

Surgical Management of GISTs in the Era of TKIs

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THE LIFE RAFT GROUP

MIAMI FL

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Historical Perspective

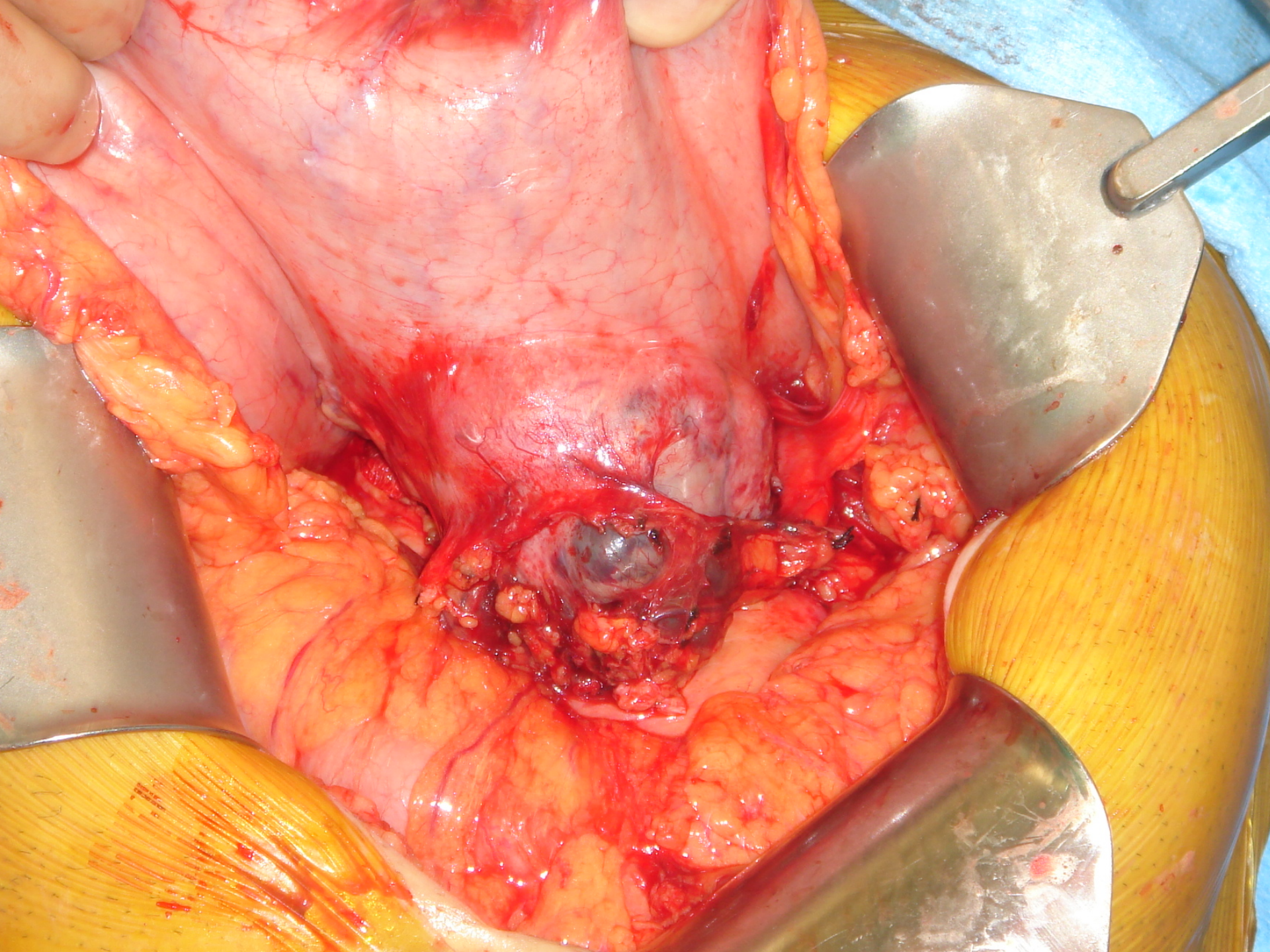
- Term GIST coined in 1983
- Cells arise from intestinal pacemaker cells (Interstitial cells of Cajal)
- c-kit was identified as a marker of GIST in 1998 resulting in distinguishing these tumors from leiomyosarcomas

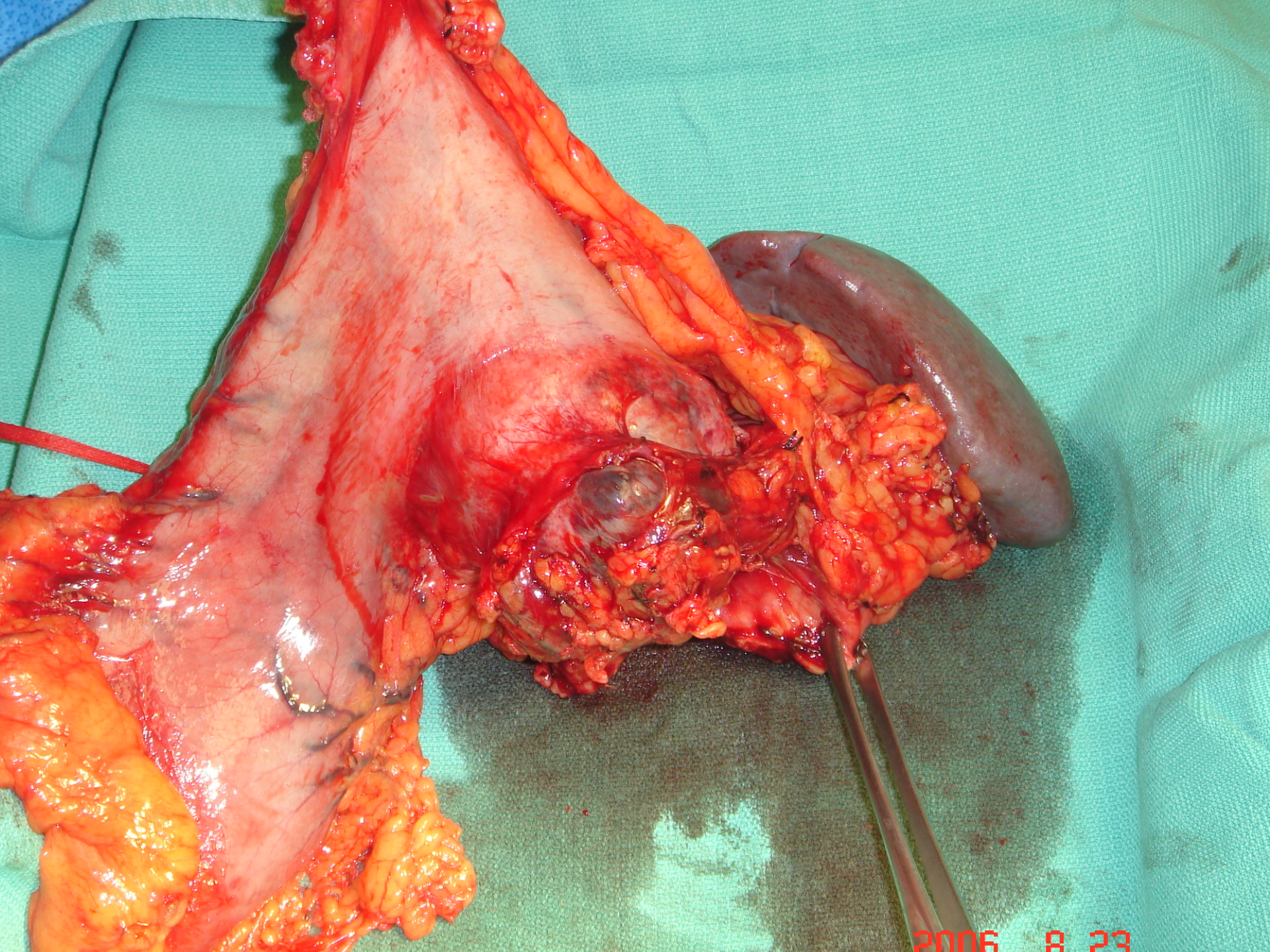
GIST: What is it?

