The Surgeon's Role in Contemporary GIST Surgery How much is enough?

Danny Yakoub MD PhD

On behalf of

Dr Alan Livingstone MD FACS

Division of Surgical Oncology

University of Miami-Miller School of Medicine

Jackson Memorial Hospital

Sylvester Comprehensive Cancer Center

DISTRIBUTION OF GIST AND OTHER GI MESENCHYMAL NEOPLASMS

- Stomach 44%
- Small Intestine 32%
- Rectum 10%
- Large intestine 5%
- Other* 9%

* intraabdominal , mesentery , omentum , esophagus , diaphragm

PRESENTATION

- Nonspecific
- 50% bleeding
- SB obstruction
- Rare perforation
- 30-50% present ‘urgently’

GIST: PROGNOSTIC FACTORS
MOST IMPORTANT

- size greater than 5.0 cm
- > five mitoses per 50 HPFs
- Necrosis
- Metastases
- Distal location
- High proliferation index: Ki-67 >10%

GIST: NIH RISK ASSESSMENT

	Size,mm	*Mitotic Index 50 HPF*
Very Low risk	<20	<5
Low risk	20-50	<=5
Intermediate Risk	<=50	6-10
	50-100	<=5
High Risk	>50	>5
	>100	Any
	Any	>10

HISTORICAL PERSPECTIVE

- Before 2000, surgery only effective therapy for 1^0 or 2^0 disease
- Even today, no cure without surgery
- Radiation, chemotherapy, IORT, HIPEC ineffective

GIST – PRE IMATINIB –SURGERY ± CHEMO

Author (Institution)	Years	Total Patients	Complete Resection	5-year Survival
Bearhs (Mayo)	1950-74	108	52	50
Shiu (MSKCC)	1949-73	38	20	65
Parker (MCV)	1951-84	51	30	63
Pollock (MDACC)	1957-97	191	99	48
DeMatteo (MSKCC)	1982-98	200	80	54

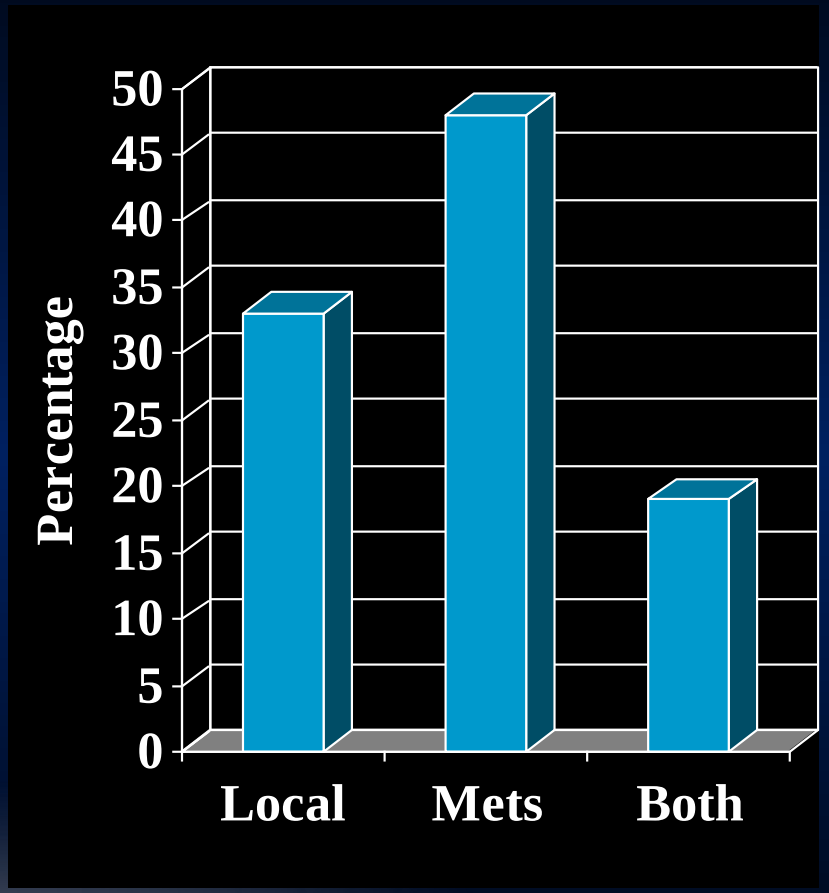
GIST :
SURVIVAL BY PRESENTATION

	Median Survival (months)
Primary	60
Metastatic	19
Locally Recurrent	12
Metastasis Only	22
Primary + mets	23
Local Recurrence + mets	9

DeMatteo Ann Surg 2000

GIST : RECURRENCE AFTER COMPLETE RESECTION

- Recurs in >40% of patients
- Predominant site is intra-abdominal
  - — Liver: 2/3
  - — Local
  - — Peritoneal



EMERGENCY PRESENTATION

- 1/3 of patients have bleeding, obstruction, or perforation
- GIST found unexpectedly
- Must know principles
- Resect if possible
- Do FS before radical surgery to R/O lymphoma or germ cell tumor

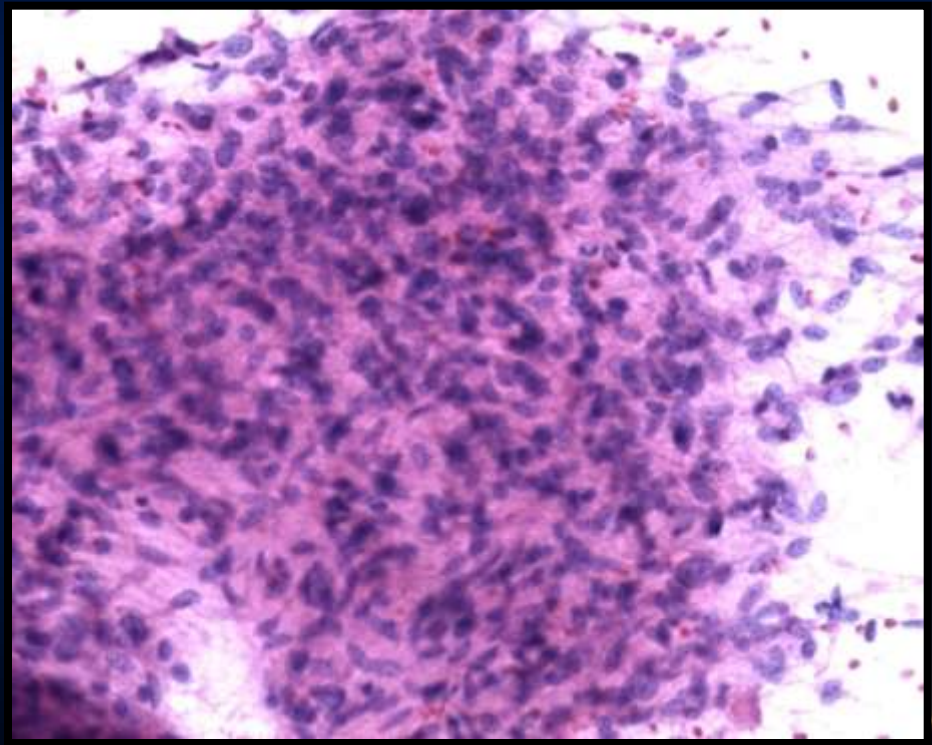
PRINCIPLES IN ERA OF IMATINIB

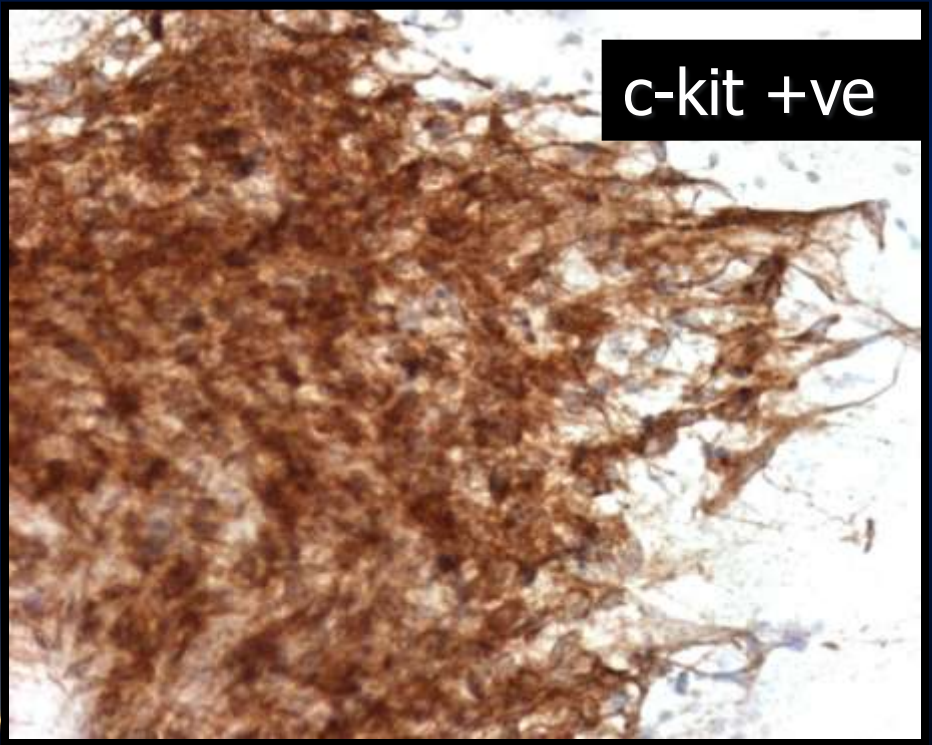
1) Percutaneous biopsy not routinely recommended unless lesion unresectable or change in diagnosis would alter therapy e.g lymphoma or germ cell tumor

- EUS with FNA and IHC helpful

GIST: CYTOLOGY

Increasing FNAC performed endoscopically





PRINCIPLES OF SURGERY IN ERA OF IMATINIB

2) Main Rx for primary resectable GIST is still surgery:

- clear margins but not radical
- en bloc resection of involved organs
- rupturing tumor worsens prognosis
- no routine lymphadenectomy

PRINCIPLES OF SURGERY IN ERA OF IMATINIB

3) Imatinib cannot compensate for inadequate initial surgery:

- get grossly clear margins

- microscopic margins may not impact survival

PRINCIPLES IN ERA OF IMATINIB

4) Locally advanced disease:

- downstage with imatinib (4-6 months)

5) Unsuspected metastases:

- usually poor prognosis

- avoid radical surgery unless can safely get clear margins

PRINCIPLES OF SURGERY IN ERA OF IMATINIB

1. Metastatic primary disease - initially Rx with imatinib

    a. if good global response, consider resection with relapse

    b. if global progression, surgery unhelpful

    c. resect single imatinib-resistant clone

PRINCIPLES OF SURGERY IN ERA OF IMATINIB

7) Recurrent disease (>40% of pts.)

   usually intraabdominal

- prior to imatinib, 1/3 resectable with median survival of 15 months
- resect isolated liver met with long disease free interval
- treat local recurrences initially with imatinib

EVALUATING IMATINIB RESPONSES

- Clinical response
- CT can be misleading - no shrinkage
- PET scan - decreased FDG uptake, and often rapid response

