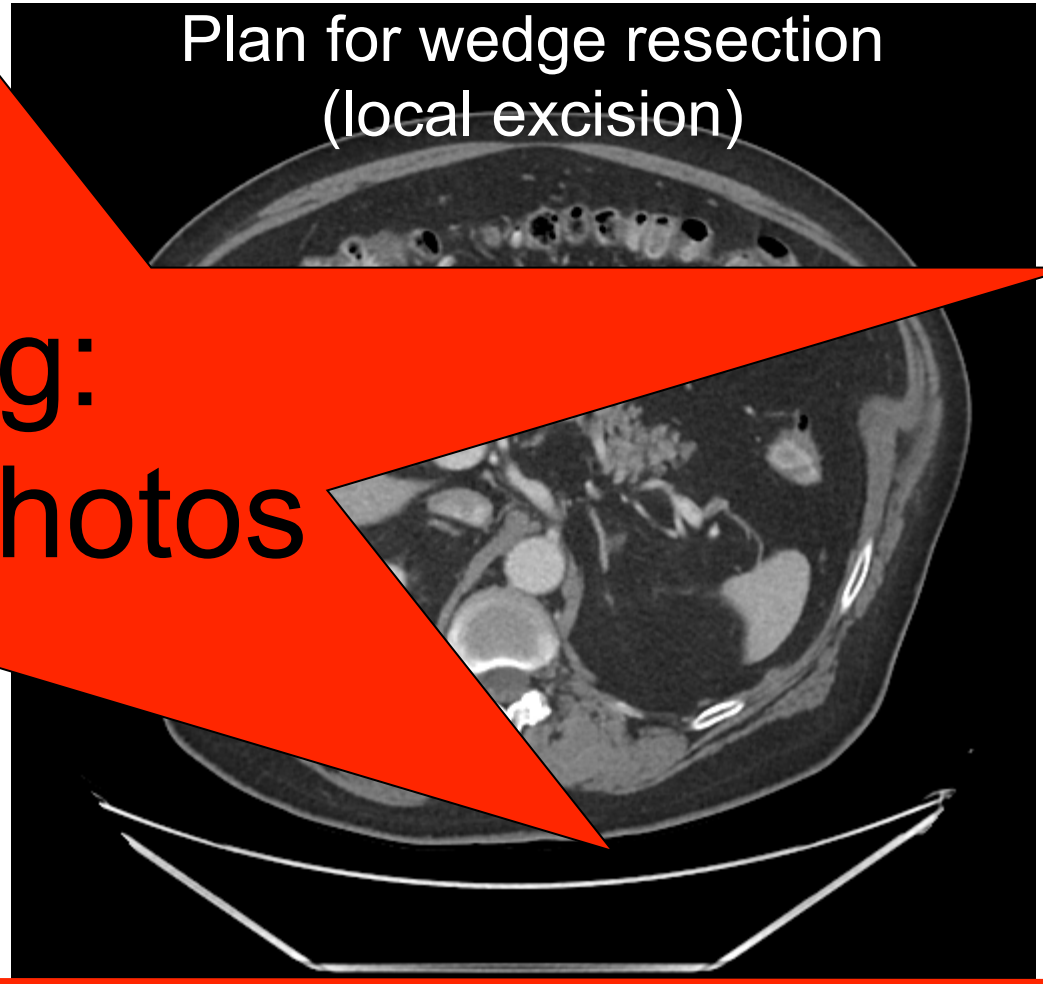
Biopsy: Exon 11 mutant GIST

75 yo M Diagnosed with anemia

- OR- partial gastrectomy & splenectomy
- Path- 6 x 3.5 cm, < 5% tumor viable, margins negative, 0 mitosis
- Continued adjuvant Gleevec 300 mg/day
- Last F/U 3.5 years → No disease