- The most common GI mesenchymal tumor
- About 5000/year in USA
- Most express CD34 and c-kit tyrosine kinase (CD117) by IHC

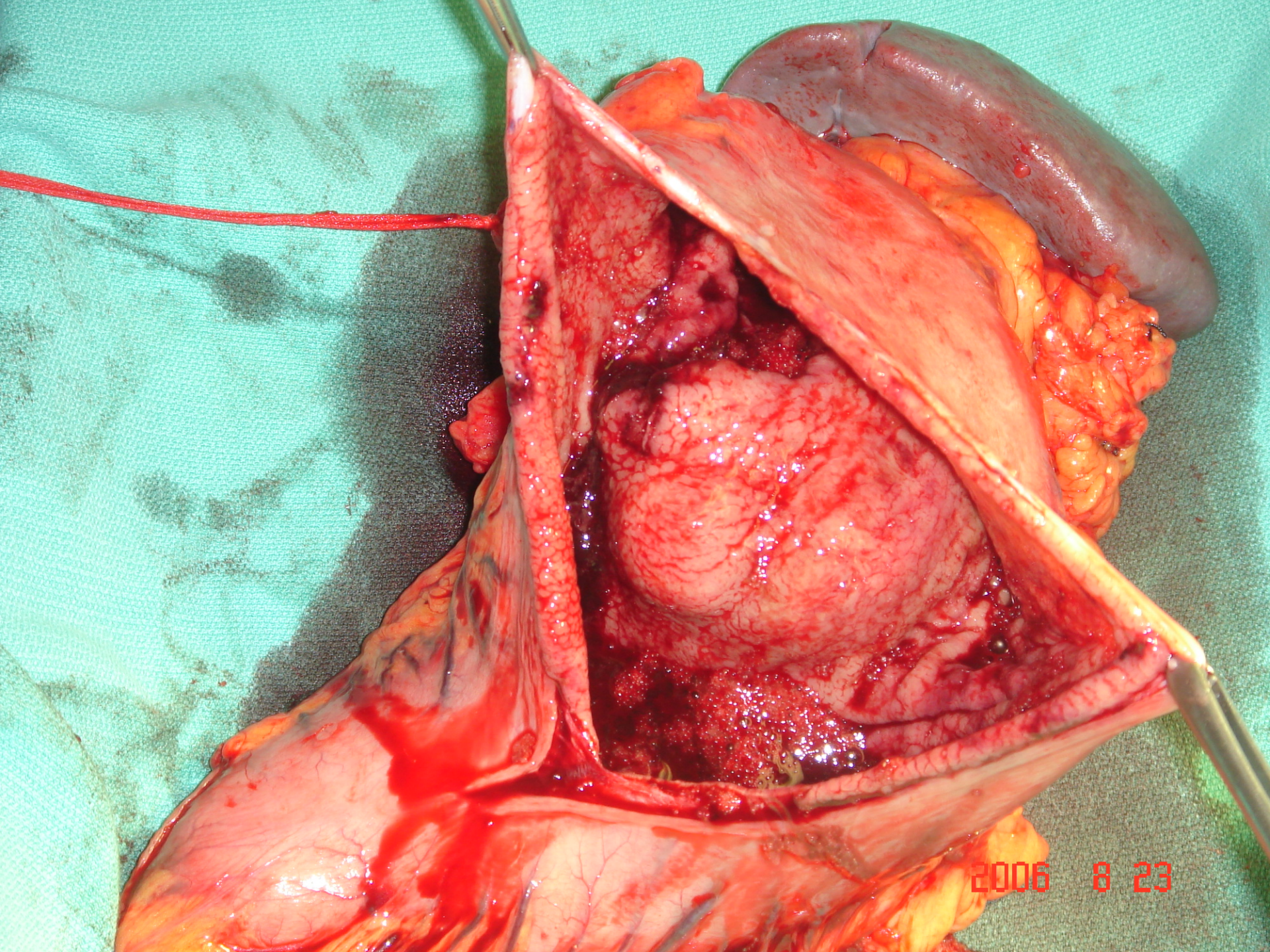
Presentation

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





2006 8 23



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Distribution Of GIST And Other GI Mesenchymal Neoplasms

- Found anywhere in the GI tract
- <3% of all GI cancers
- 20% of SB cancers

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

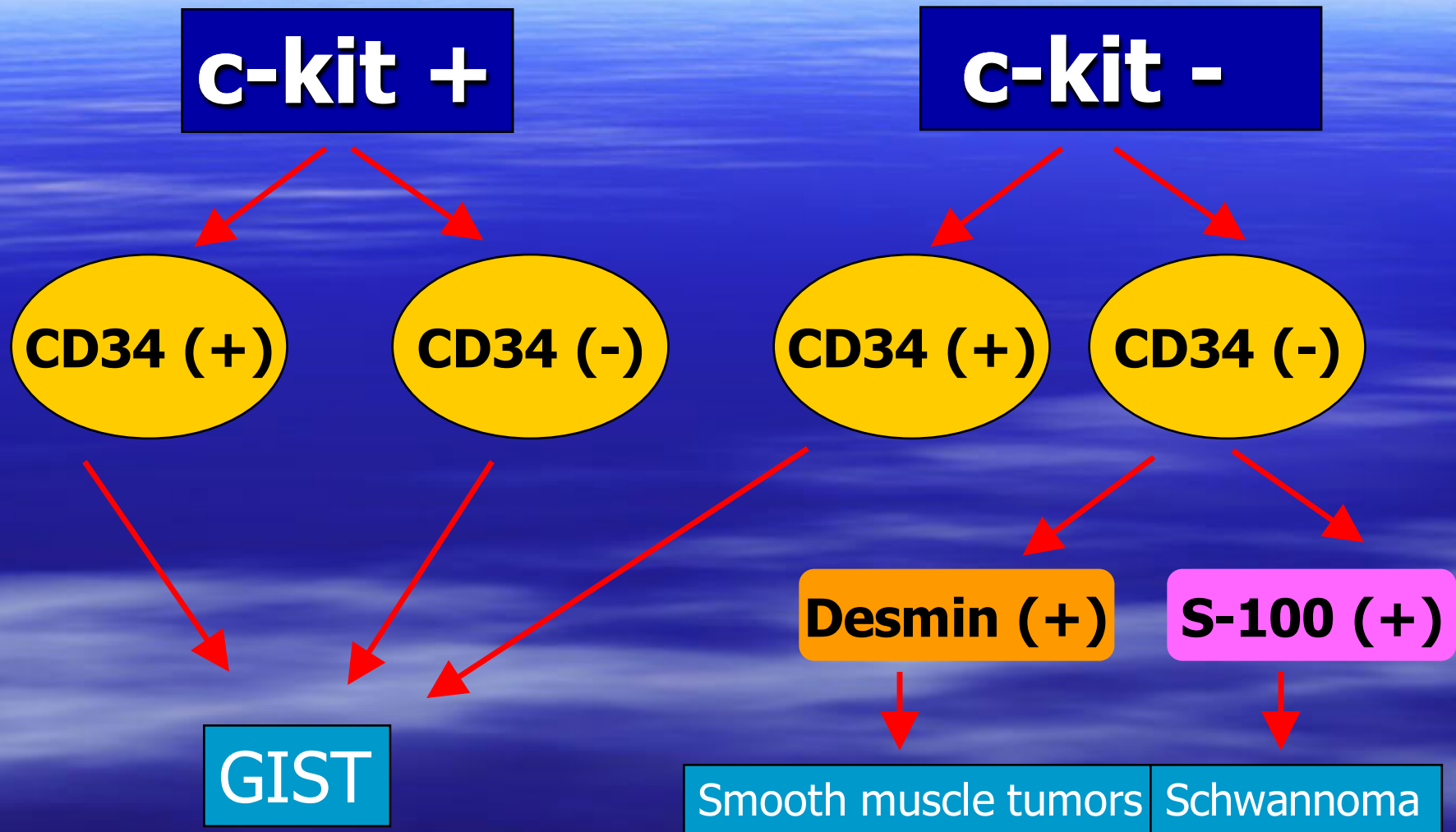
Incidence

- Prior to use of c-kit IHC, GIST was misdiagnosed as smooth muscle tumor
- SEER data set after 2000 indicates 82% of all GI mesenchymal tumors and 96% of gastric tumors are GISTS

Pathology

- 70% spindle cell: cf. leiomyosarcoma
- 30% epithelioid: cf. leiomyoblastoma
- CD 34: 70-80%
- c-kit: 95%
- Often PDGFRA
- Actin: 30%
- Rarely desmin or S100