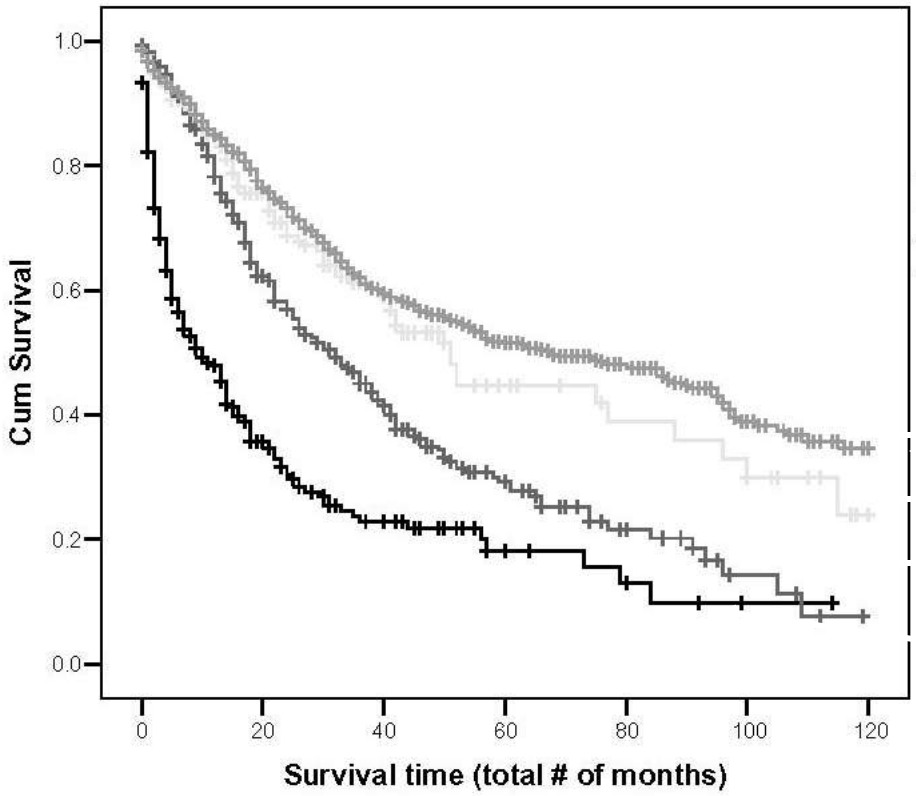
WHAT RESULTS CAN BE ANTICIPATED APPLYING THESE PRINCIPLES?

SEER data

BENEFITS OF SURGERY

- Surgery: curative or palliative intent
- DFS only with surgical resection
- Palliative resection can extend survival
- Optimal extent of surgical resection?

BENEFITS OF SURGICAL RESECTION



Total

None

Table 1

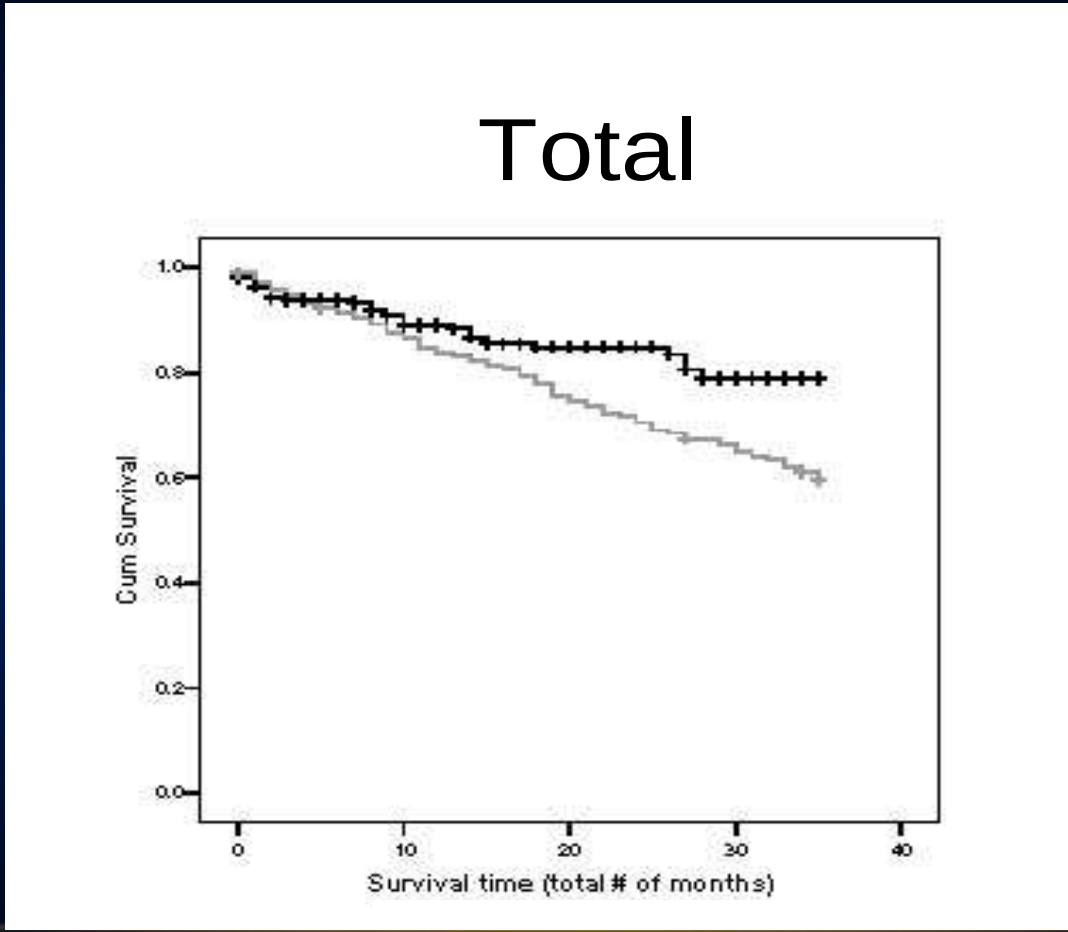
	Median survival (months)	n	5 year survival (%)	No resection	Partial resection	Total resection	Radical resection
No resection	10	317	18.2		p>0.000	p>0.000	p>0.000
Partial resection	51	258	44.7	p>0.000		p=0.218	p>0.000
Total resection	68	919	51.6	p>0.000	p=0.218		p>0.000
Radical resection	32	349	29.3	p>0.000	p=0.010	p>0.000	

Perez et al.

EFFECTS OF IMATINIB ON SURVIVAL

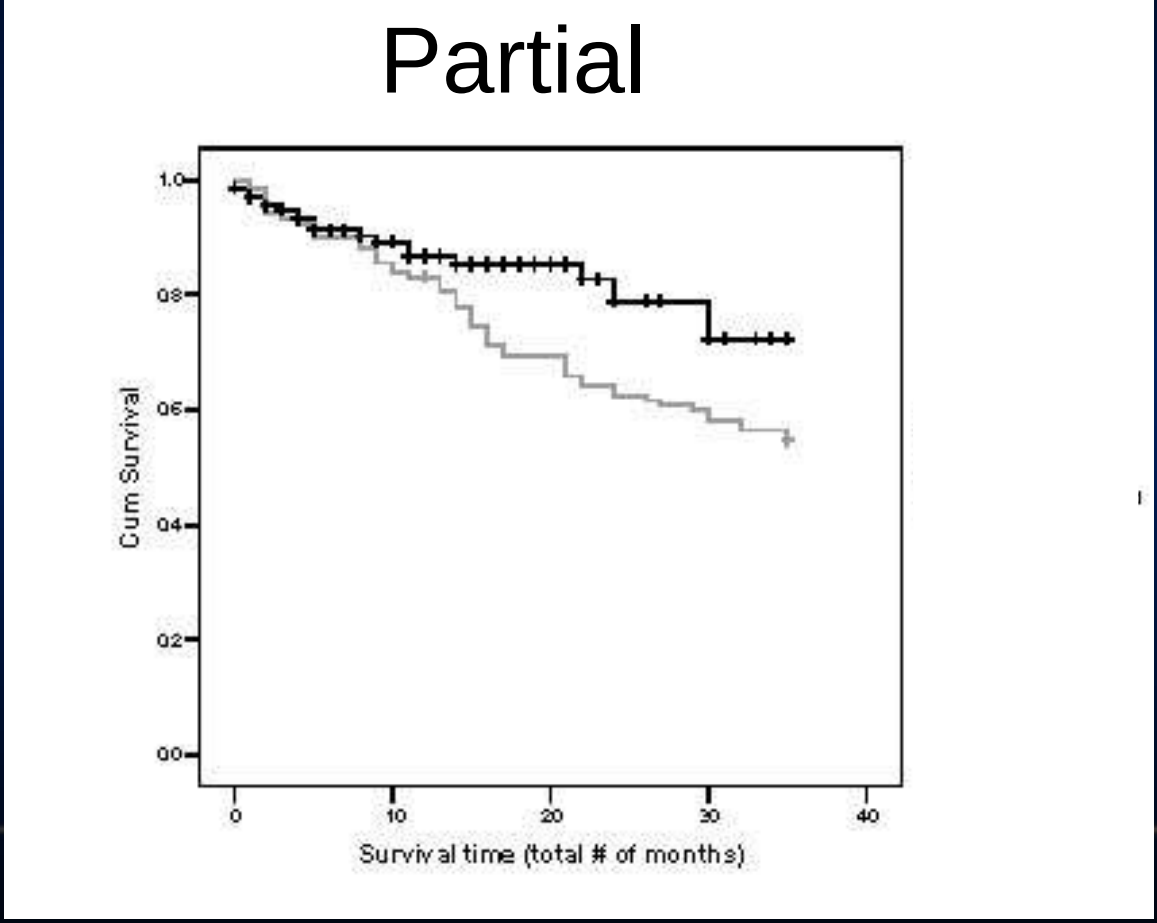
- FDA approval of Imatinib in 2000
- Improved survival in advanced and metastatic GIST
- Initially unclear how to integrate surgery with imatinib
- Clues from SEER data and trials

IMPROVING OUTCOMES OF PATIENTS FOLLOWING SURGICAL RESECTION: THE IMPACT OF IMATINIB



Perez et al

IMPROVING OUTCOMES OF PATIENTS FOLLOWING SURGICAL RESECTION: THE IMPACT OF IMATINIB



Perez et al

WHO SHOULD RECEIVE IMATINIB?

ACOSOG Z9001: PHASE III TRIAL

- All R0, >3cm, and c kit positive
- Adjuvant Gleevec for 1 year
- Median follow-up 19.7 months
- Recurrence free survival (RFS)- 98 vs 83%
- RFS ↑ regardless of size (esp high risk)

DeMatteo, Lancet 2009

WHO SHOULD RECEIVE IMATINIB?

ACOSOG Z9001: PHASE III TRIAL

- See recurrences 6 months after stopping
- Continue imatinib indefinitely if high risk?
- OS similar due to short follow up and crossover design
- Need longer follow up to show if adjuvant Rx increases cure rate

DeMatteo, Lancet 2009

ONE VS 3 YRS ADJUVANT IMATINIB?

HIGH RISK GISTS (SCANDINAVIA)

RFS at 5 years: 66% vs 48% (HR 0.46)

- OS at 5 years: 92% vs 82% (HR 0.45)
- Benefit in exon 11 > exon 9?
- Is longer treatment justified?

Joensuu JAMA 2012

IMATINIB- HOW LONG?

FRENCH SARCOMA GROUP

- Advanced GIST with 1 year of tumor control
- Continuous Rx arm-26 patients with 31% progression
- Interrupted arm- 32 pts 81% progression at median 6 mths even if had no detectable tumor

JCO 2007

IMATINIB- HOW LONG?

FRENCH SARCOMA GROUP

- 92% again responded to imatinib
- Drug holiday not recommended

JCO 2007

IMATINIB- HOW LONG?