77yo M Diagnosed with gastric GIST: Bad Location





Warning:
Surgery Photos

- No need for post-operative imatinib

GIST prior to Therapy

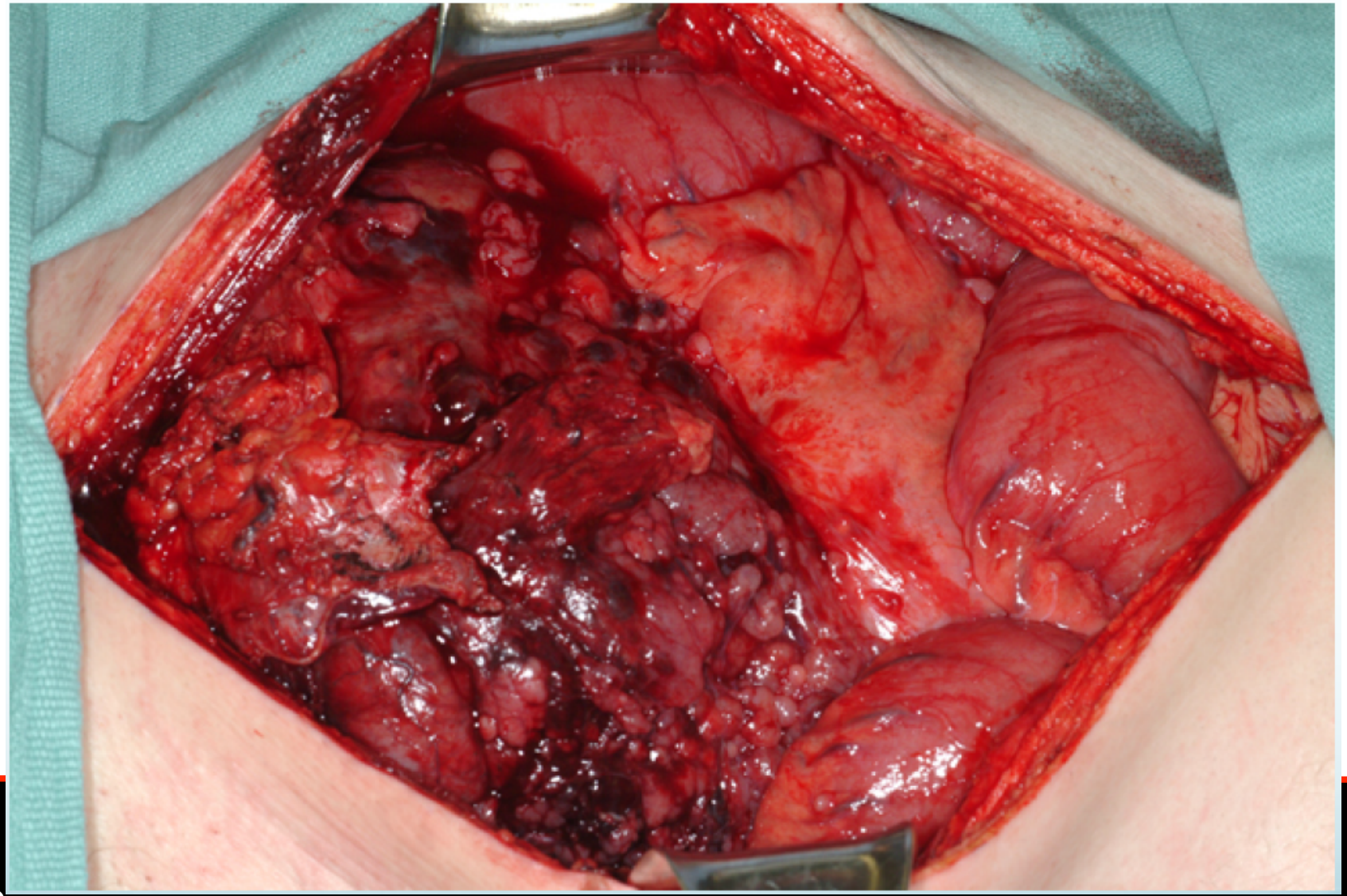


Photo: Kelly Hunt, MD

GIST after Therapy

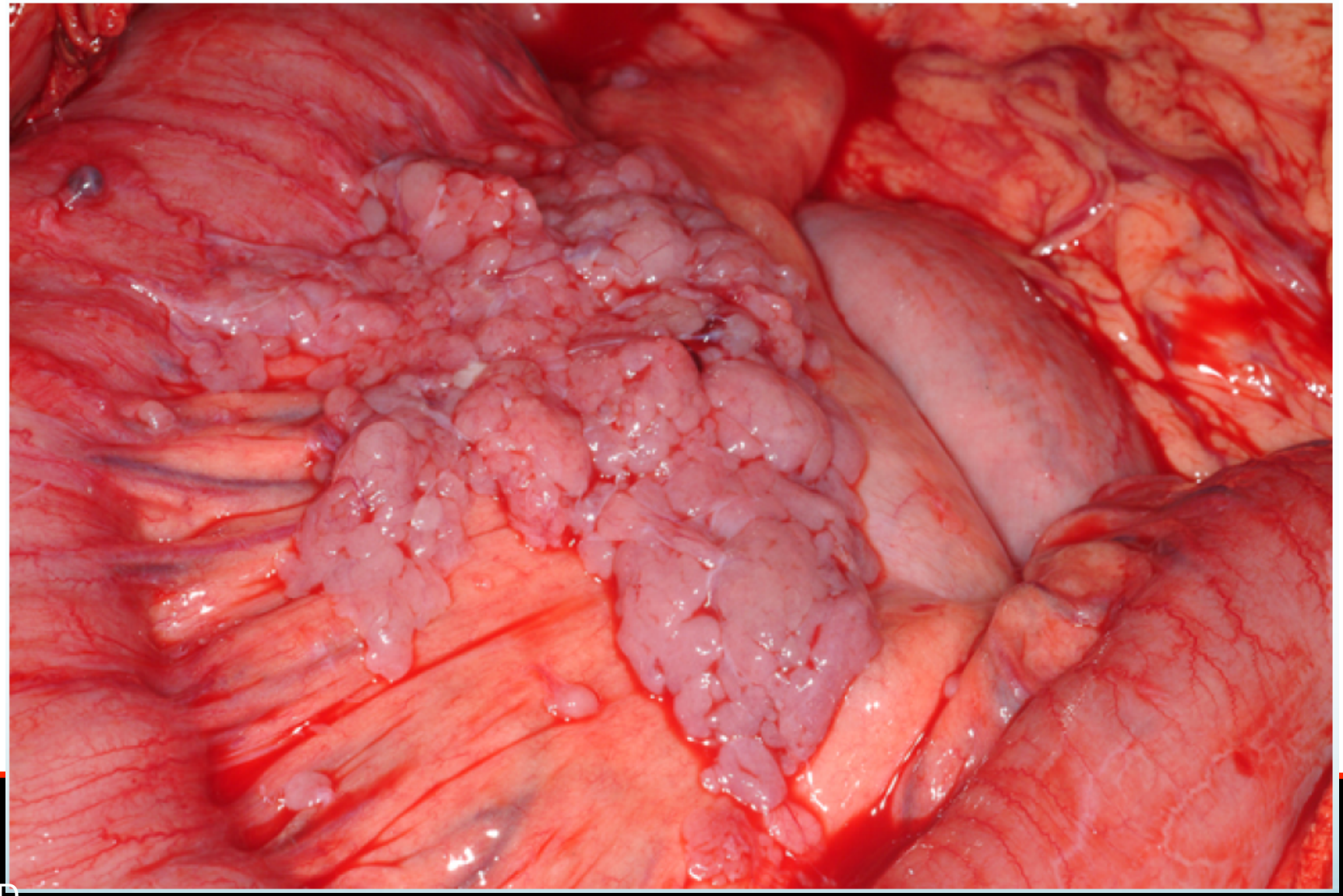


Photo: Kelly Hunt, MD

Preoperative Therapy: Little to lose, lots to gain

- Rationale:
  - Decrease the size of the tumor
  - Decrease the vascularity
  - Diminish extent of resection required

- For locally advanced primary GIST patients receiving preoperative therapy
  - 1% complete response, 73% partial response, 9% stable, 1% progressive disease

Andtbacka et al, *Ann Surg* Onc 2007

Preoperative imatinib is safe

- Randomized Phase II trial
  - 19 patients: preoperative therapy for 3, 5 or 7 days
  - No effects on surgical complications
  - 62% had evidence of radiographic reponse

- RTOG 0132
  - Multi-institutional study: 53 patients
  - 2 months preoperative imatinib + 2 years post-op
  - No significant effects on surgical complications

McAuliffe et al, *Ann Surg* Onc 2009
Wang et al, *Ann Surg Onc* 2012

How long to treat for localized disease?

- Treat to maximal effect
- ~ 6 months but up to 12 months or longer
- Imaging after 2-3 months and discuss: Med Onc, Surg Onc and patient.
  - Is now the right time for surgery?
  - Will further shrinkage change to extent or approach of surgery?

Laparoscopic resection of GIST-Feasible?

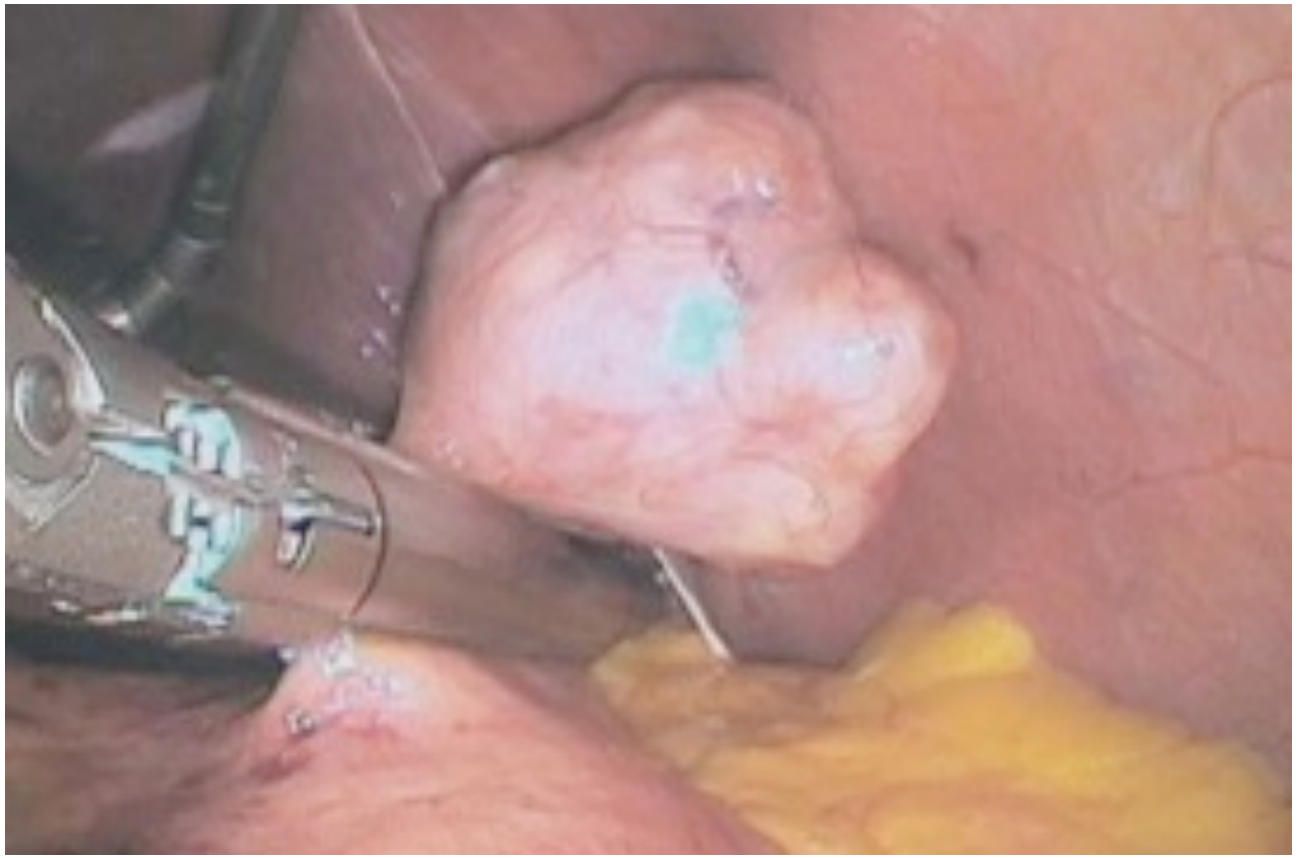


Photo: Chan Raut, MD

Tumor size important for determining approach
Need to get the tumor out!