GI mesenchymal tumors: Classification

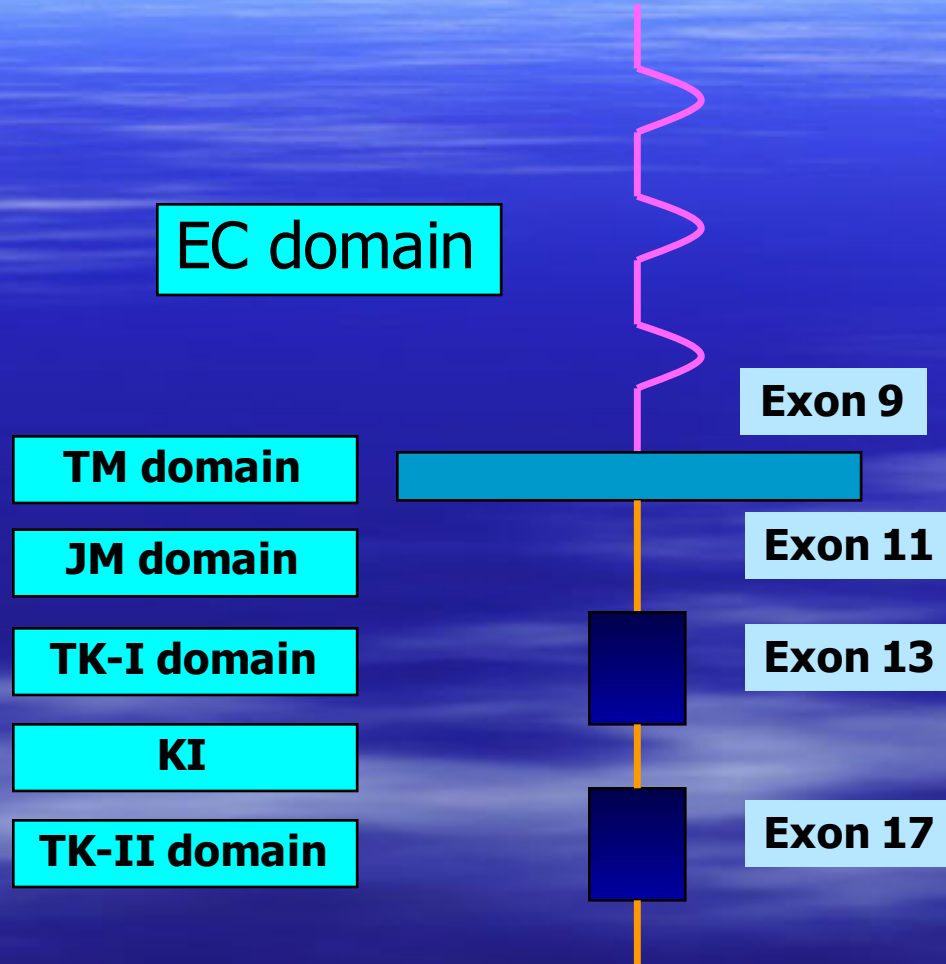


GIST: Pathogenesis

Most sporadic

- Sporadic (90%) and familial (100%) cases show gain of function mutations of the *c-kit* gene.
 - Sporadic: somatic
 - Familial: Germ-line
- C-kit is a Tyrosine Kinase receptor encoded by the protooncogene *c-kit*

GIST: Pathogenesis: c-kit



Hirota S and Isozaki K. Pathology International 2006

GIST: Pathogenesis: c-kit

- Natural ligand: Stem cell factor (SCF)
- Two wild-type molecules form a dimer by the binding of 2 molecules of SCF



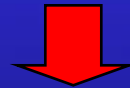
DIMERIZATION

GIST: Pathogenesis: c-kit

Dimerization



Phosphorylation of intracellular TK



Cell proliferation and differentiation
2^o to IC signaling cascade

RAS/MAP Kinase, PI3k/Akt pathway

mTOR, p70/85S6K

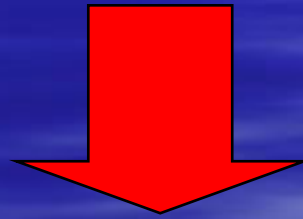
STAT1, STAT3

Rubin BP. Histopathology 2006

Hirota S and Isozaki K. Pathology International 2006

GIST: Pathogenesis

Gain-of-function mutations of *c-kit*
protooncogene



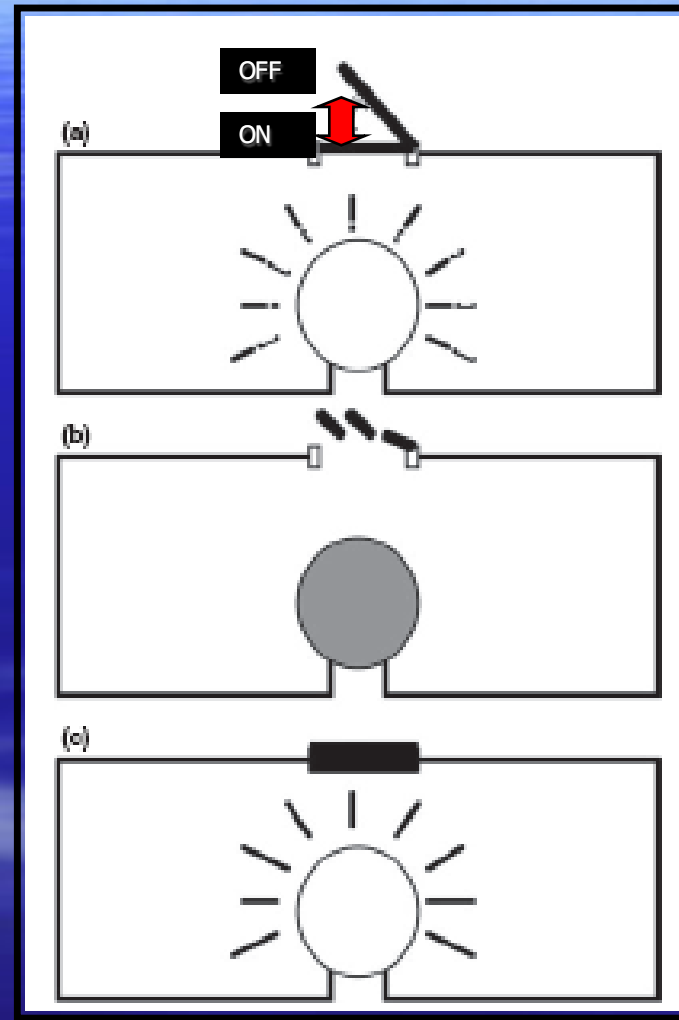
Constitutive tyrosine phosphorylation
without SCF