FRENCH SARCOMA GROUP (2)

- Advanced GIST with 5 years of tumor control
- Continuous Rx arm-no progression
- Interrupted arm- 45% progression at 1 yr
- Imatinib does not cure advanced GISTs

Lancet Onc 2010

BENEFIT OF SURGERY(DEBULKING) AFTER IMATINIB FOR ADVANCED DISEASE- F/UP 12 MTHS

- If stable disease: NED 78%,OS 95%
- Limited progression: NED 25%,OS 88%
- General progression: NED 7%,OS 0%

Raut C, JCO 2006

BENEFIT OF SURGERY AFTER IMATINIB FOR ADVANCED DISEASE (134 PTS KOREA)

- If stable disease: resect residual disease
- Time to progression with resection 88 months vs. 43 months with imatinib alone
- Surgery decreased risk of progression by 3X and risk of death by 5X

Park, ASCO 2013

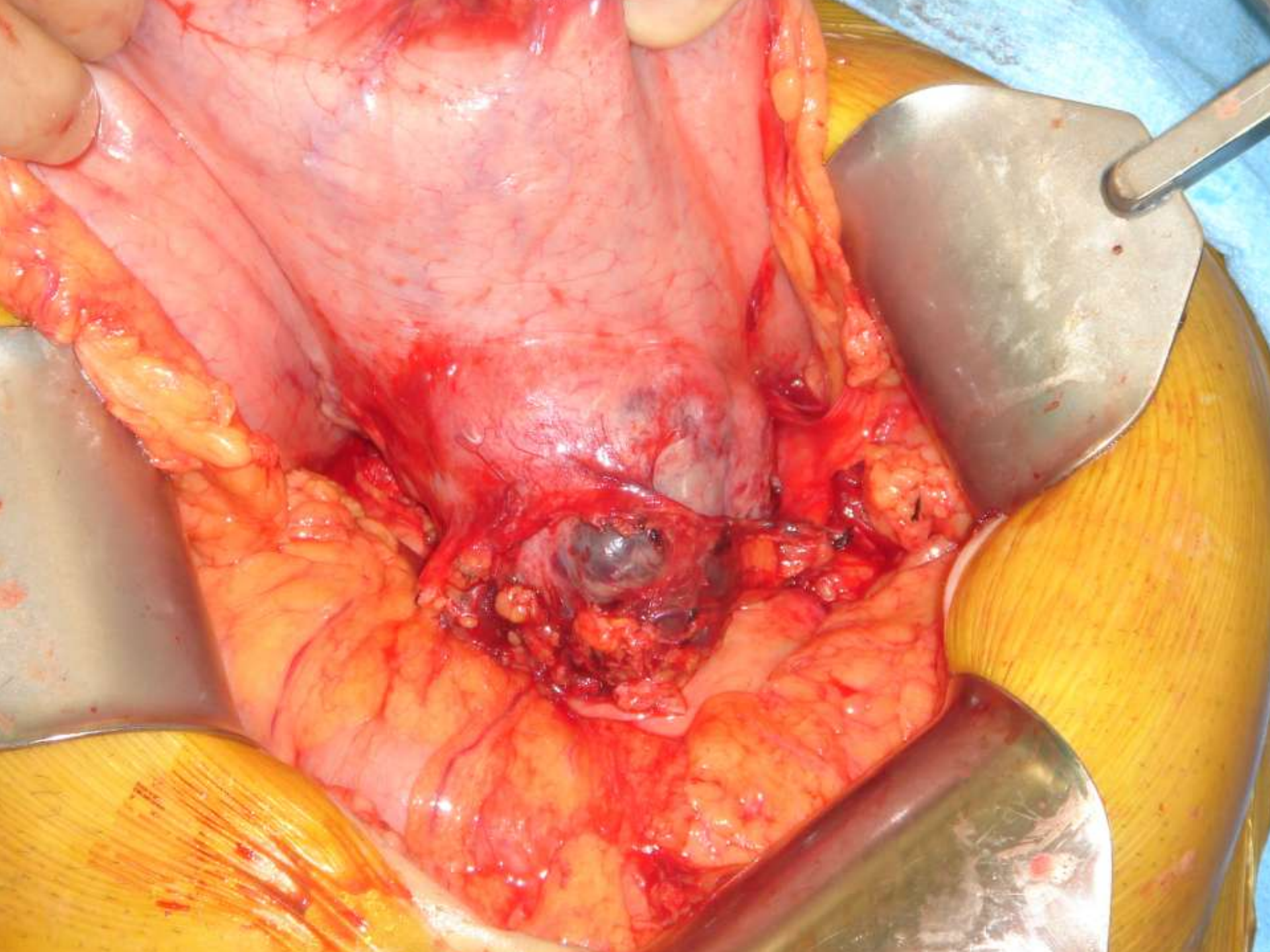
COST EFFECTIVENESS 3 YEARS ADJUVANT IMATINIB (USA COST) QUALITY ADJUSTED LIFE YEARS

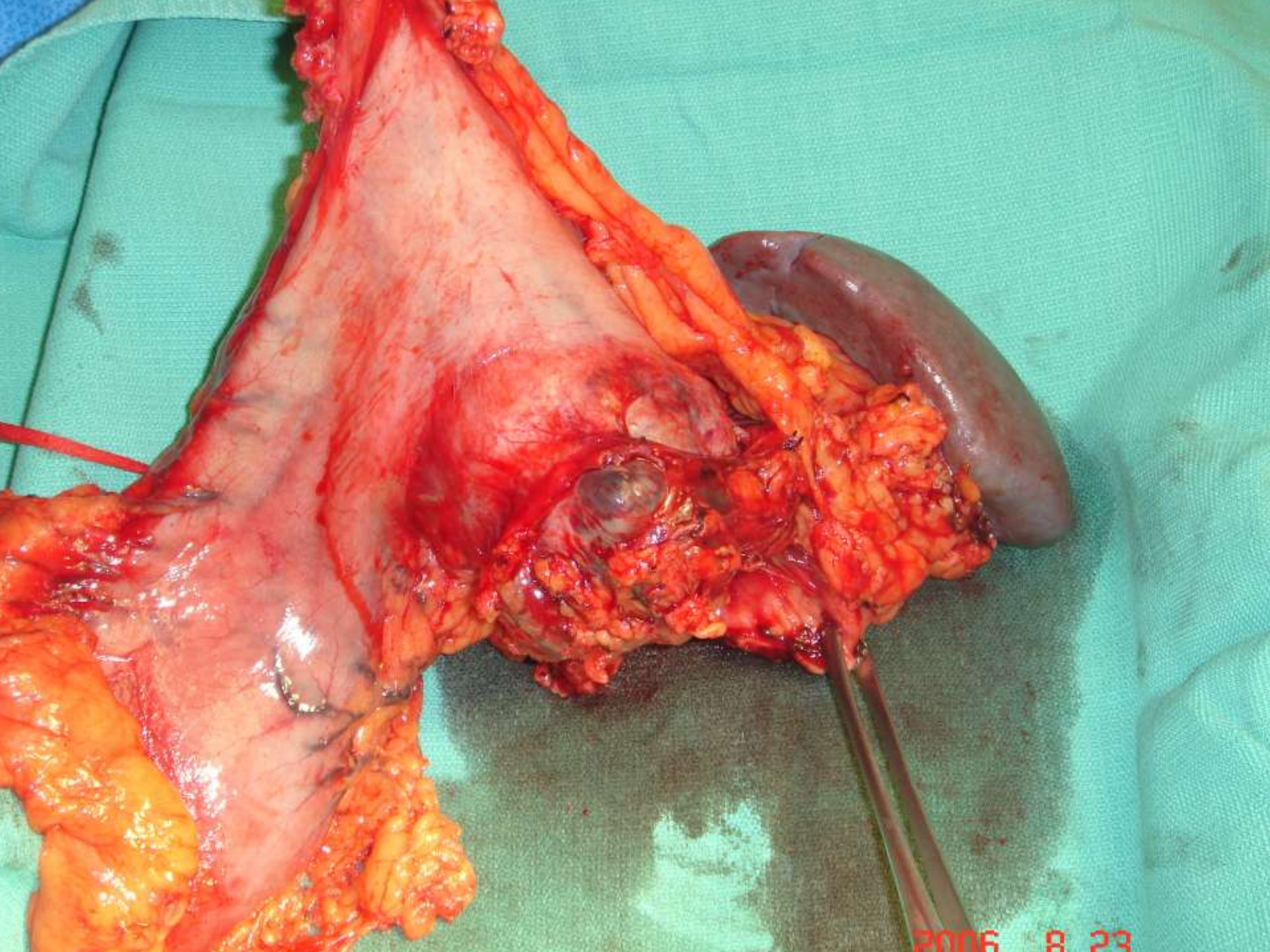
- QALYs 8.53 vs 7.18
- Cost $302K vs $217K
- Cost $62K/QALY

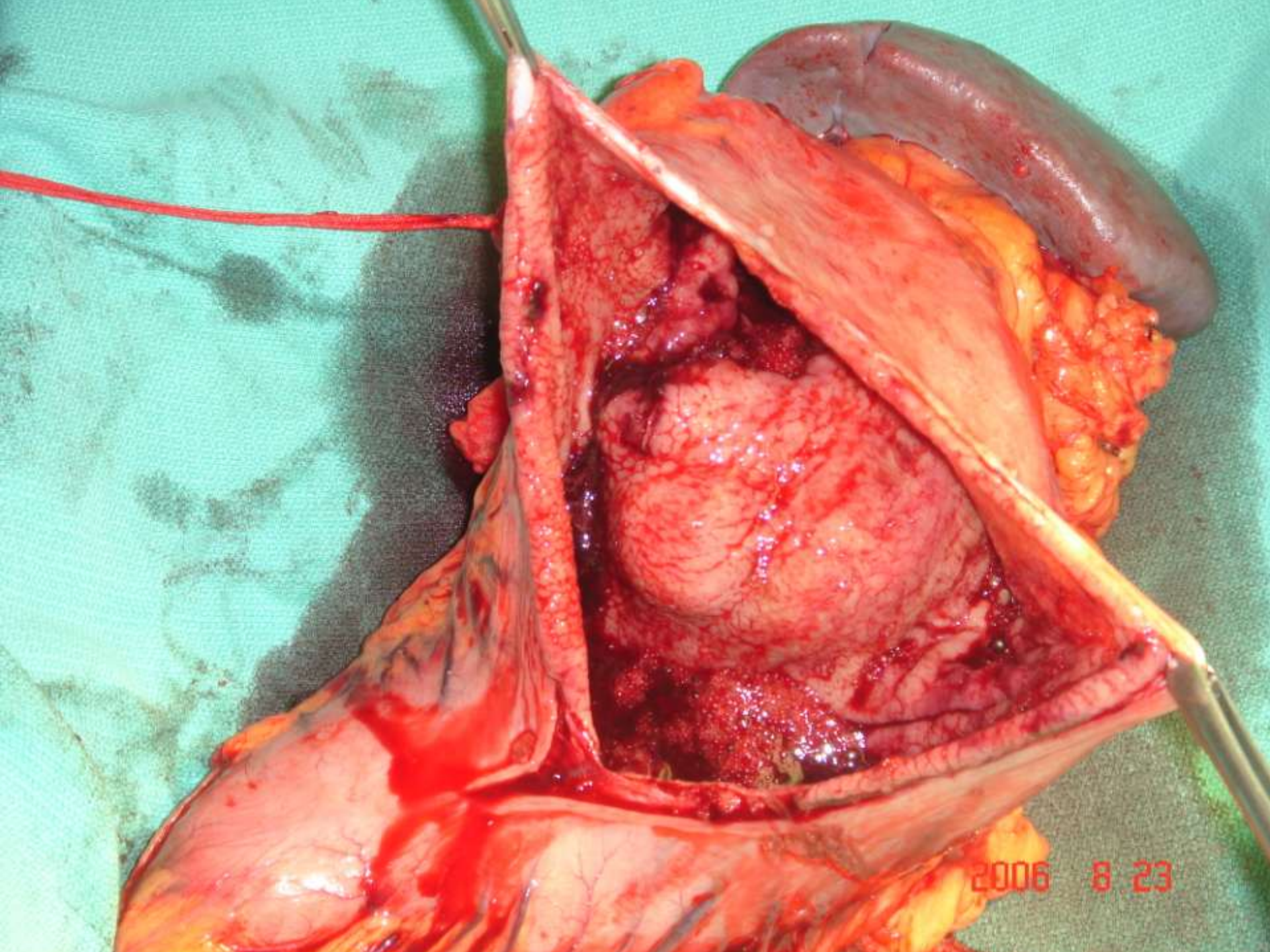
Sanon J Med Econ 2013

INTERESTING CASES?