Trocar size: 0.5 cm-1.2 cm

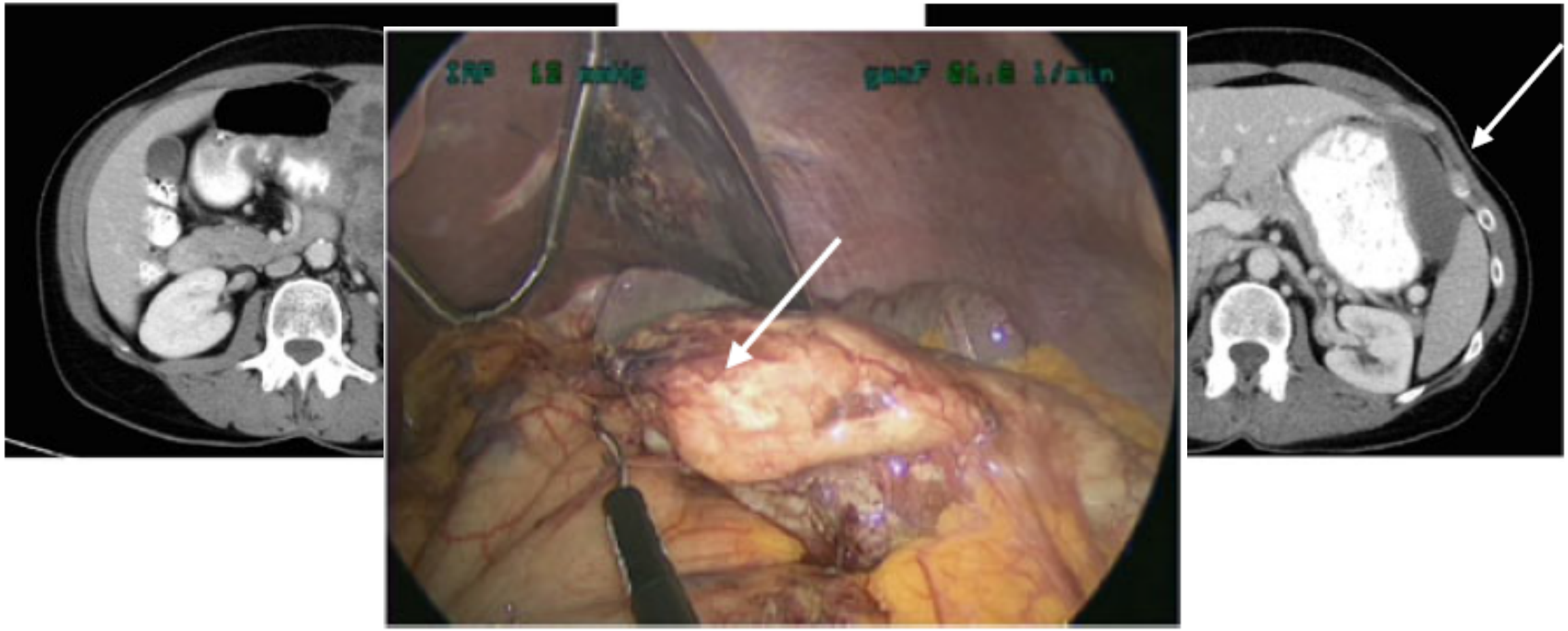
https://www.ncbi.nlm.nih.gov/books/NBK65959.3/figure/CDR0000062957__234/?report=objectonly

Laparoscopic resection of GIST-Reasonable?

- Review of 11 nonrandomized studies of 765 patients
  - 381: laparoscopy
  - 384 open
- Higher proportion of high-risk tumors and gastrectomies in open group
- Laparoscopy: superior short-term outcomes without compromising oncologic safety
- Best approach: what the surgeon is most comfortable with

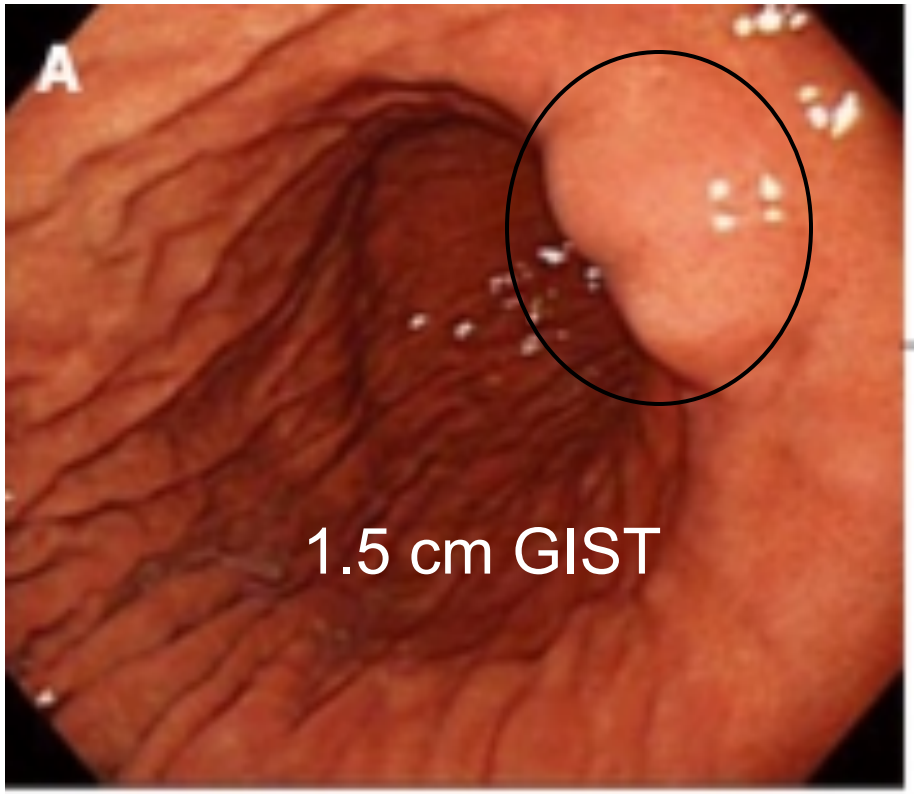
Koh et al, *Ann Surg Onc* 2013

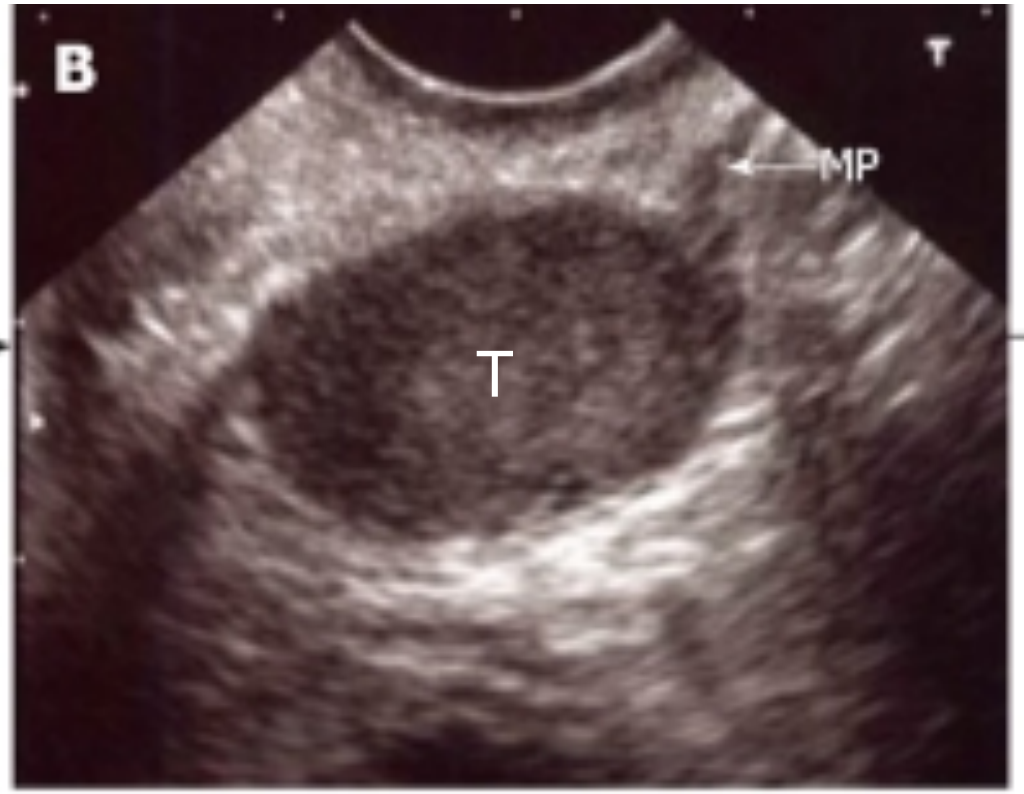
Preoperative imatinib-smaller operation



Gronchi & Raut, *Ann Surg Onc* 2012

70 yo M with abdominal pain-What to do?