GIST: Pathogenesis: c-kit

Normal Switch

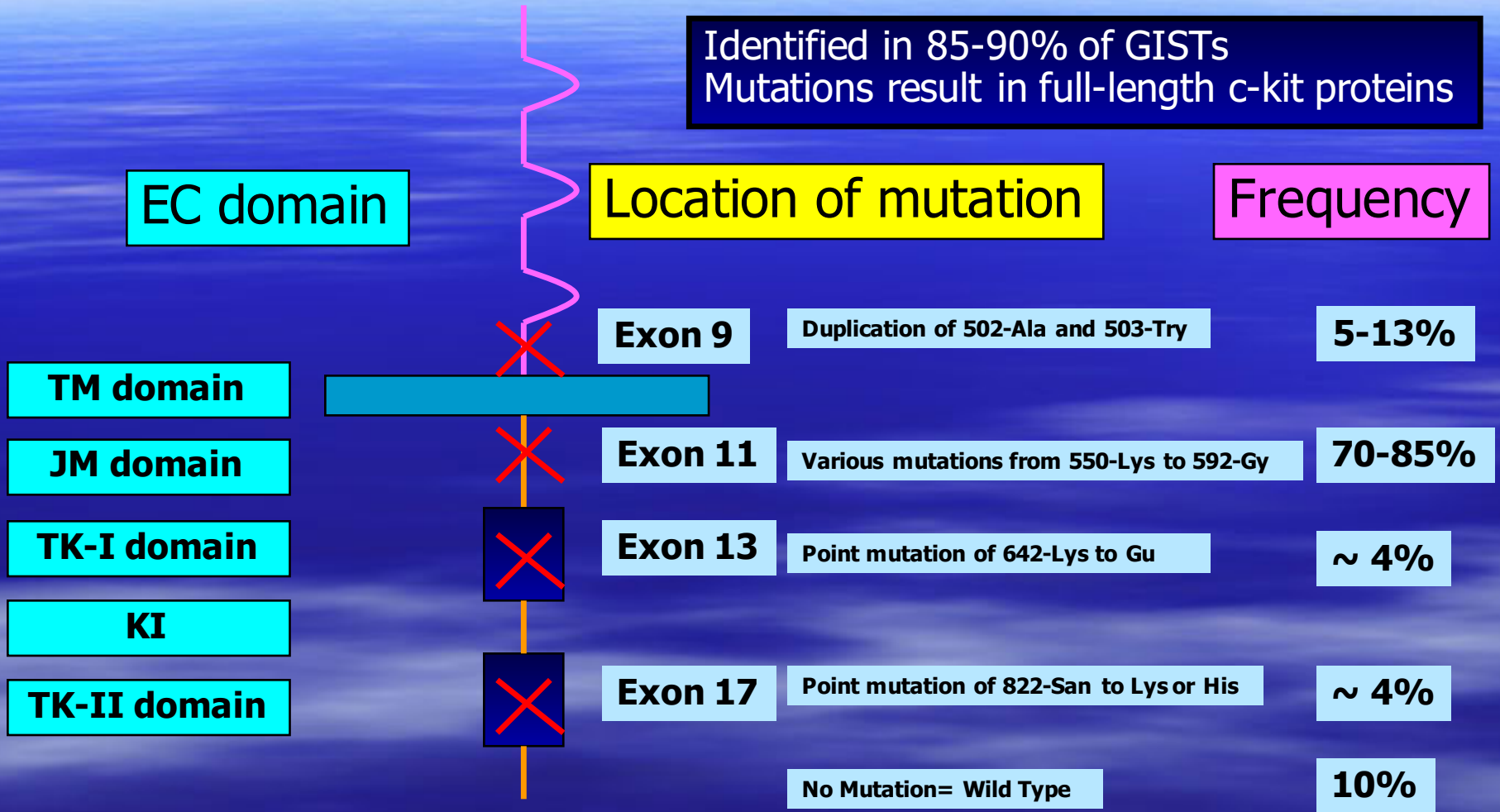
Loss of function mutation

Gain of function mutation



GIST: *c-kit* Mutations

Identified in 85-90% of GISTs
Mutations result in full-length *c-kit* proteins



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%

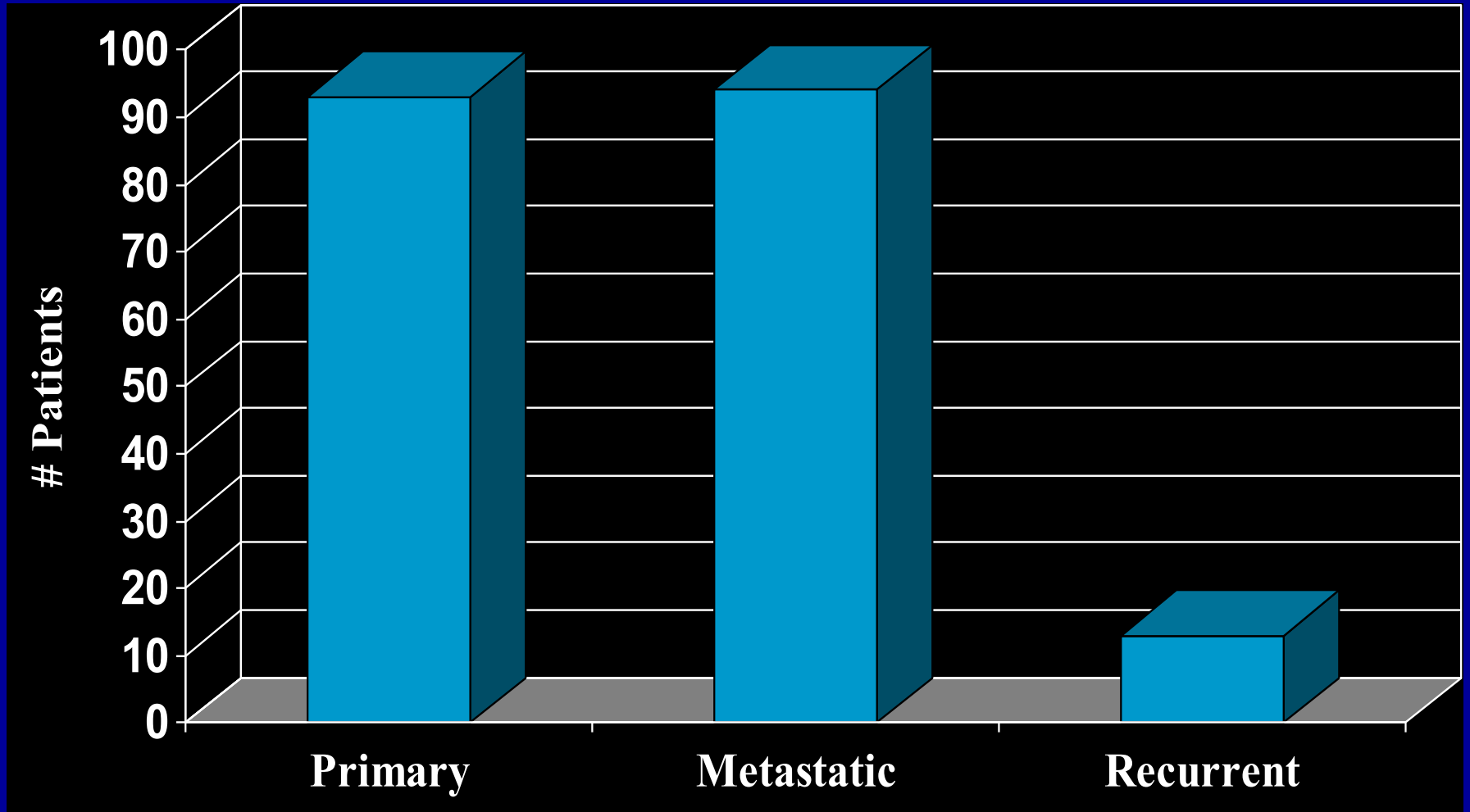
Historical Perspective

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

GIST – Pre Imatinib

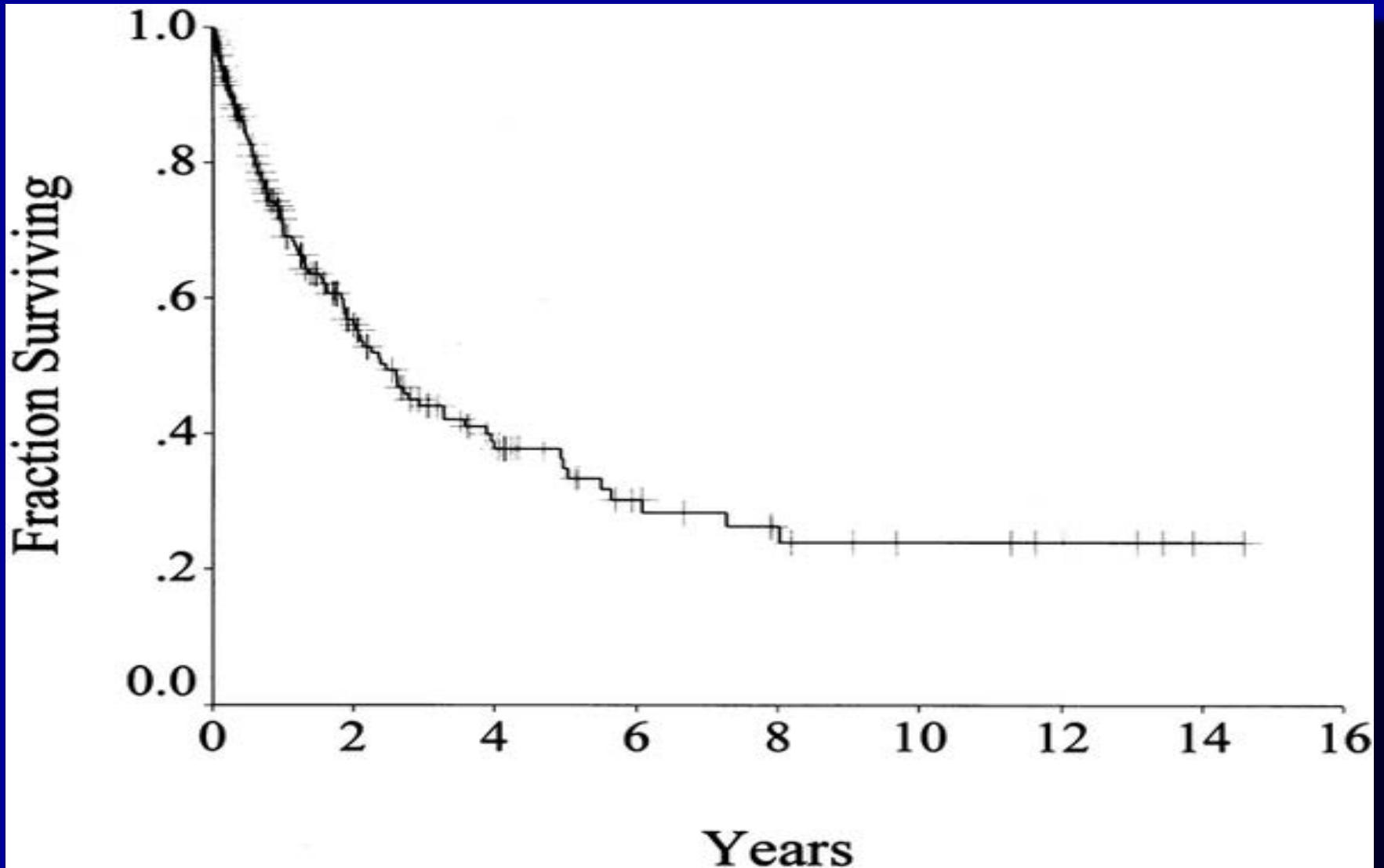
Author (Institution)	Years	Total Patients	Complete Resection	5-year Survival
Bearhs (Mayo)	1950-74	108	52	50
Shiu (MSKCC)	1949-73	38	20	65
Parker (MCV)	1951-84	51	30	63
Pollock (MDACC)	1957-97	191	99	48
DeMatteo (MSKCC)	1982-98	200	80	54