DYSPEPSIA AND ABDOMINAL DISCOMFORT




2006 8 23


2006 8 23

ACUTE ABDOMINAL PAIN


kV 120
mA 240
TI 0.75
GT 0.0
SL 8.0/10.0
354 -1/57
AB50 LO IV OPTIRAY & PO GASTROVIEW W 370
1215313 ABDOMINAL BLOATING C 80


kV 120
mA 240
TI 0.75
GT 0.0
SL 8.0/10.0
354 -1/57
AB50 LO IV OPTIRAY & PO GASTROVIEW W 370
1215313 ABDOMINAL BLOATING C 80


NAU, ALIX 51/M
CS189749
15-AUG-2004
08:54:21.19
TP -228.5
IMA 66
SPI 3
Coral Springs MC/OP
SOMATOM PLUS 4
VC10C
H-SP-CR
A
R
kV 120
mA 240
TI 0.75
GT 0.0
SL 8.0/10.0
354 -1/57
AB50 LO IV OPTIRAY & PO GASTROVIEW W 370
1215613 ABDOMINAL BLOATING C 80


NAU, ALIX 51/M
CS189749
15-AUG-2004
08:54:21.79
TP -236.5
IMA 67
SPI 3
A
R
kV 120
mA 240
TI 0.75
GT 0.0
SL 8.0/10.0
354 -1/57
AB50 LO IV OPTIRAY & PO GASTROVIEW W 370
1215313 ABDOMINAL BLOATING C 80

AUG 23 2004


kV 120
mA 240
TI 0.75
GT 0.0
SL 8.0/10.0
360 -13/42
AB50 LO IV OPTIRAY & PO GASTROVIEW
1215613 ABDOMINAL BLOATING
W 370
C 80


kV 120
mA 240
TI 0.75
GT 0.0
SL 8.0/10.0
360 -13/42
AB50 LO IV OPTIRAY & PO GASTROVIEW
1215313 ABDOMINAL BLOATING


NAU, ALIX 51/M
CS189749
A
Coral Springs MC/OP
SOMATOM PLUS 4
VC10C
H-SP-CR
15-AUG-2004
08:54:26.60
TP -300.5
IMA 76
SPI 3
R
10 cm
kV 120
mA 240
TI 0.75
GT 0.0
SL 8.0/10.0
360 -13/42
AB50 LO IV OPTIRAY & PO GASTROVIEW
1215913 ABDOMINAL BLOATING
W 370
C 80


NAU, ALIX 51/M
CS189749
A
15-AUG-2004
08:54:27.20
TP -308.5
IMA 77
SPI 3
R
kV 120
mA 240
TI 0.75
GT 0.0
SL 8.0/10.0
360 -13/42
AB50 LO IV OPTIRAY & PO GASTROVIEW
1215613 ABDOMINAL BLOATING
W 370
C 80


NAU, ALIX 51/M
CS189749
A
Coral Springs MC/OP
SOMATOM PLUS 4
VC10C
H-SP-CR
15-AUG-2004
08:54:29.01
TP -332.5
IMA 80
SPI 3


NAU, ALIX 51/M
CS189749
A
Coral Springs MC/OP
SOMATOM PLUS 4
VC10C
H-SP-CR
15-AUG-2004
08:54:29.61
TP -340.5
IMA 81
SPI 3
AUG 23 2004


AUG 23 2004


AUG 23 2004


AUG 23 2004


AUG 23 2004


AUG 23 2006

Before

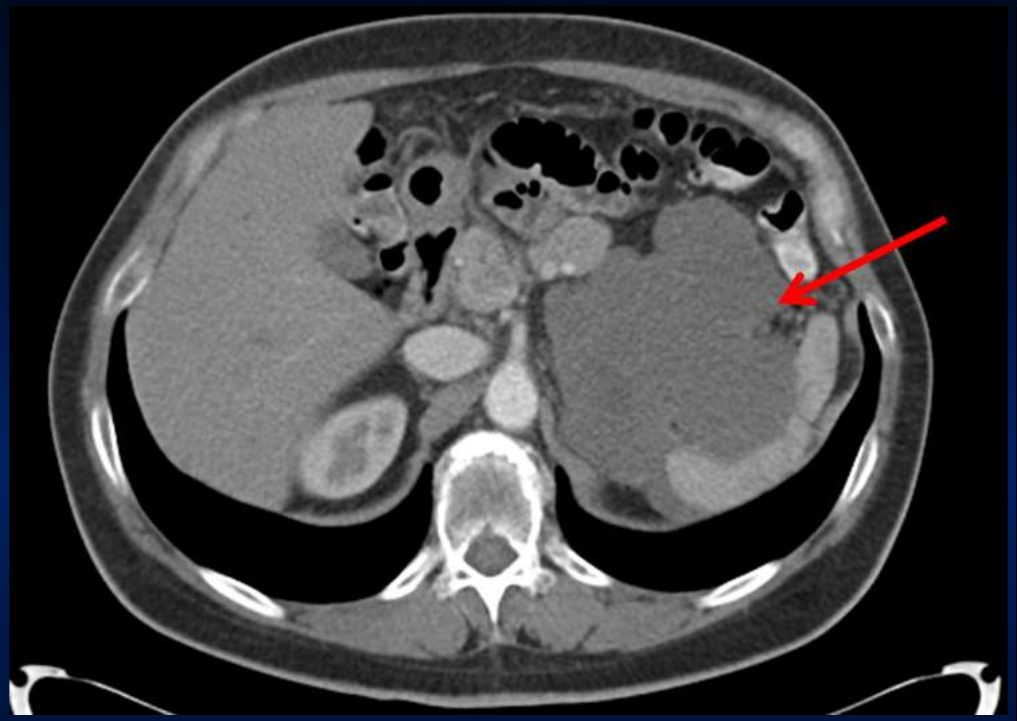
After

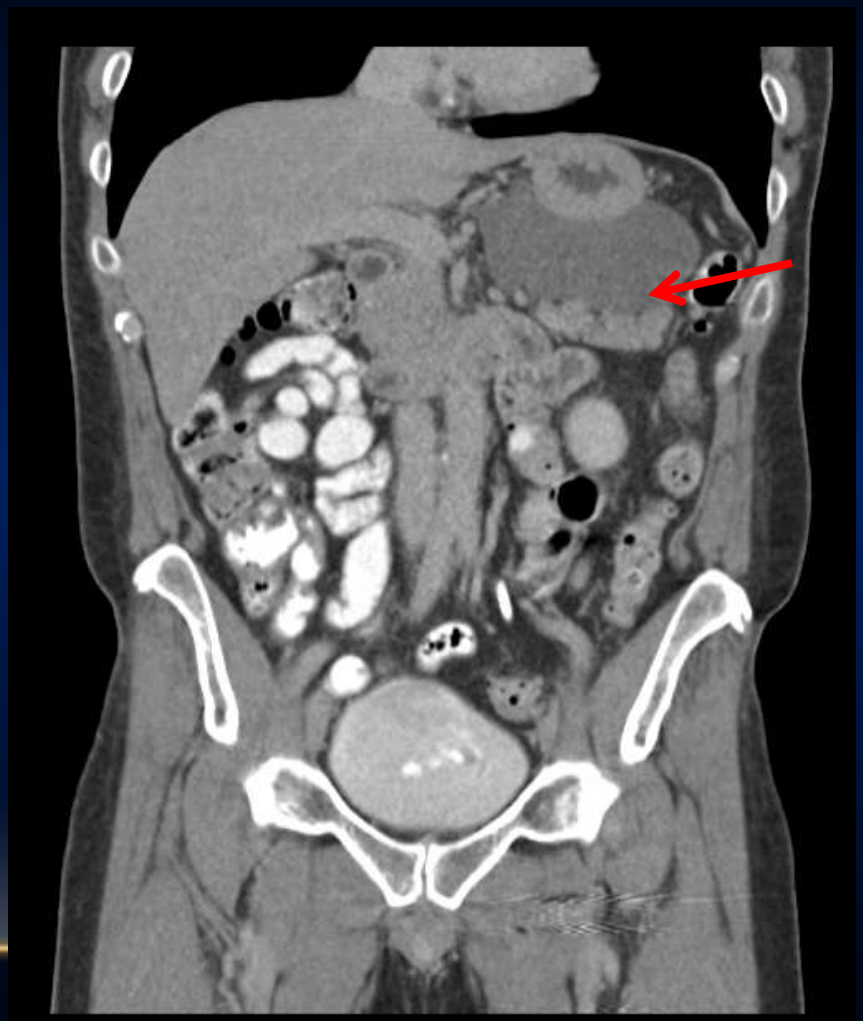
PREVIOUS RESECTION, STABLE DISEASE ON IMATINIB

REPEAT EXPLORATION, R0 RESECTION

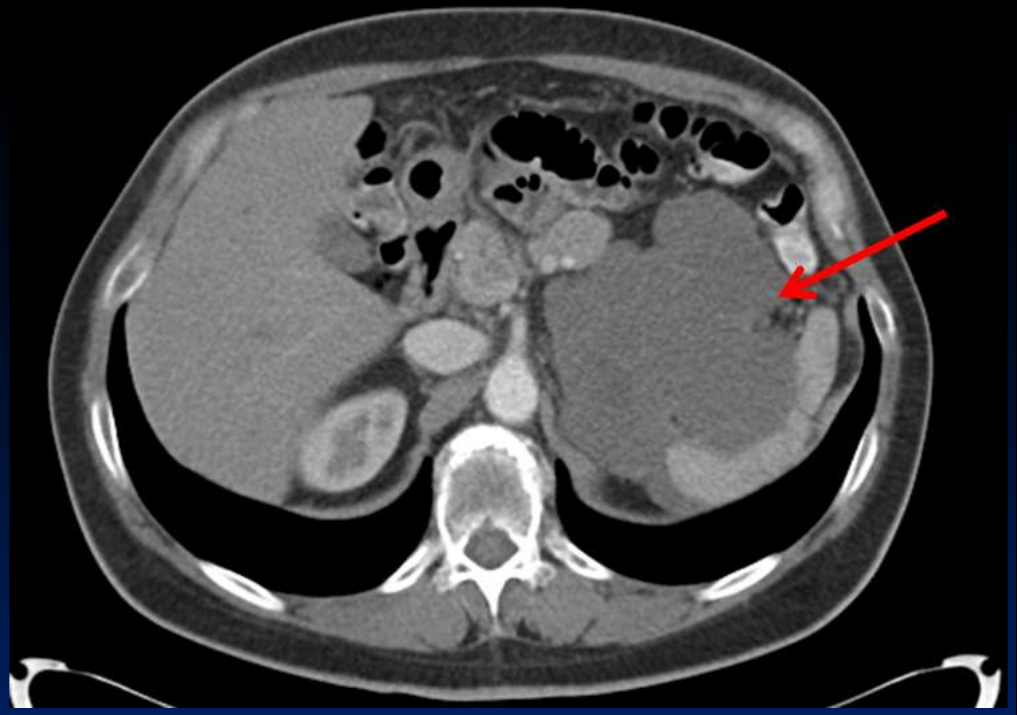
GIST arising from Jejunum and attached to distal sigmoid colon