APPROACH TO PATIENTS WITH VERY SMALL GASTRIC GISTS (<2 CM)[i]

WORKUP AT PRIMARY PRESENTATION	RESULTS OF INITIAL DIAGNOSTIC EVALUATION	INITIAL MANAGEMENT	FOLLOW-UP

Why not just take it out?

- Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA)
- Imaging[b]

No high-risk EUS features → Consider periodic endoscopic or radiographic surveillance[k]

High-risk features: irregular border, cystic spaces, ulceration, heterogenity

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Summary: Localized Disease

1. Where is the tumor located?
   - Stomach vs. other: different outcomes
2. Need for preoperative imatinib? Treat to maximal response
   - Additional organs involved?
   - Bad location?
   - Approach?

What do Surgeon's think about when evaluating a patient with GIST?

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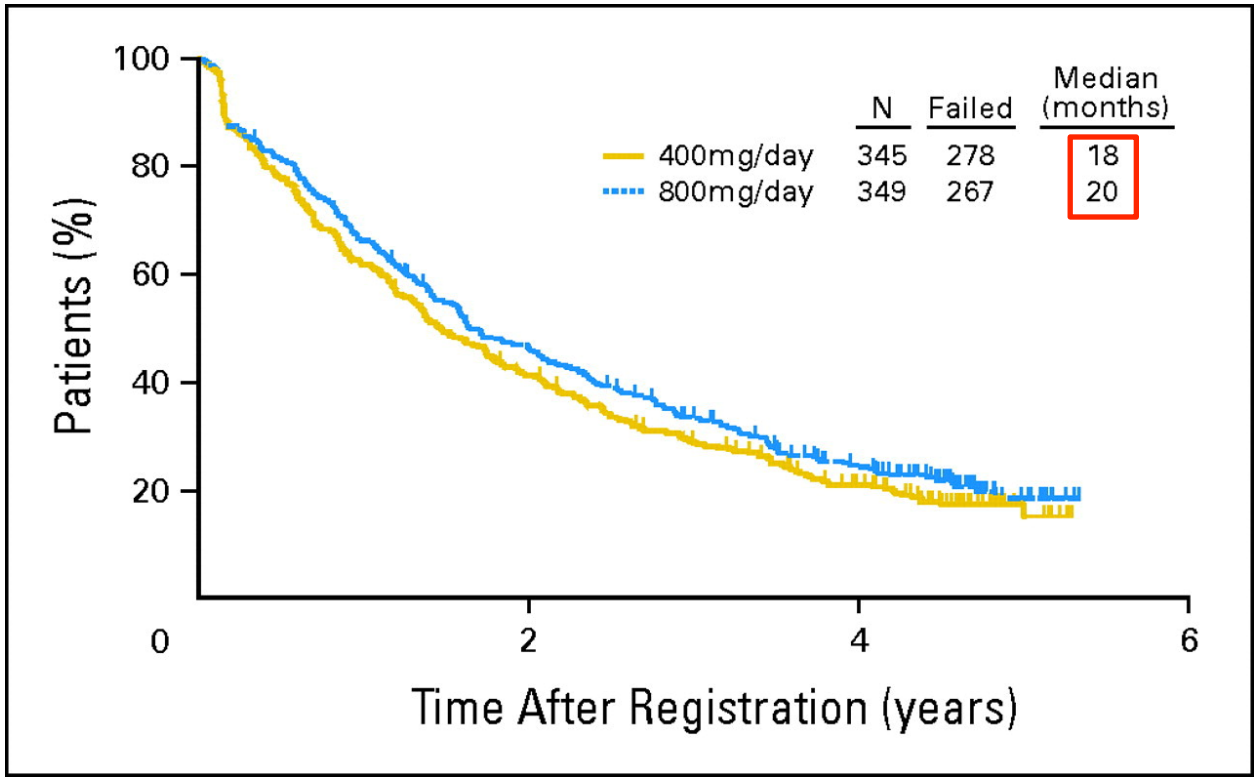
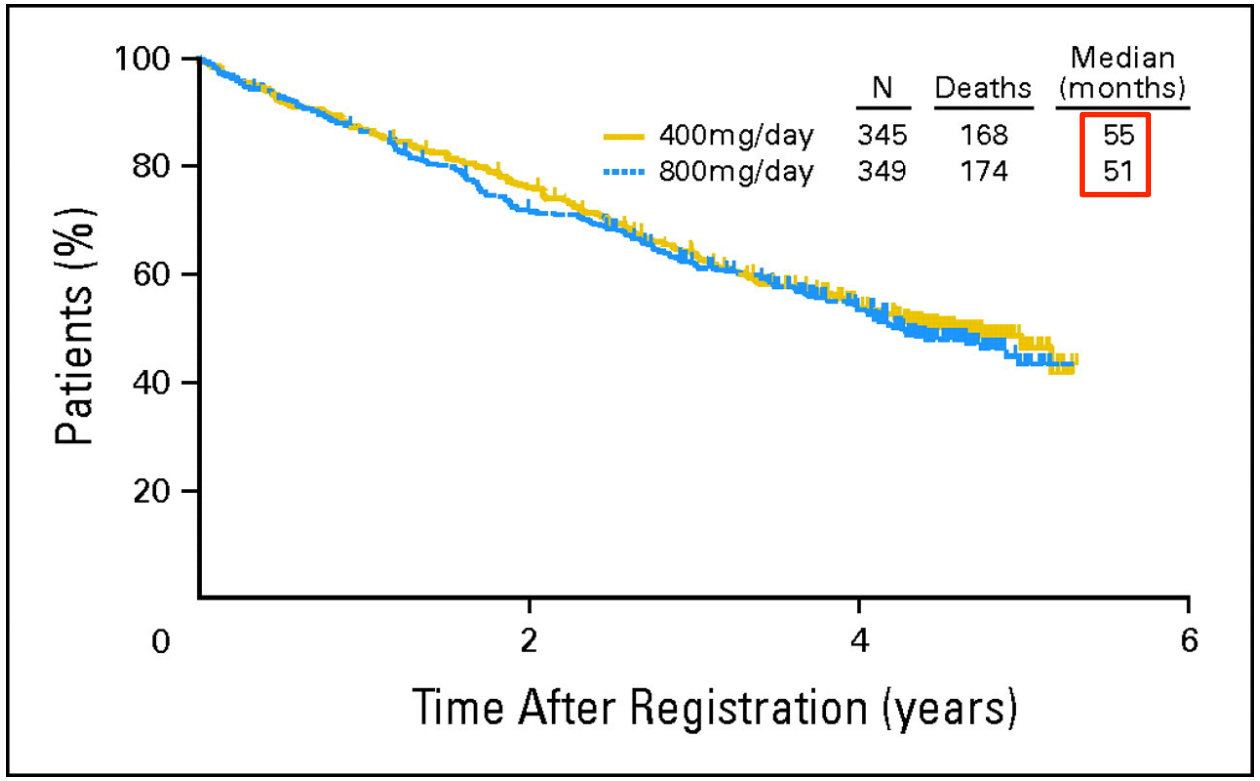
4. Bad Biology? 
5. Approach?
   - Role for laparoscopy
   - ? Role for Observation