GIST - Presentation

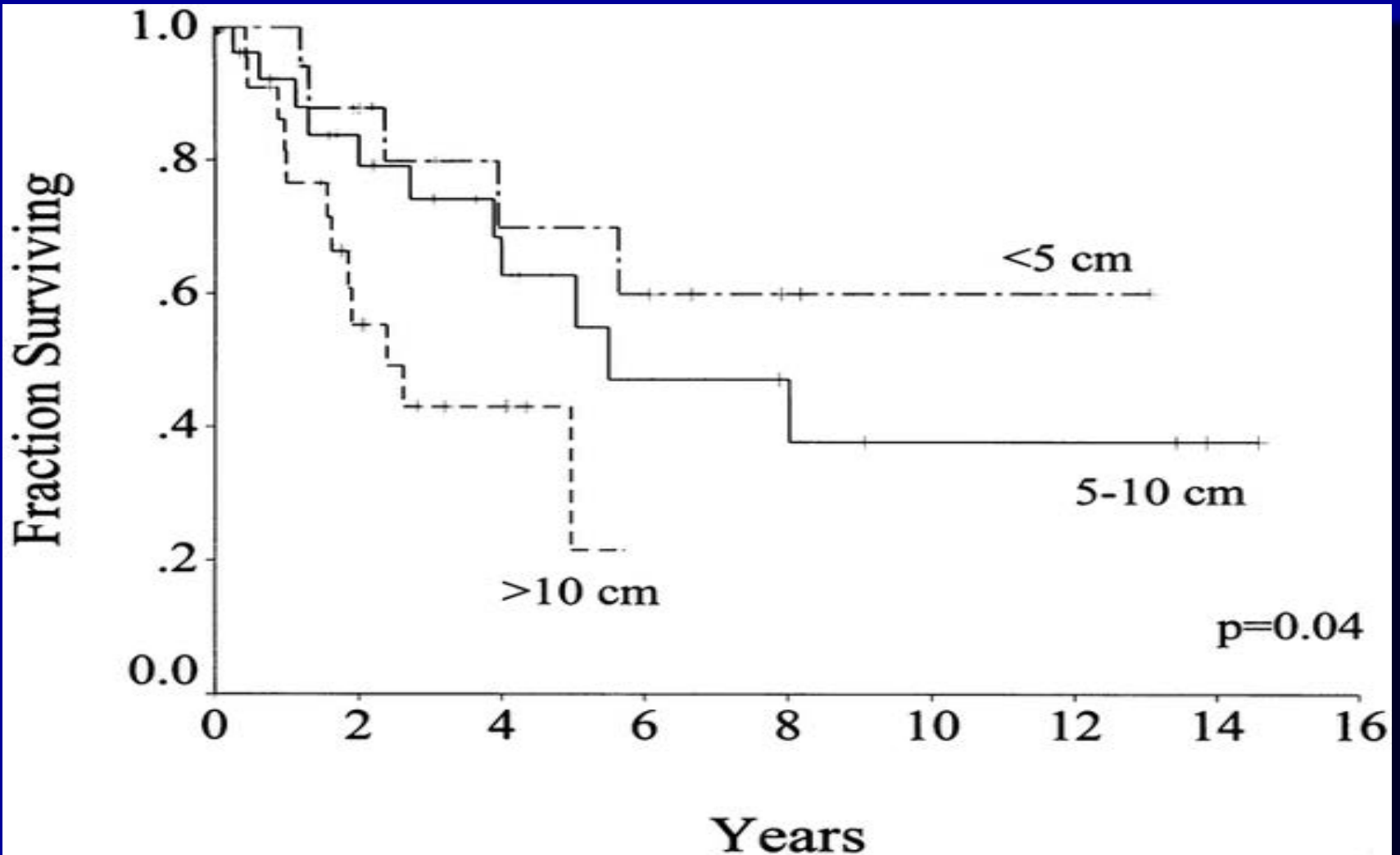


DeMatteo, Ann Surg 231:51-58, 2000

GIST – Survival Pre imatinib Era

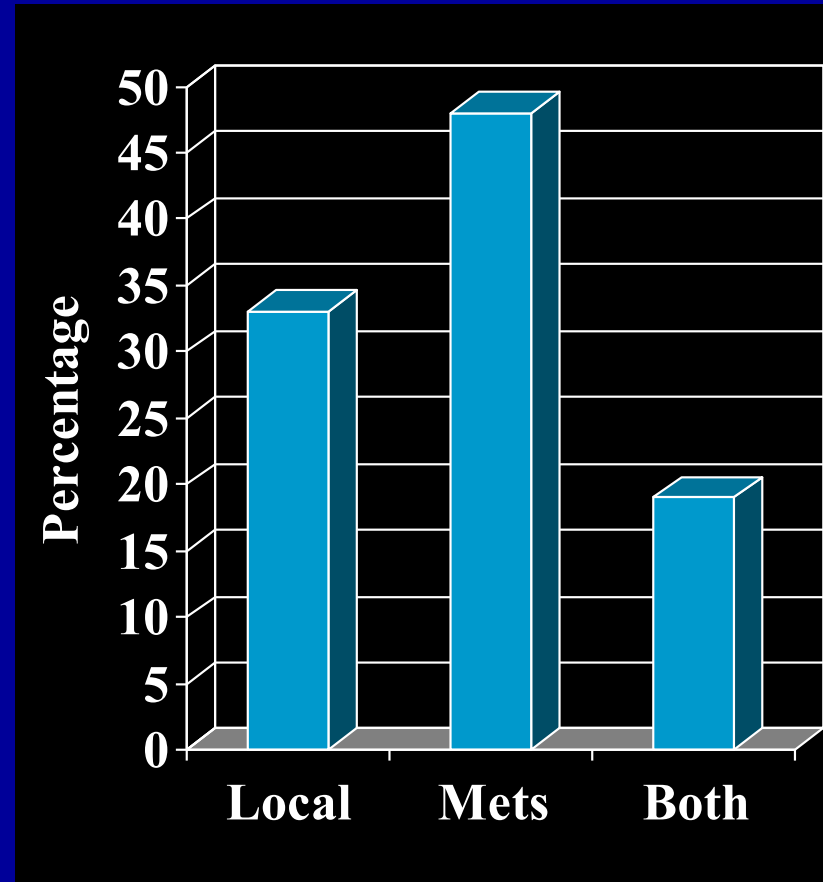


GIST : DFS By Tumor Size



GIST : Recurrence After Complete Resection

- Recurs in >40% of patients – most will die from disease.
- Predominant site is intra-abdominal
 - Liver: 2/3
 - Local
 - Peritoneal



Challenges

(1) Diagnosis

- H & P- mass, bleeding (GI or peritoneal), obstruction, or perforation
- Endoscopy
- EUS
- CT/MRI
- PET-including response to Rx

Challenges

(2) Criteria For malignancy

- Metastases
- Invasion of adjacent structures
- Size >5 cm (20% <5 cm metastasize)
- Mitotic index: >5 per 50 HPF
- Necrosis
- Ki-67 index $>10\%$