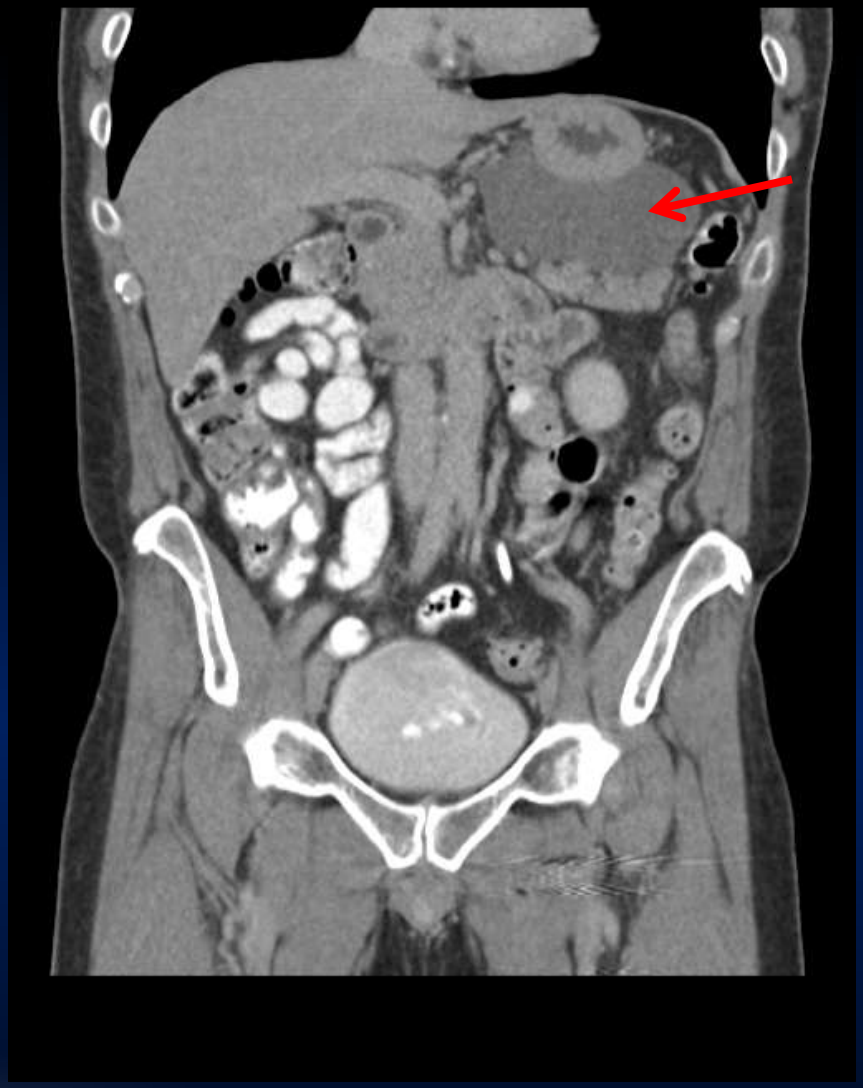
STOMACH, PANCREAS,SPLEEN, ADRENAL, DIAPHRAGM





GIST arising from the back of the stomach-prolonged imatinib



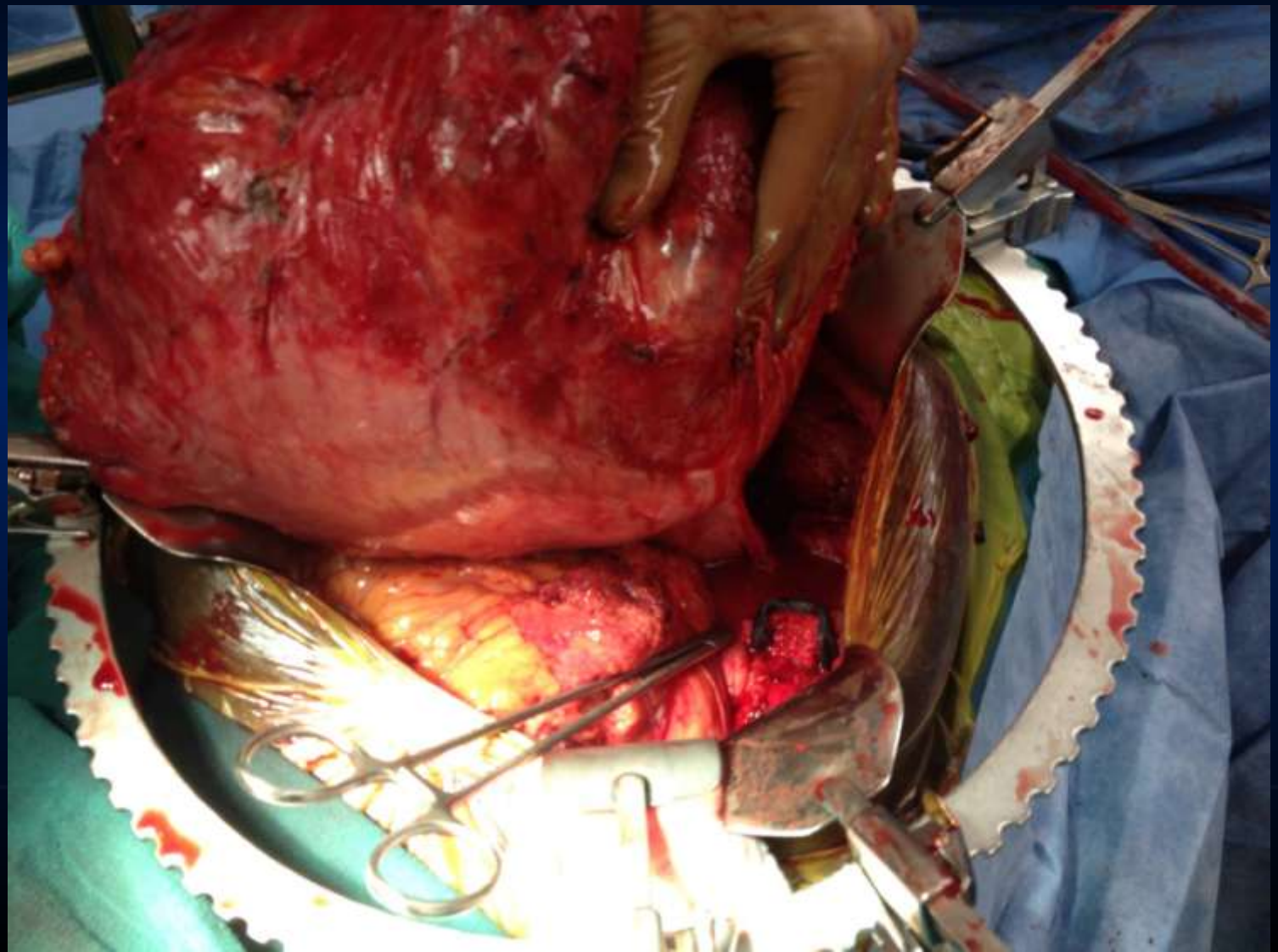


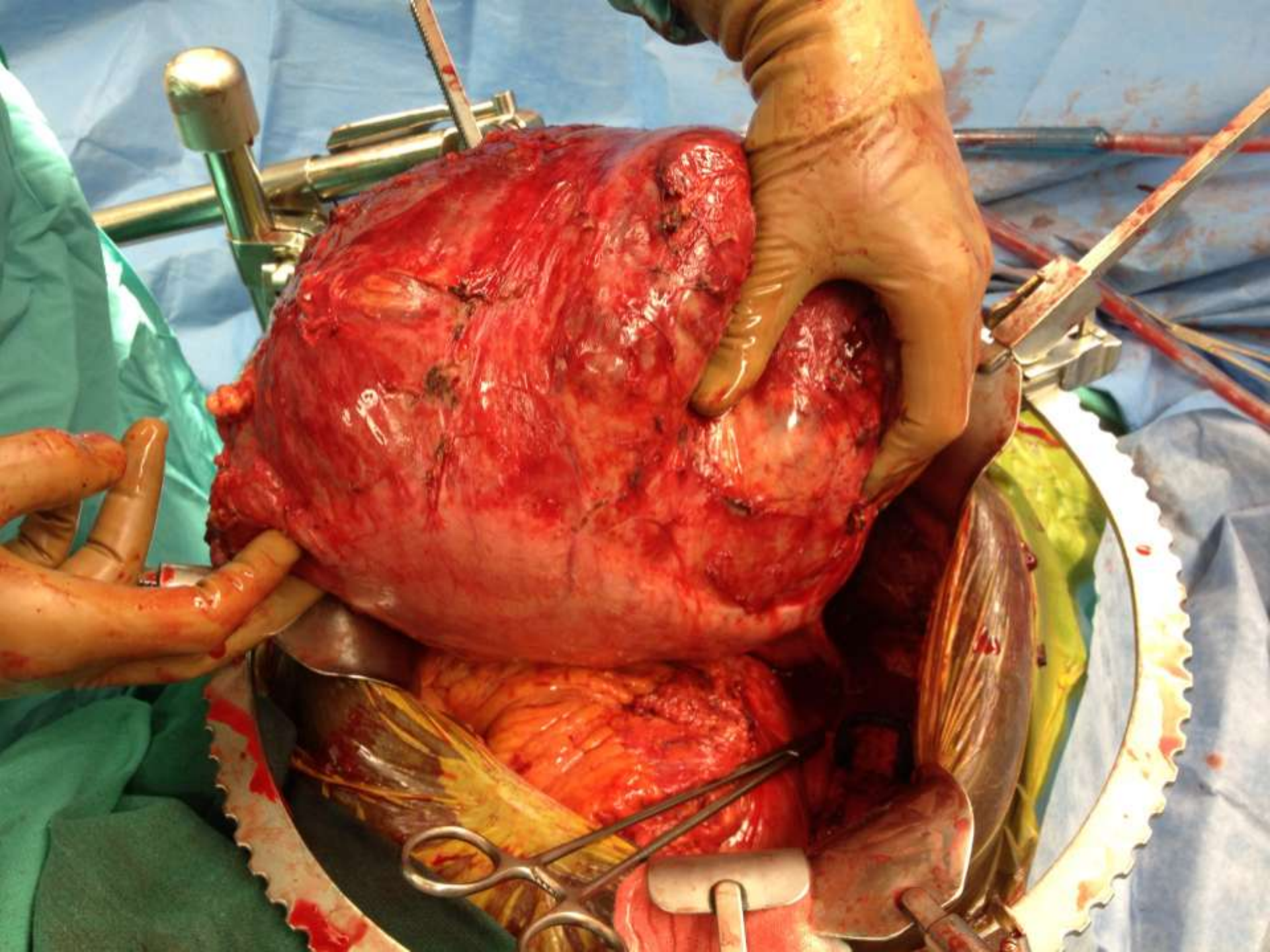
R0 resection-
Partial gastrectomy, distal pancreas, spleen, left adrenal