Treatment of Metastatic GIST: Evolution over time

Progression-free Survival

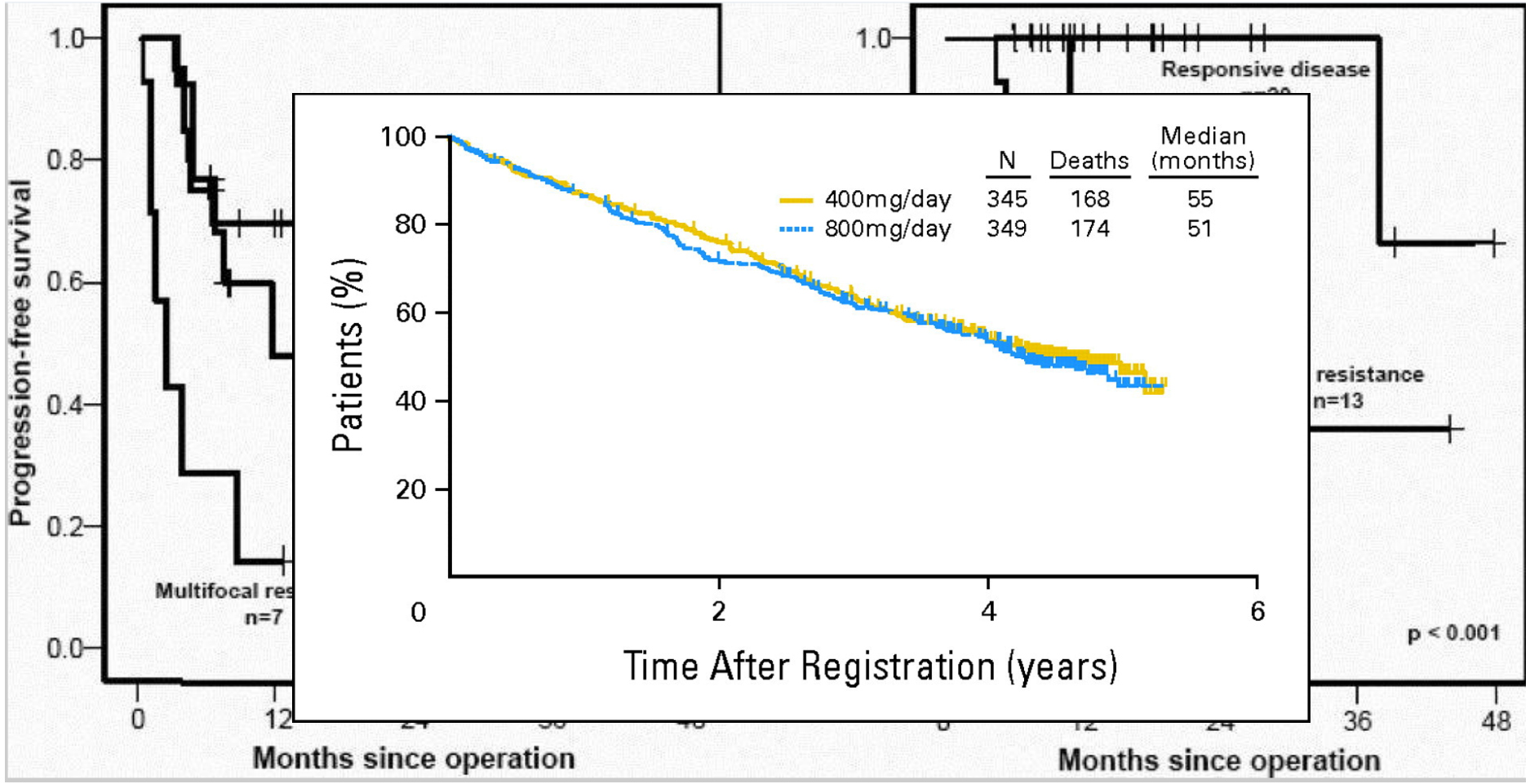


Overall Survival



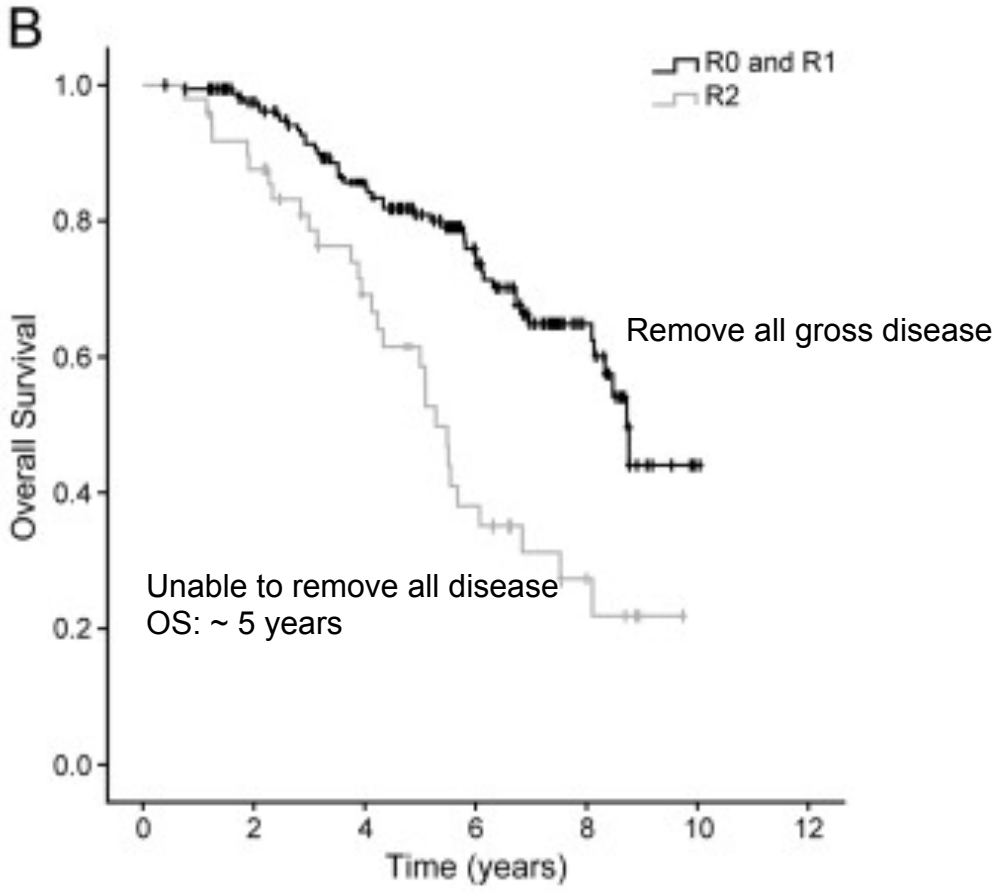
Blanke et al, *JCO* 2008

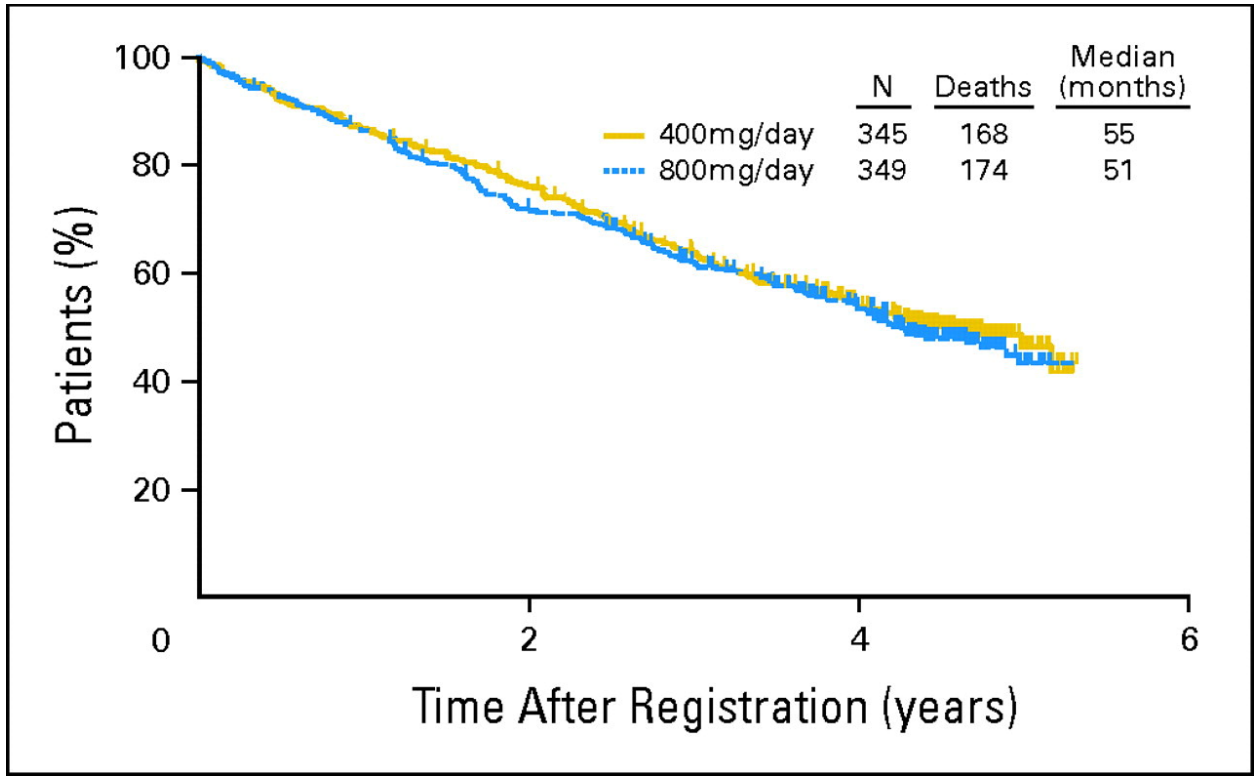
Surgery for Metastatic GIST: Who is Benefitting?