Challenges

(3) 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

Challenges

(4) Local Extension Or Metastases

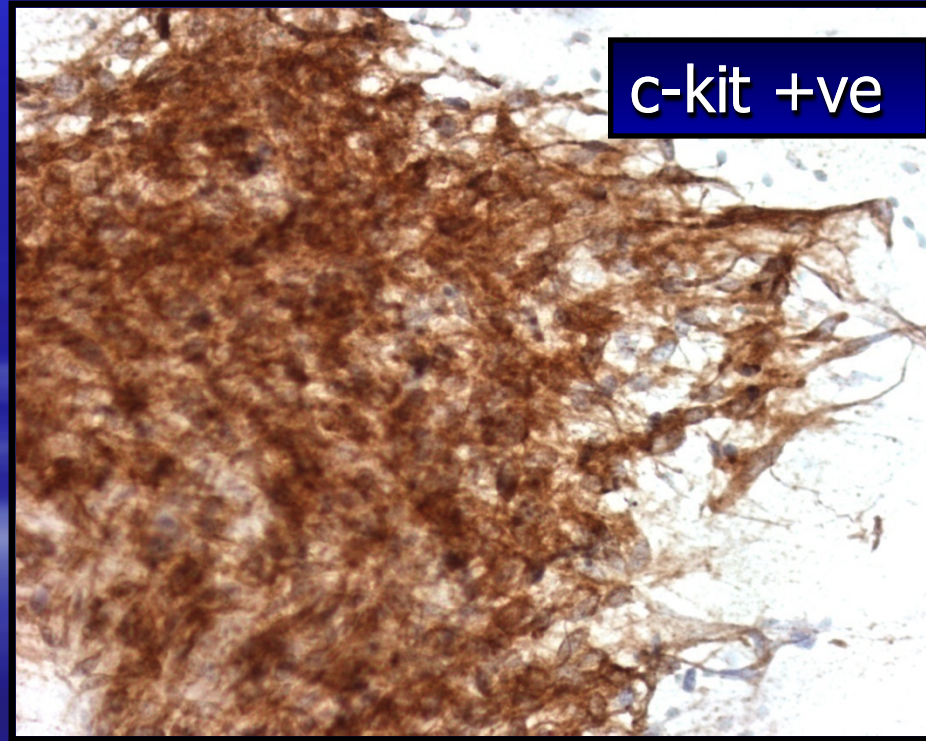
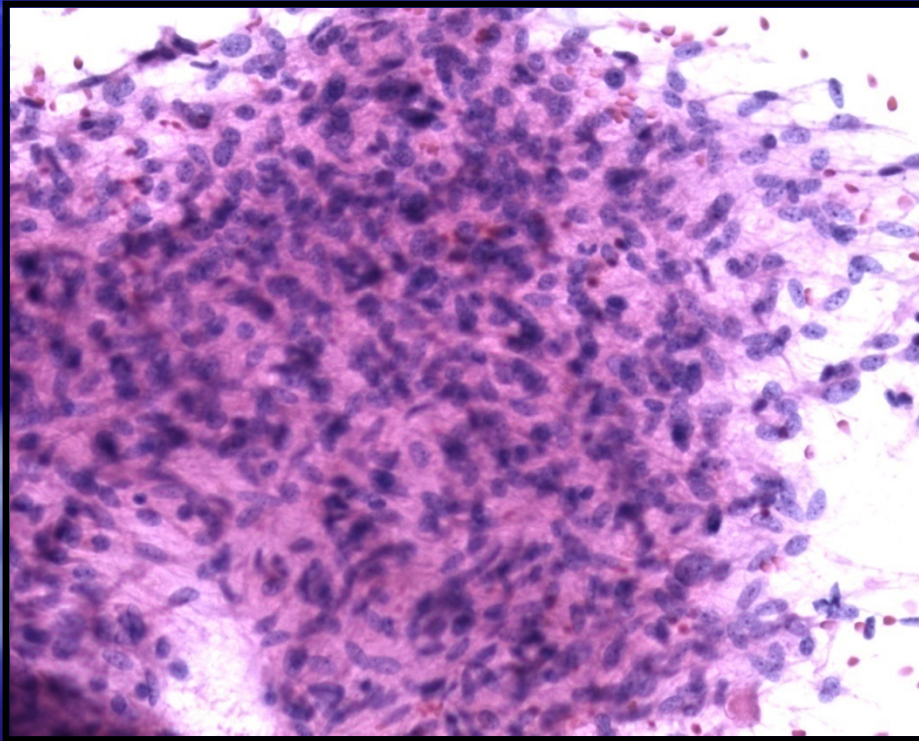
- Therapy evolving in era of imatinib

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 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 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 In Era Of Imatinib

- 6) 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 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?

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

Improved Survival for Gastric Mesenchymal Neoplasms Including GIST after 2000

	<i>2-Year Survival Pre-2000</i>	<i>Median Survival (Months)</i>	<i>2-Year Survival Post-2000</i>	<i>Median Survival (Months)</i>	<i>P value</i>
<i>Overall</i>	58.88% (n=525)	>35	73.09% (n=307)	>35	0.0031
<i>Stage</i>					
Localizad	78.94% (n=302)	>35	88.3% (n=175)	>35	0.0439
Regional	36.86% (n=86)	17.78	74.58% (n=54)	>35	0.0117
Distant	16.67% (n=102)	9.14	35.94% (n=58)	13.3	0.0391
<i>Size</i>					
Less than 4.9cm	76.96% (n=80)	>35	89.18% (n=54)	>35	0.1319
5-9.9cm	68.7% (n=158)	>35	86.39% (n=103)	>35	0.0104
10- 20cm	57.74% (n=155)	33.23	73.72% (n=80)	>35	0.1762
Greater than 20cm	40% (n=45)	18.83	43.26% (n=20)	12.01	0.3961
<i>Grade</i>					
I,II	80.03% (n=143)	>35	87.22% (n=41)	>35	0.5829
III,IV	38.24% (n=102)	16	52.22% (n=51)	>35	0.1146

Imatininb for Advanced Disease

B2222 trial- ASCO 2006

- Objective response rate - 68%
- Exon 11 response rate - 87%
- No *KIT* or *PDGFRA* mutation – 0% response
- Median time to response – 13 weeks
- Median duration of response - 118 weeks
- Median time to failure – 84 weeks
- Median survival – 4.8 years

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)

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 f-up and crossover design
- Need longer f-up to show if adjuvant Rx increases cure rate

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?

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

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

Benefit of Surgery After Imatinib For Advanced Disease- f/up 15 mths

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

Brigham, 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

Cost Effectiveness 1 vs 3 Yrs

Adjuvant Imatinib (USA cost)

Quality Adjusted Life Years

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

Interesting Cases

Esophageal Primary

- Dysphagia
- GI bleeding

Se: 5/6

Im: 33/42

Ax: S1476.5

Acq Tm: 14:36:37.150

512 x 512

FC10

R

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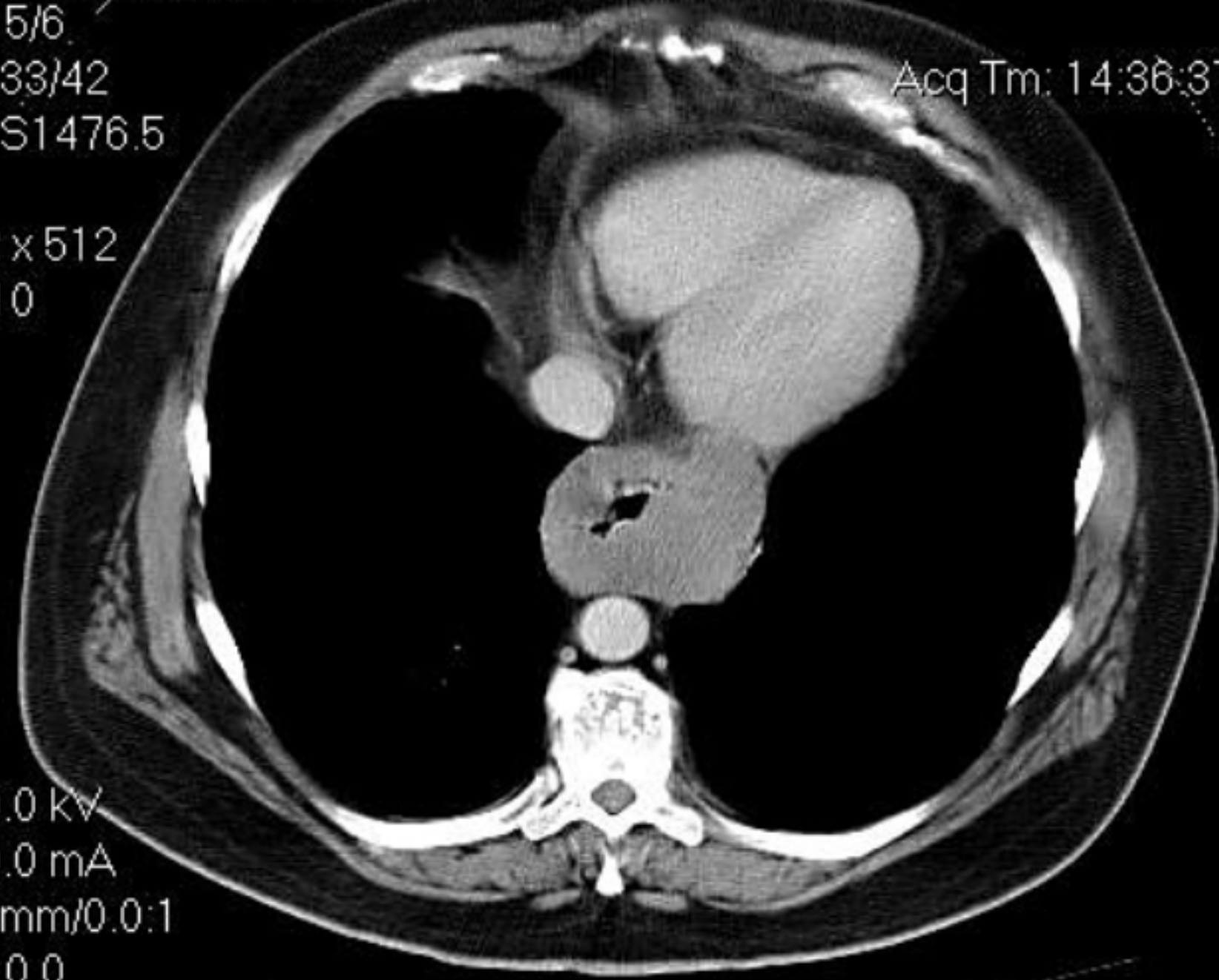
120.0 kV