STOMACH, LIVER, SPLEEN, AND TRANSVERSE COLON

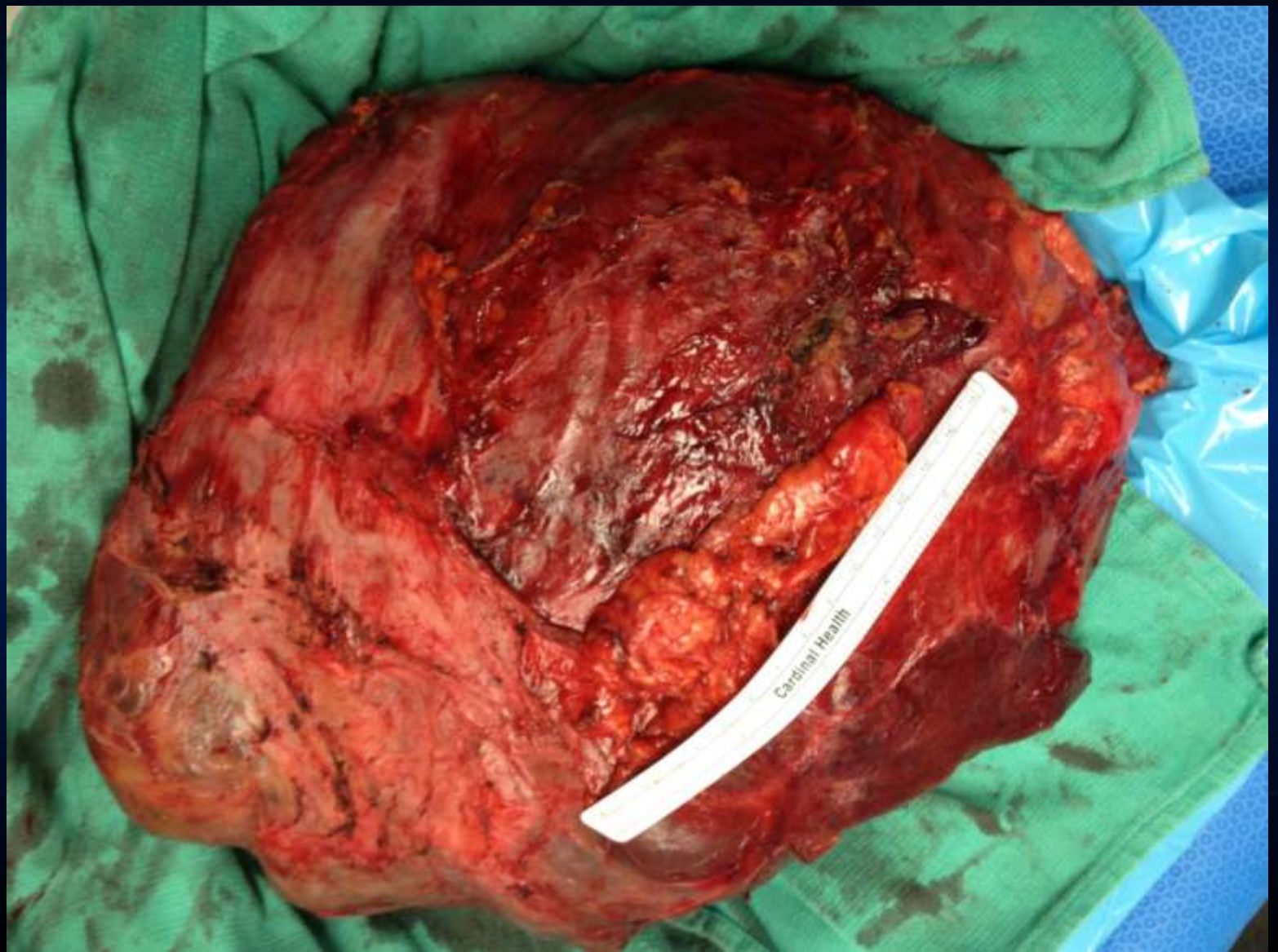
EIGHT MONTHS OF IMATINIB

EN BLOC RESECTION OF STOMACH, LEFT LOBE OF LIVER, COLON,SPLEEN





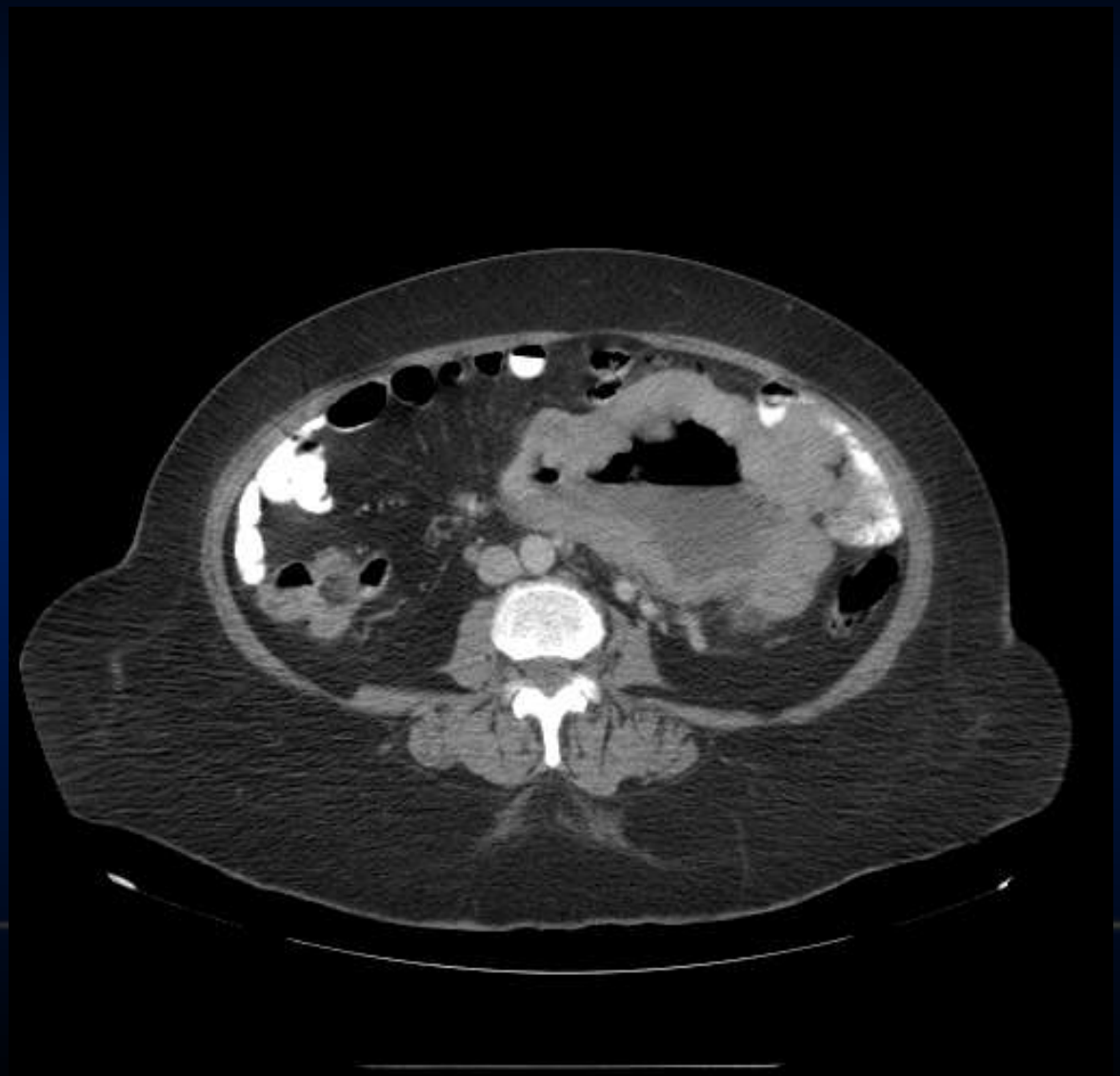
R0 RESECTION-INDEFINITE IMATINIB



GIST INVOLVING LIGAMENT OF TREITZ WITH FISTULIZATION

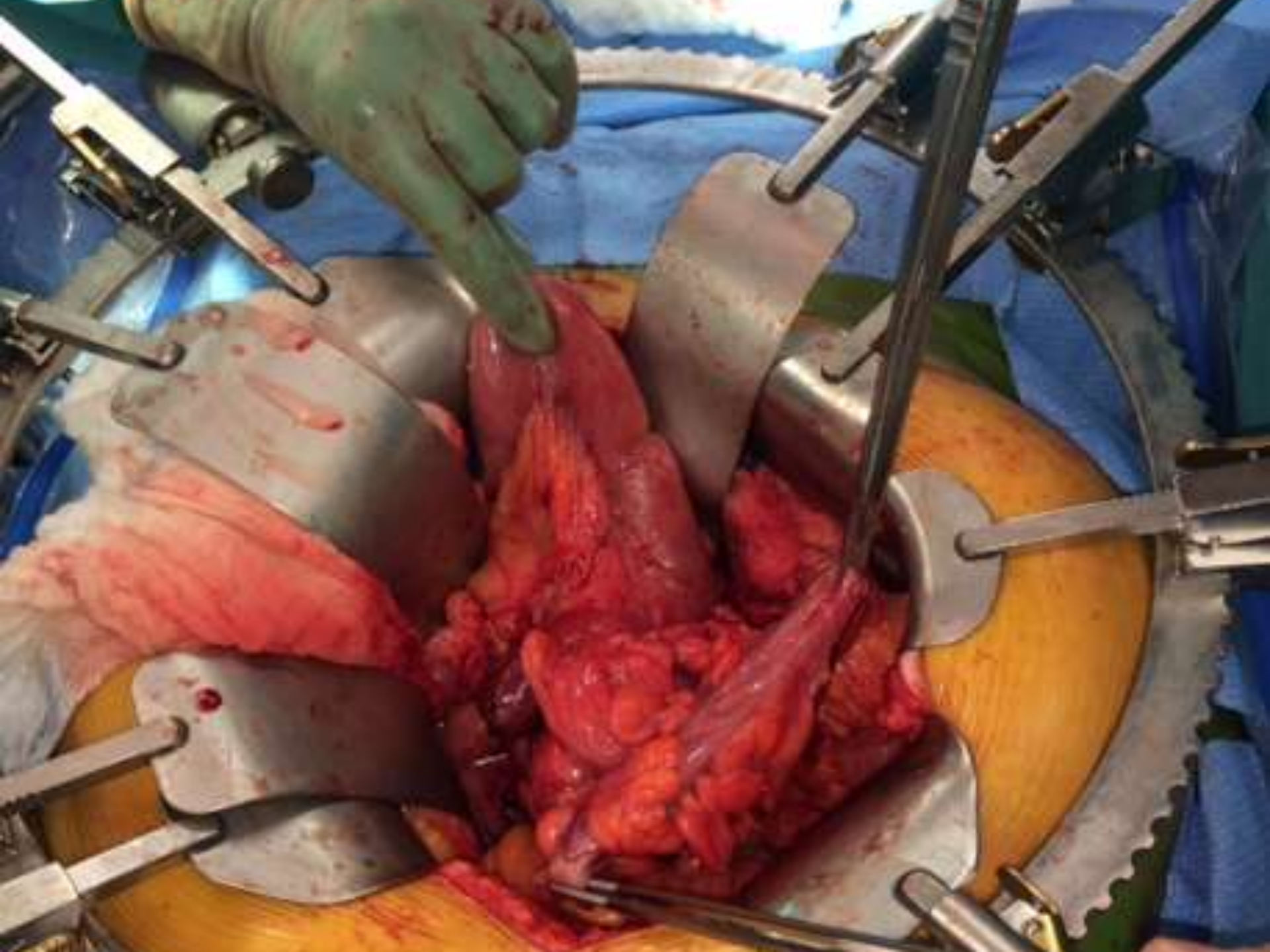
IMAGES PRIOR TO IMATINIB

IMAGES PRIOR TO IMATINIB