Dematteo et al, *Ann Surg* 2007

Surgery for Metastatic GIST: Who is Benefitting?





Bauer et al, *Eur J Surg Onc* 2014

Identification of preoperative factors associated with improved prognosis in patients with metastatic GIST

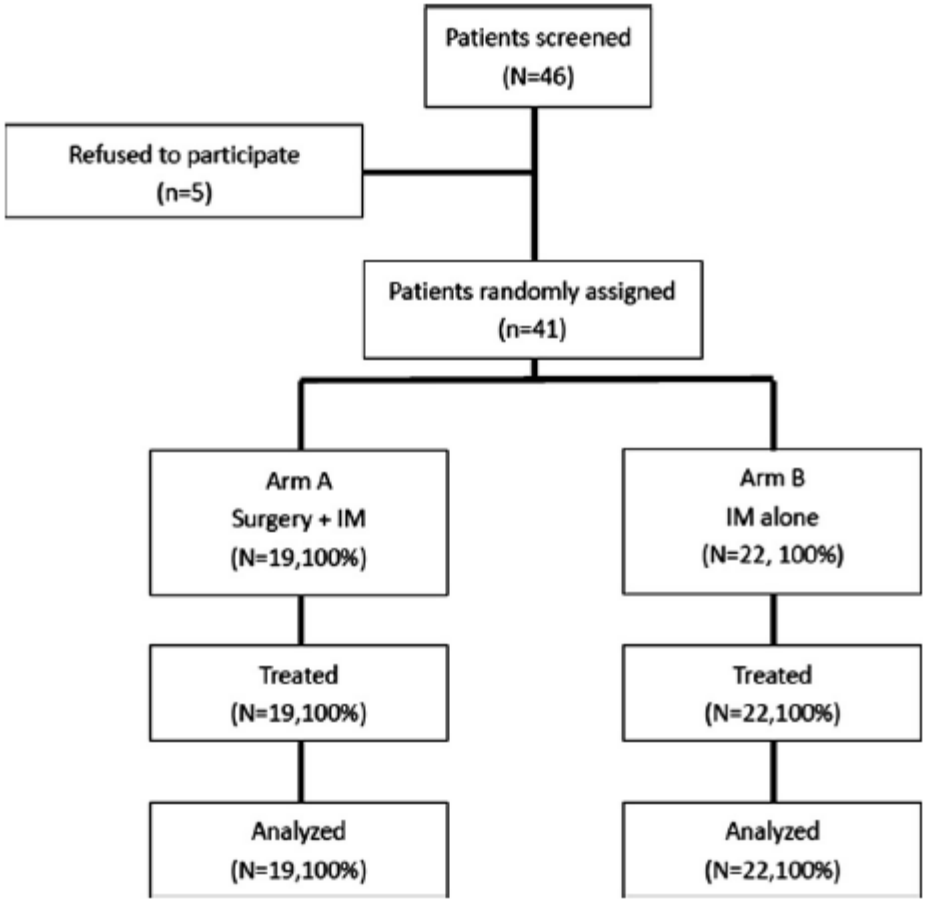
- 87 patients
  - Complete resection of metastatic/ recurrent GIST
  - Treated with TKI preoperatively

	Time to Recurrence	GIST-Specific Survival
No Progression	62 months	Not reached
Progression	8 months	35 months
Unifocal Disease	41 months	106 months
Multifocal Disease	15 months	51 months

Roland et al, *Eur J Surg Onc 2018*

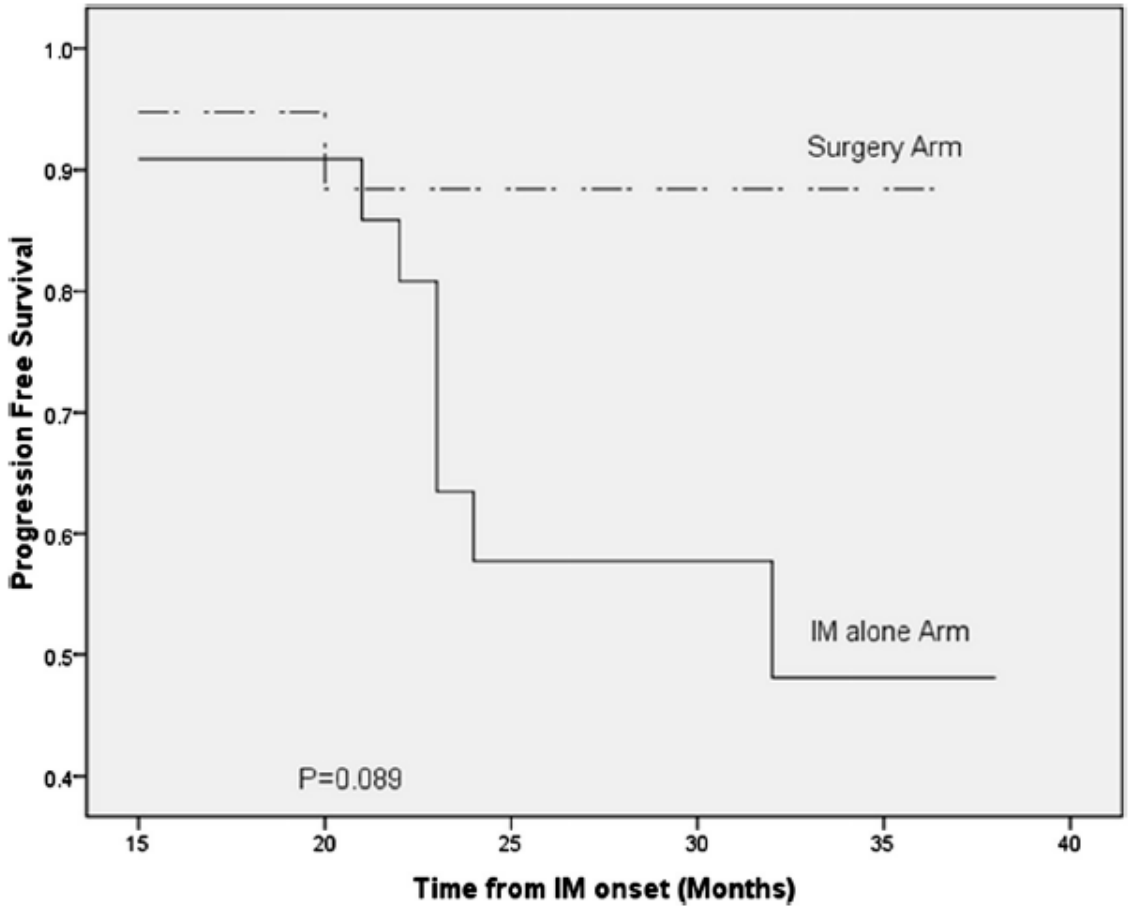
Clinical trial of surgery vs. no surgery for metastatic GIST: failure to enroll