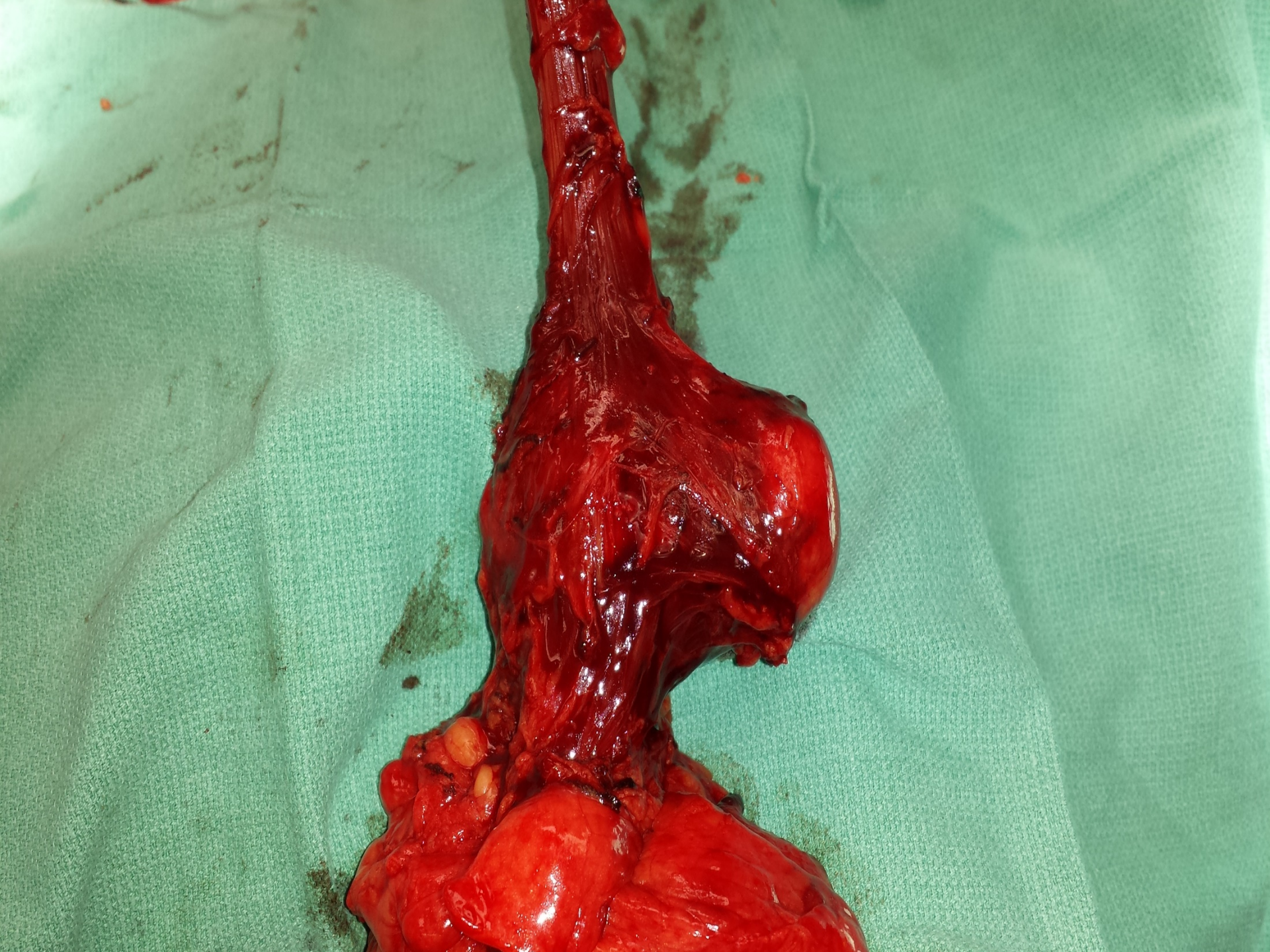
400.0 mA

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Tilt: 0.0

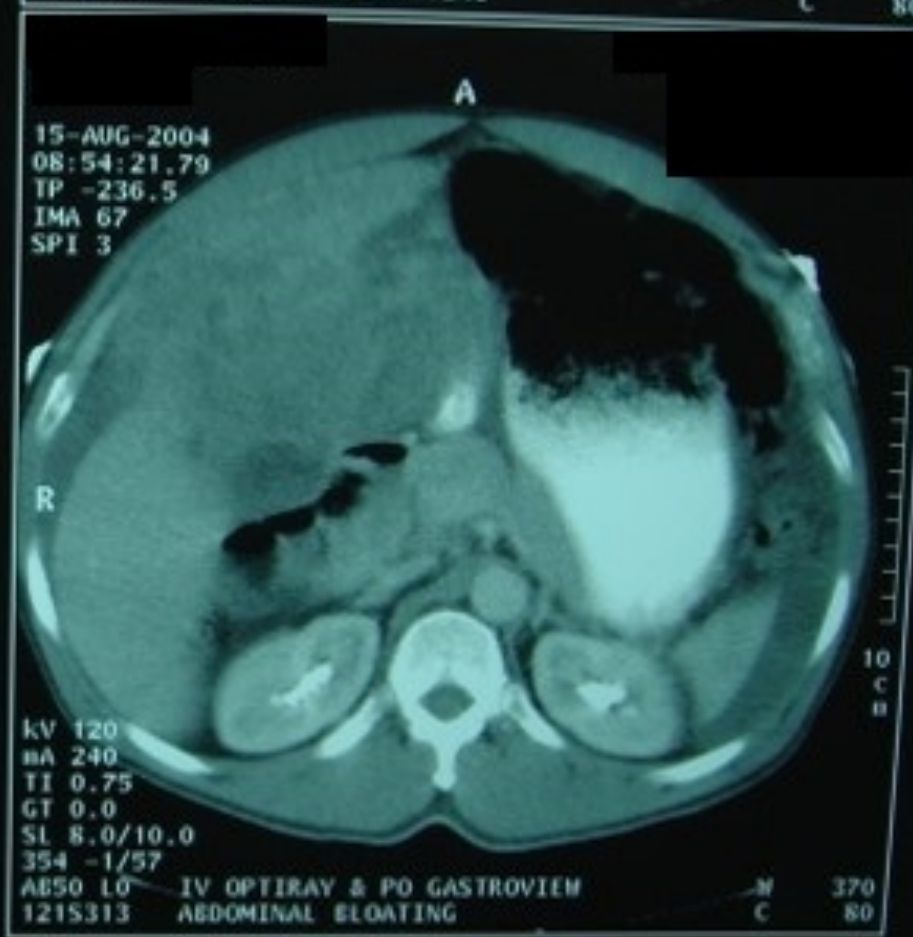
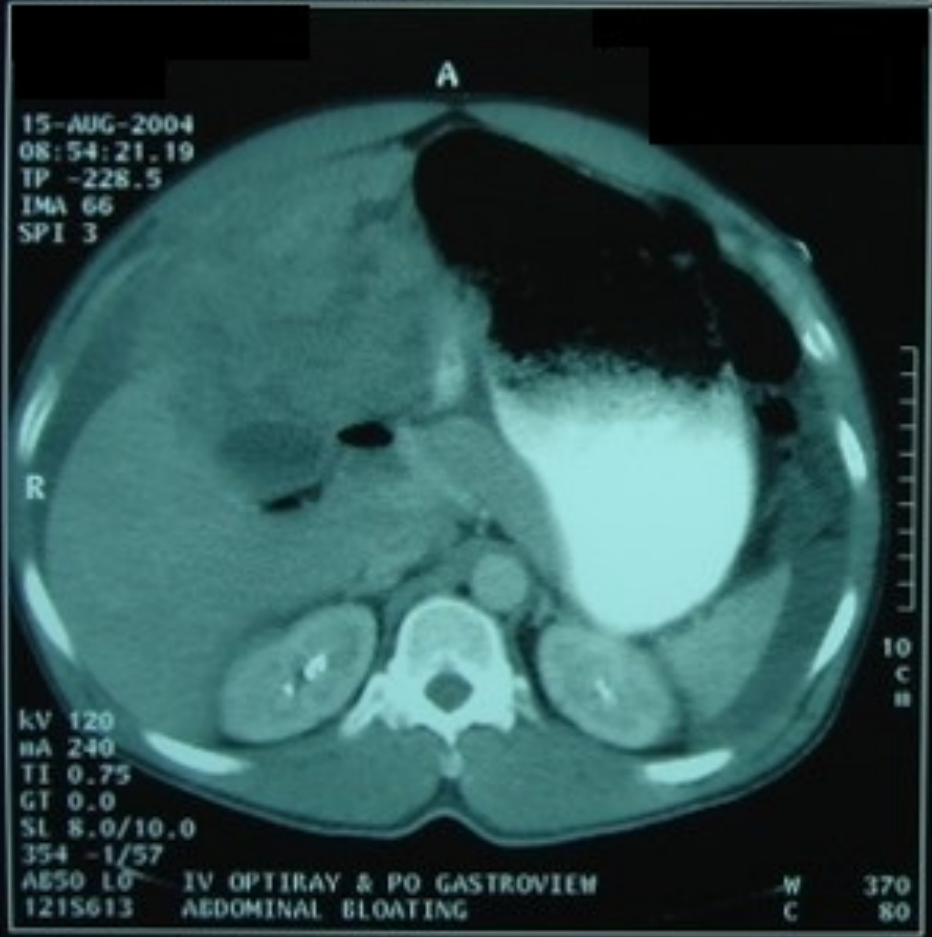
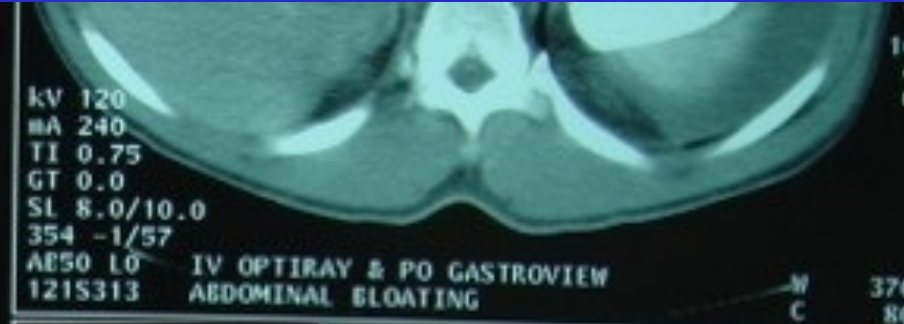
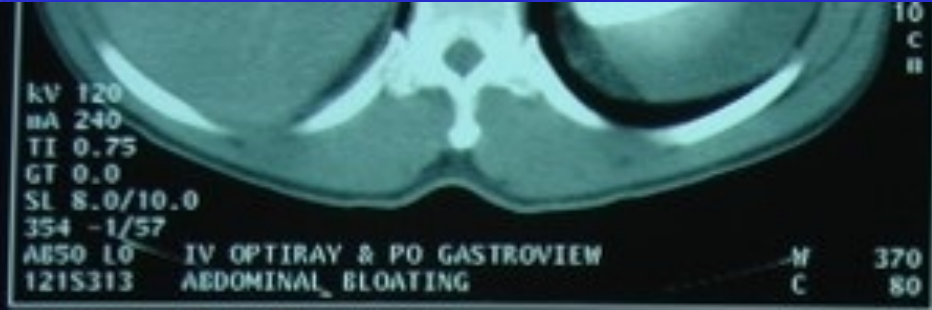