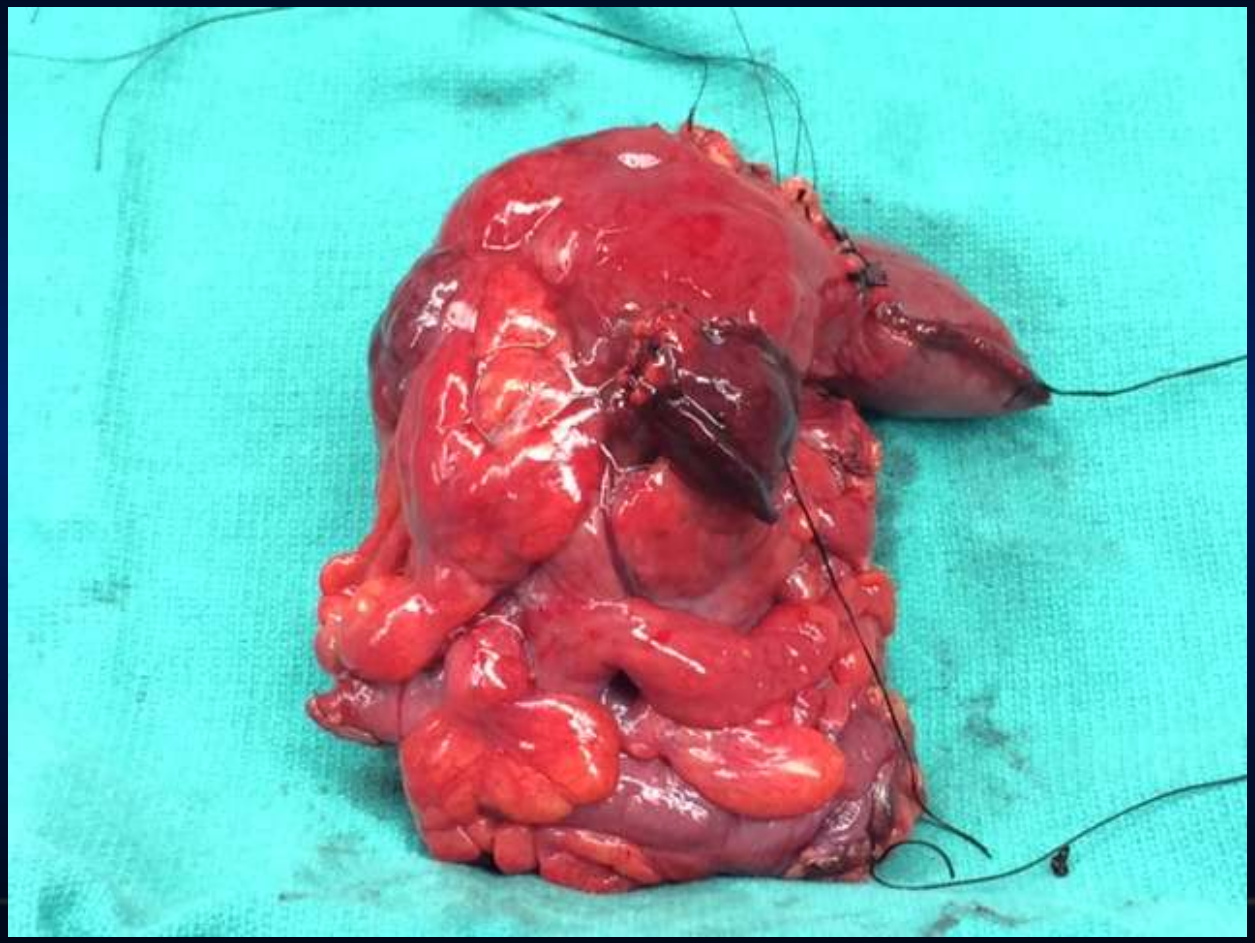


POST IMATINIB/PRE-OP IMAGES

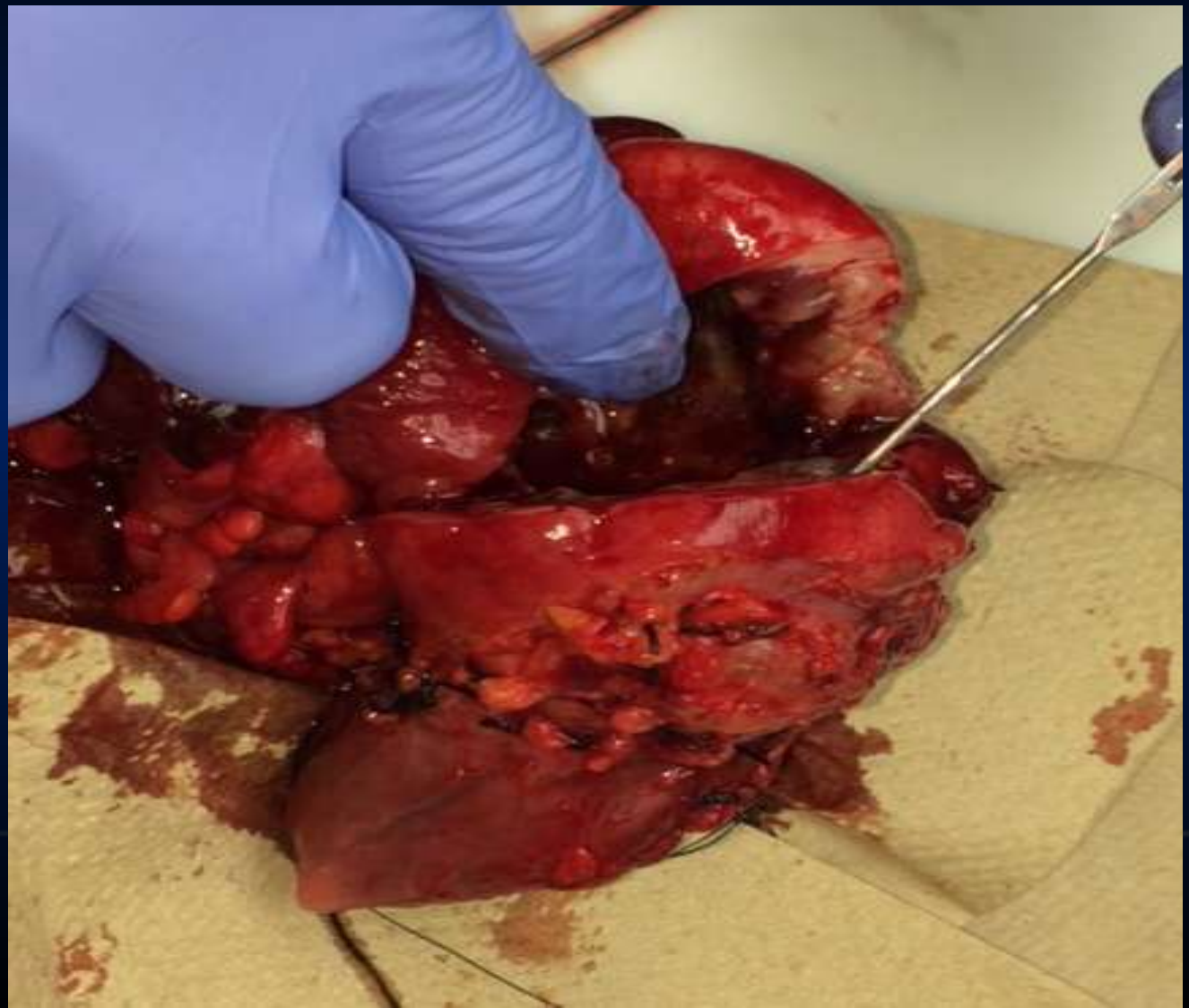
POST IMATINIB/PRE-OP IMAGES



D3, D4, PROXIMAL JEJUNUM



NECROTIC GIST
FISTULA INTO DUODENUM



R0 RESECTION- INDEFINITE IMATINIB

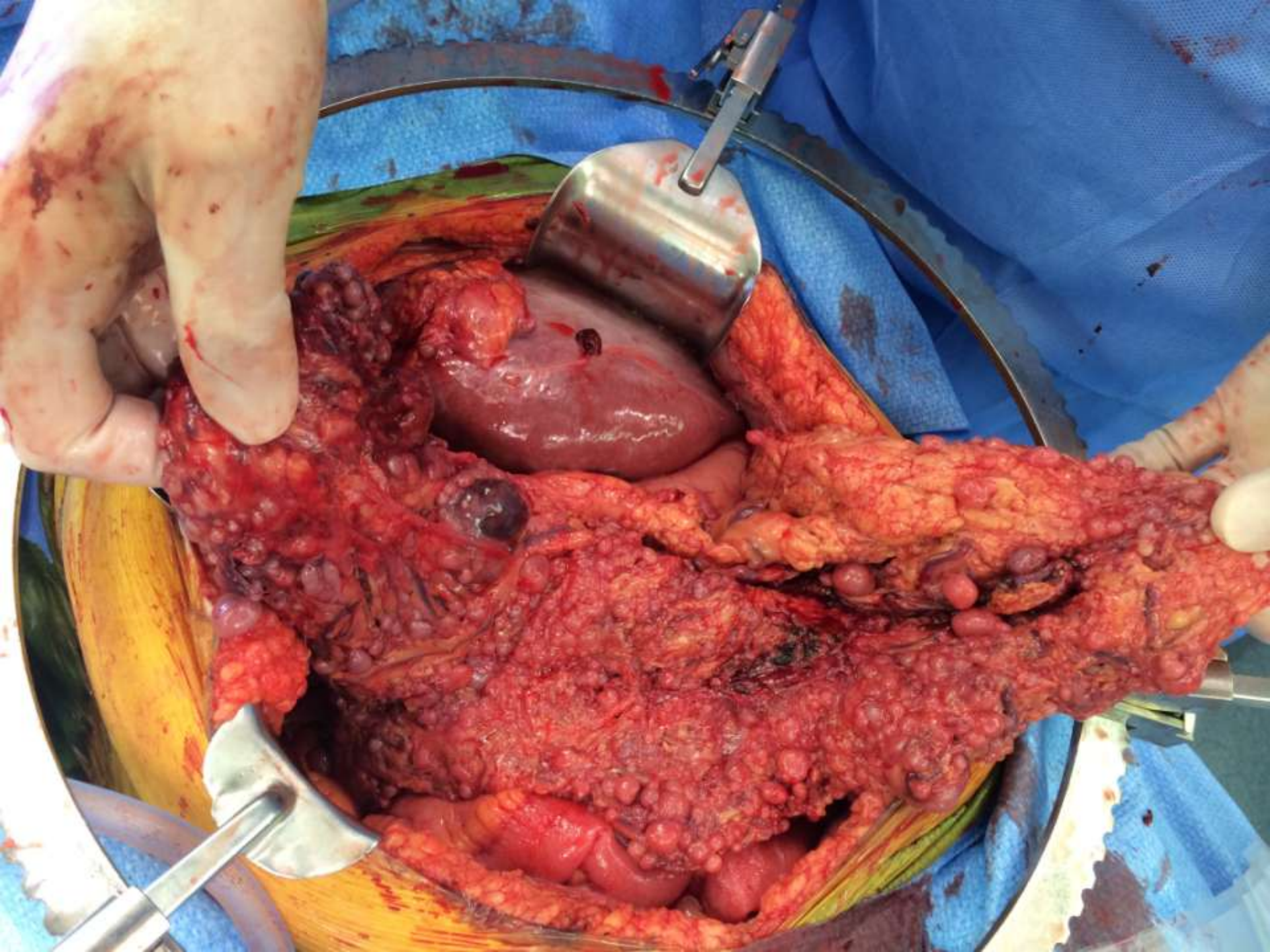
OBSTRUCTED FOR 8 MONTHS ON HYPERALIMENTATION-PREVIOUS RESECTIONS INCLUDING RIGHT HEPATIC LOBECTOMY-FLEW DOWN TO OUR HOSPITAL