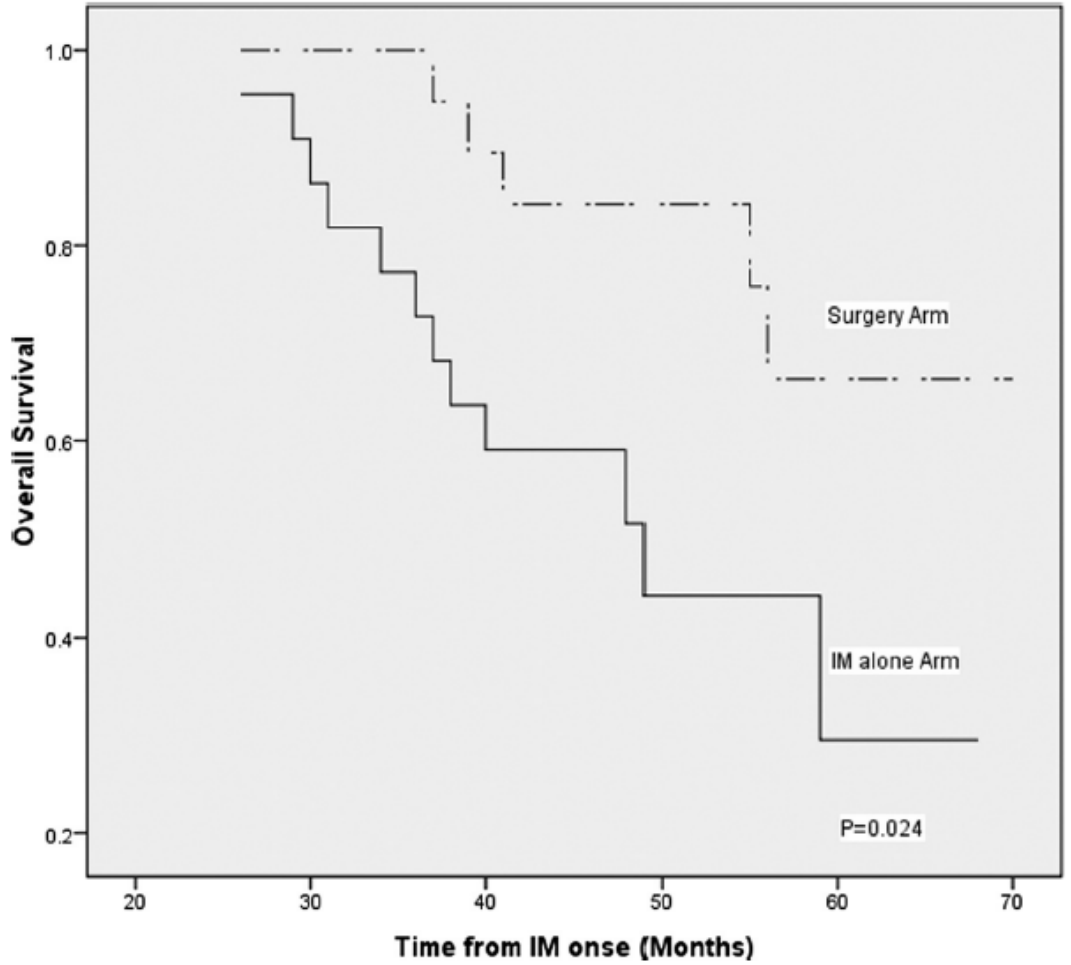
- Randomized trial in China
- Planned to enroll 210 patients
  - Recurrent or metastatic GIST
  - No prior imatinib
  - No progression on imatinib
- Stopped at 41 patients
- Primary Endpoint: Progression-free survival



Du et al, *Eu J Cancer* 2014

Clinical trial of surgery vs. no surgery for metastatic GIST: negative b/c low numbers





Du et al, *Eu J Cancer* 2014

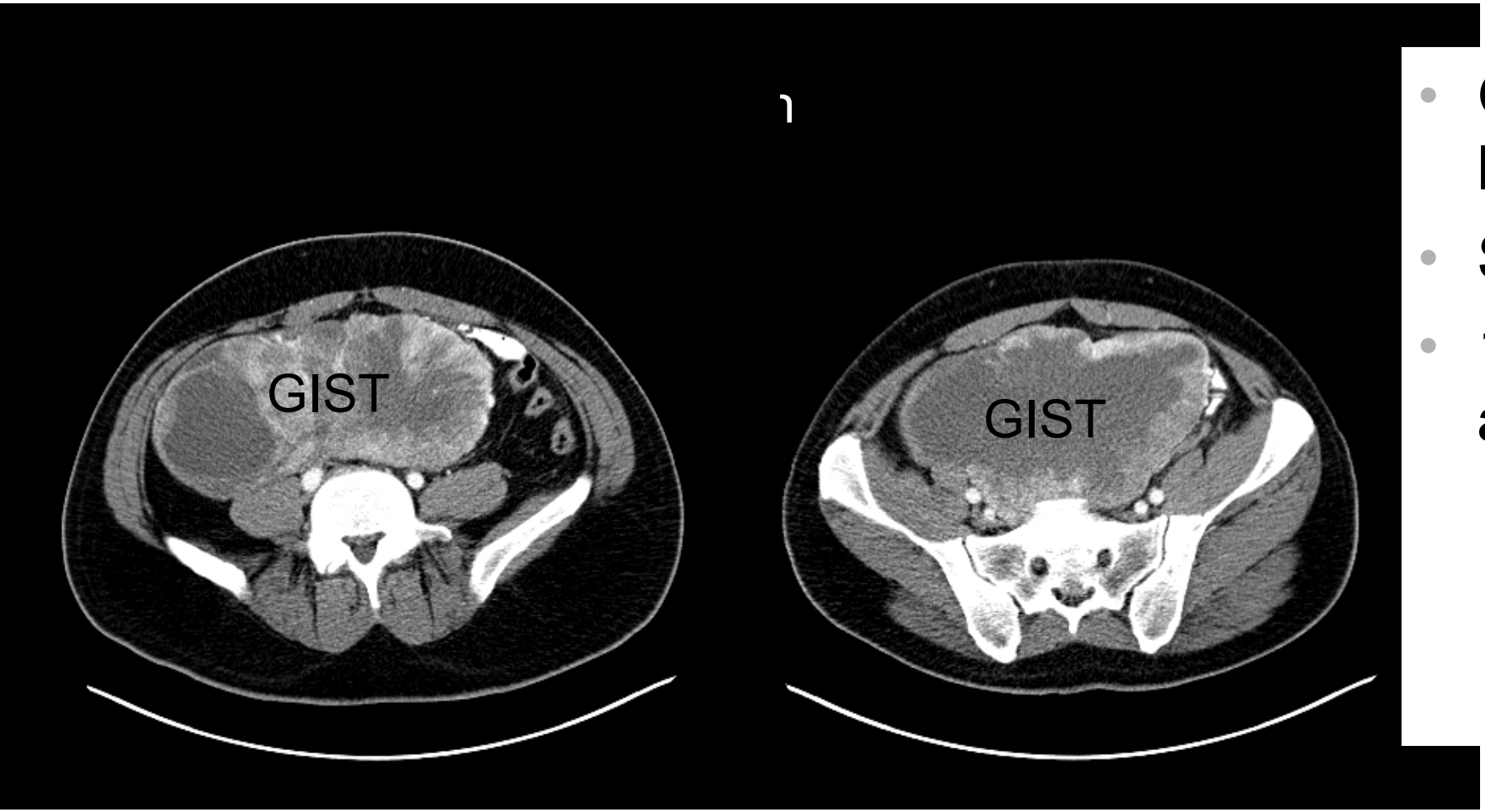
Surgery for Metastatic GIST: Who is Benefitting?

- **Patient selection is key**

How long can we wait to get to this point?

progressing

39yo M Diagnosed with metastatic small bowel GIST



- Gleevec→response but side effects
- Sunitinib→progressed
- 1 year after diagnosis- attempted resection
  - Unresectable, drained

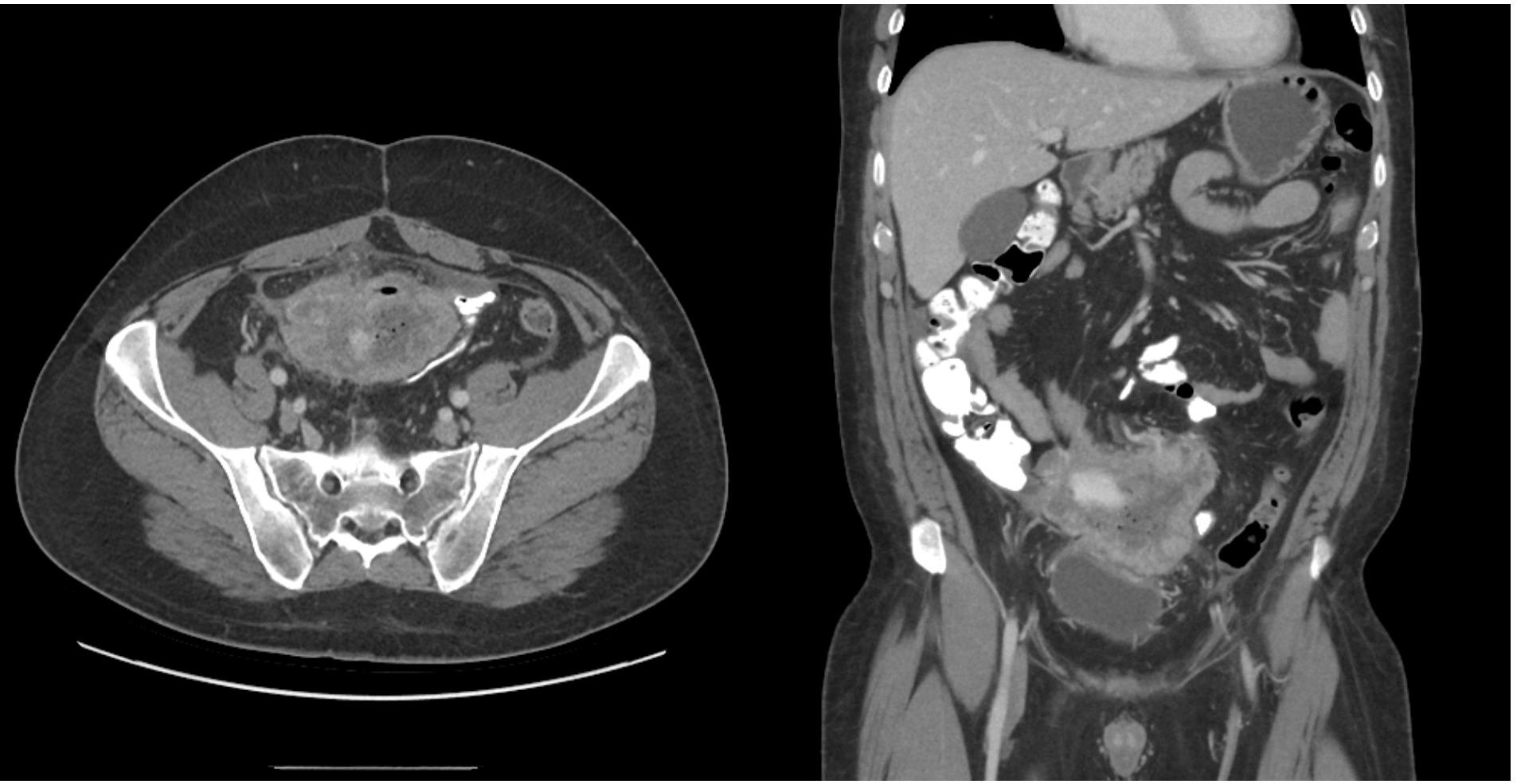
39yo M Diagnosed with metastatic small bowel GIST

- 2 years after diagnosis
- Continue gleevec

39yo M Diagnosed with metastatic small bowel GIST

- 3 years after diagnosis
- Continue gleevec
- Drain removed

39yo M Diagnosed with metastatic small bowel GIST



- 3.5 years after diagnosis
- Surgery referral
- Small bowel resection, GIST removal
- Gleevec indefnintely

Conclusions-Localized GIST

- Wide clinical spectrum based on:
  - Tumor Size
  - Location
  - Mitotic activity
- High risk GISTs require multidisciplinary management
- Preoperative therapy for:
  - Additional organs involved
  - Bad location
  - Approach

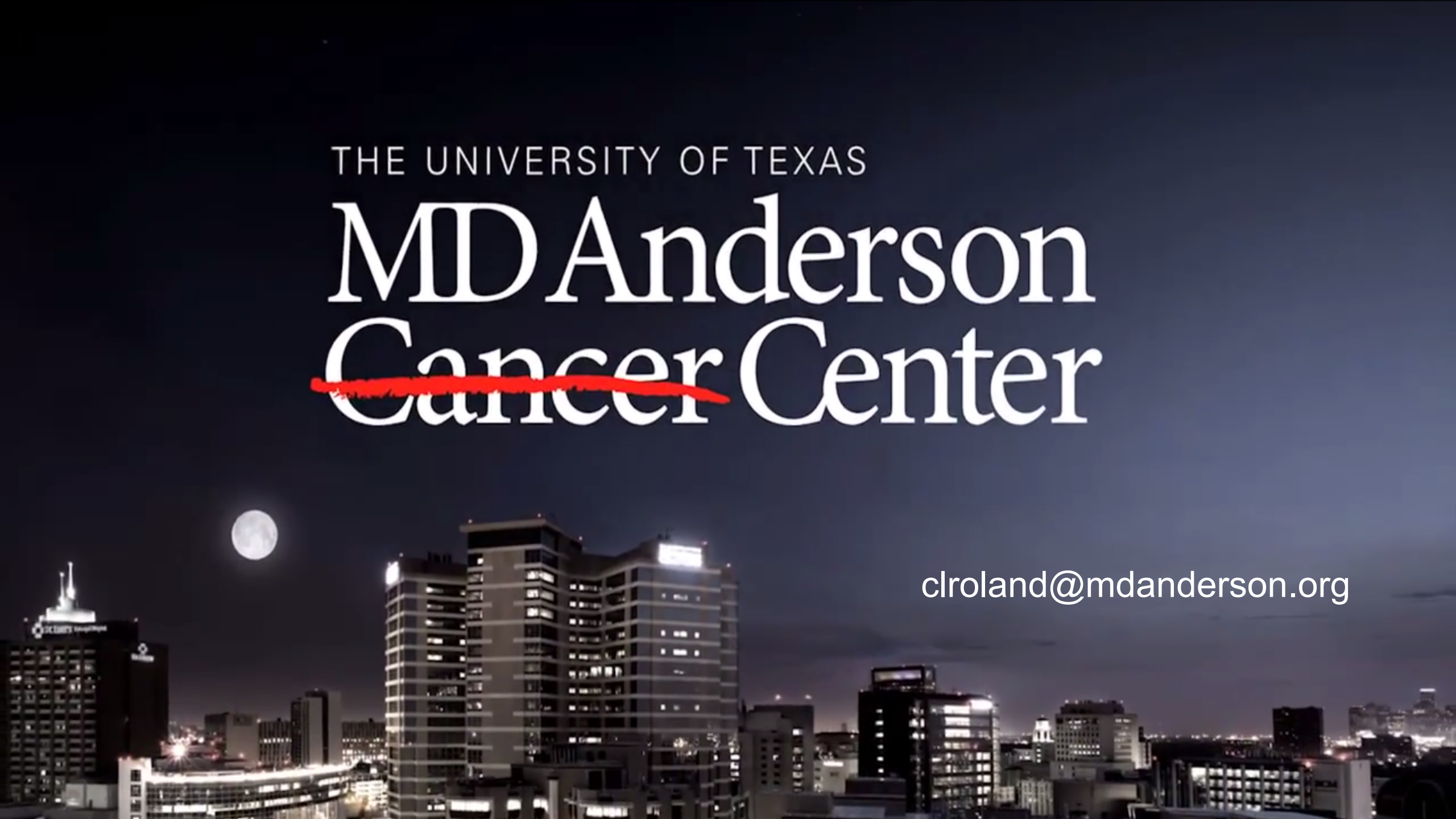
Conclusions-Metastatic Disease

- No standard management of recurrent/metastatic GIST
  - Almost always involves initiation of TKI

- Surgery may benefit highly selected patients
  - Response to imatinib
  - Location and number of tumors
  - Long disease-free interval
  - Ability to remove all tumors

Unanswered Questions

- Optimal Duration of imatinib
  - Preoperatively and after surgery
- Ability to measure response
- Better prognostic systems
  - Mutation status



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