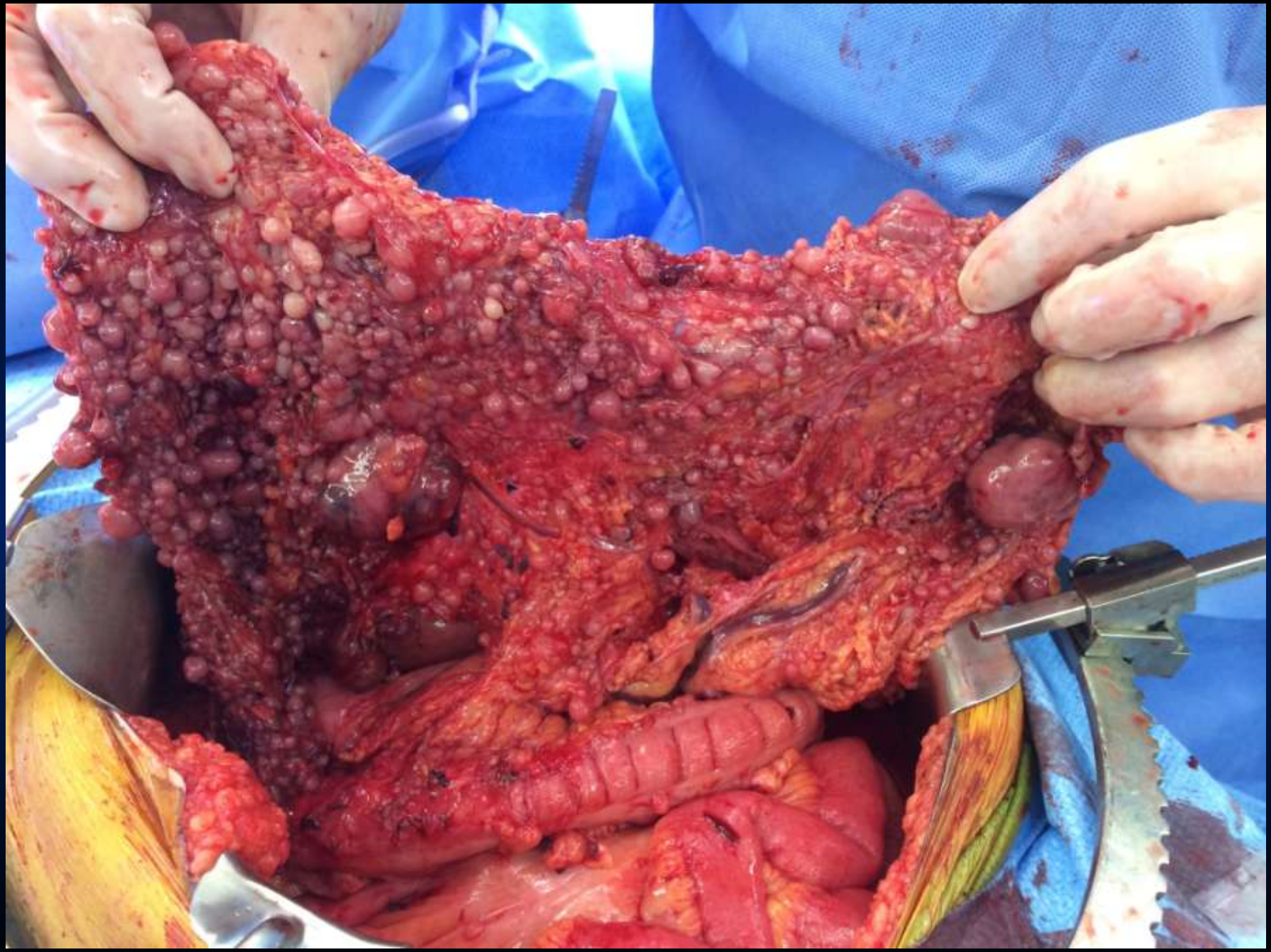
METASTATIC GIST BUT NON-MALIGNANT SBO

Don’t give up too soon!

DILATED LOOP OF SMALL BOWEL

Dilated jejunum and collapsed ileum- no disease in liver



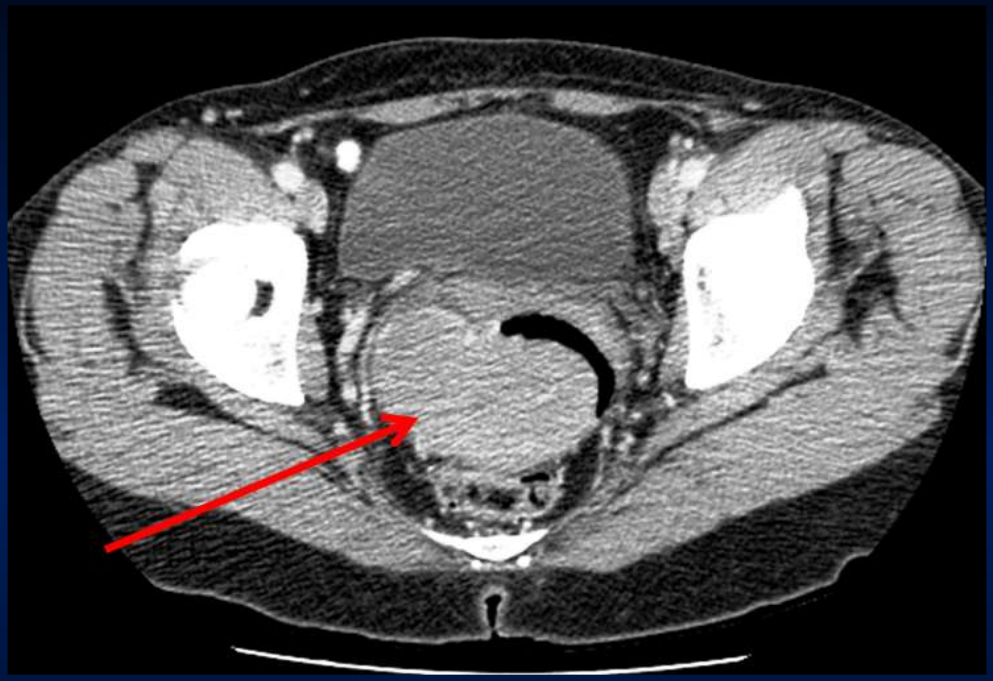


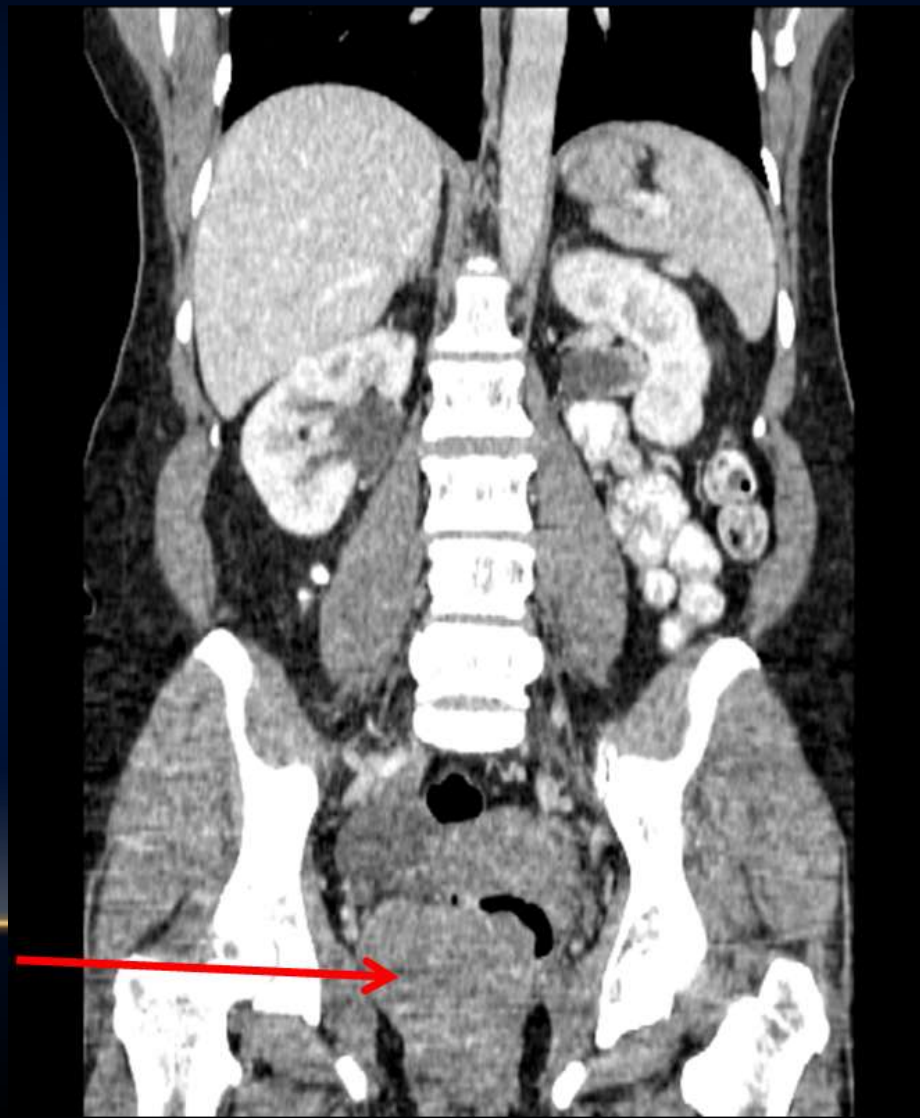
Omentectomy and R2 debulking-obstruction was due to internal hernia

ındefinite TKIs

RECTAL GISTS

SHE REFUSED A COLOSTOMY





GIST arising from Rectum
9 months of imatinib

- 66 yo male with urinary frequency and hard, frequent stools with straining
- Firm, fixed anterior mass 2cm above dentate line
- Transrectal biopsy = GIST


Abdomen^ONCO_TRIPLE_PHASE_ABD_PELVIS (Adult)
Series Abd/Pelvis 5.0 I31f 3
3/4/2013 10:41:26
5.00 mm
Image #67/87
A
UM Sylvester
GLASSMAN, ROB
DOB 3/23/1946; A
R
KV 120
Effective mAs 276
Slice Location 22
Series #4
ww/wl 400/40
ORIGINAL/PRIMARY/AXIAL/CT

- Localized to pelvis- adherent to prostate and seminal vesicles
- R1 resection on prostate
- Primary repair of rectum
- Indefinite TKIs

WHEN TO GIVE UP ON RECURRENCES?

- 61 yo woman presented with abdominal pain in Haiti, underwent exploration for presumed uterine fibroids
- TAH + BSO performed, resection of 24 x 19 x 12cm “uterine leiomyosarcoma”
- Tumor, recurred, diagnosis revised as GIST
- Multiple tumors on CT with response to imatinib
- Ultimate progression of disease


Abdomen^5_TRIPLE_PHASE_LIVER (Adult)
Series Delayed Liver 5.0 B10f
1/14/2013 10:52:22
5.00 mm
Image #42/69
A
University of mia
MARC-CHARLES
DOB 2/1/1952; A
R
KV 120
Effective mAs 128
Slice Location -512
Series #7
ww/wl 450/47
ORIGINAL/PRIMARY/AXIAL/CT


Abdomen^5_TRIPLE_PHASE_LIVER (Adult)
Series Delay 3.0 SPO cor
1/14/2013 10:52:22
3.00 mm
Image #55/89
University of mia
MARC-CHARLES
DOB 2/1/1952; A
S
R
KV 120
Effective mAs 127
Slice Location
Series #9
ww/wl 457/60
DERIVED/PRIMARY/AXIAL/CT_

- Changed from imatinib to sunitinib
- Dramatic decrease in abdominal size in just 1 month, tolerating diet, good energy level, feeling well
- Continue sunitinib repeat imaging in 2-3 months, and re-evaluate for debulking

WHO SHOULD RECEIVE IMATINIB?

- Neoadjuvant: locally advanced?
- Adjuvant: after all resections? Risk stratify.
- Therapeutic: Unresectable, metastatic, recurrent disease
- How long? -indefinitely for high risk.

- With new therapeutics, the role of surgery in treatment of GIST need to be continuously and repeatedly evaluated

THANK YOU / QUESTIONS?