0.8 s



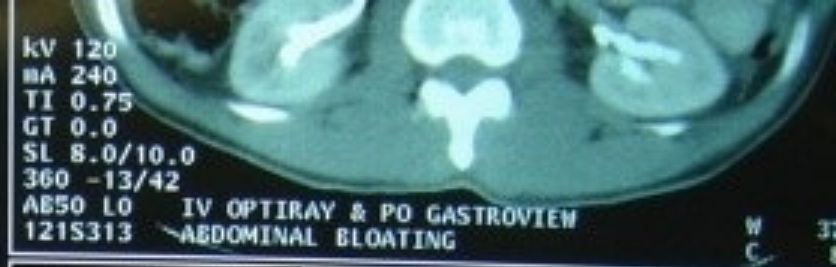
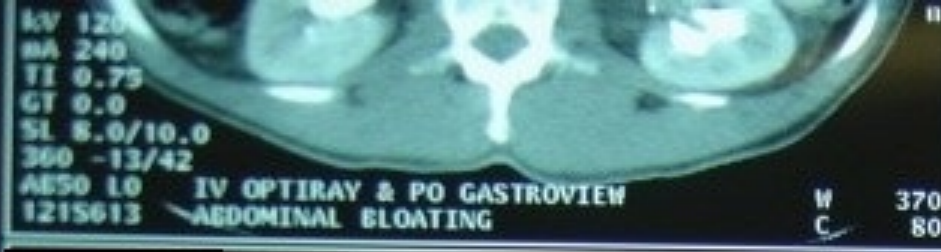




Acute Abdominal Pain



AUG 23 2004





AUG 23 2004



AUG 23 2004



AUG 23 2004

Before

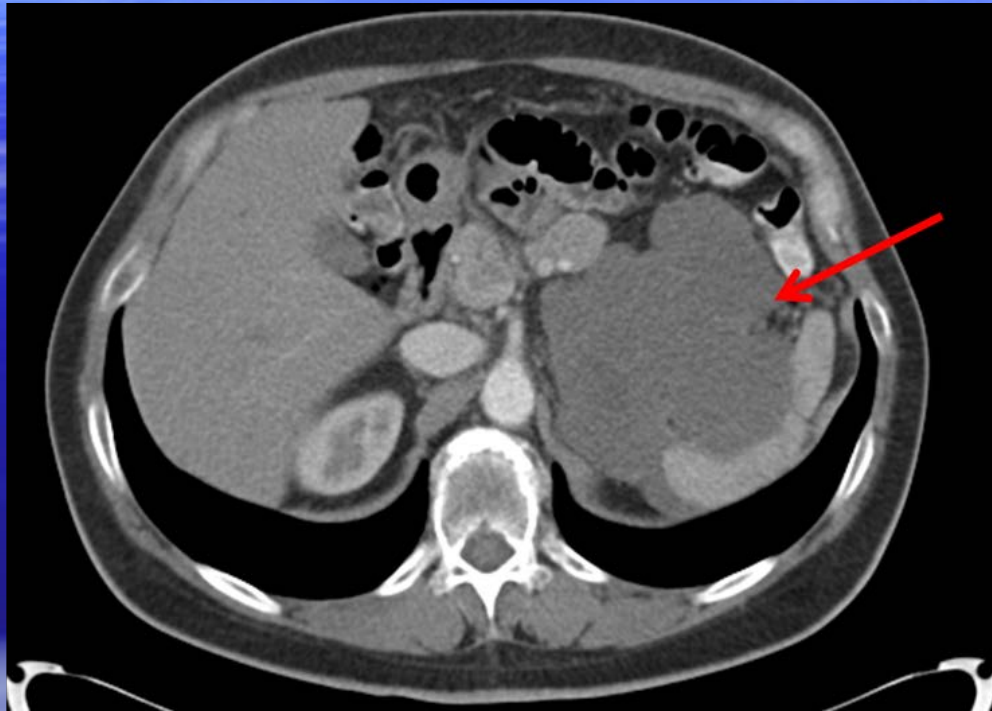


After



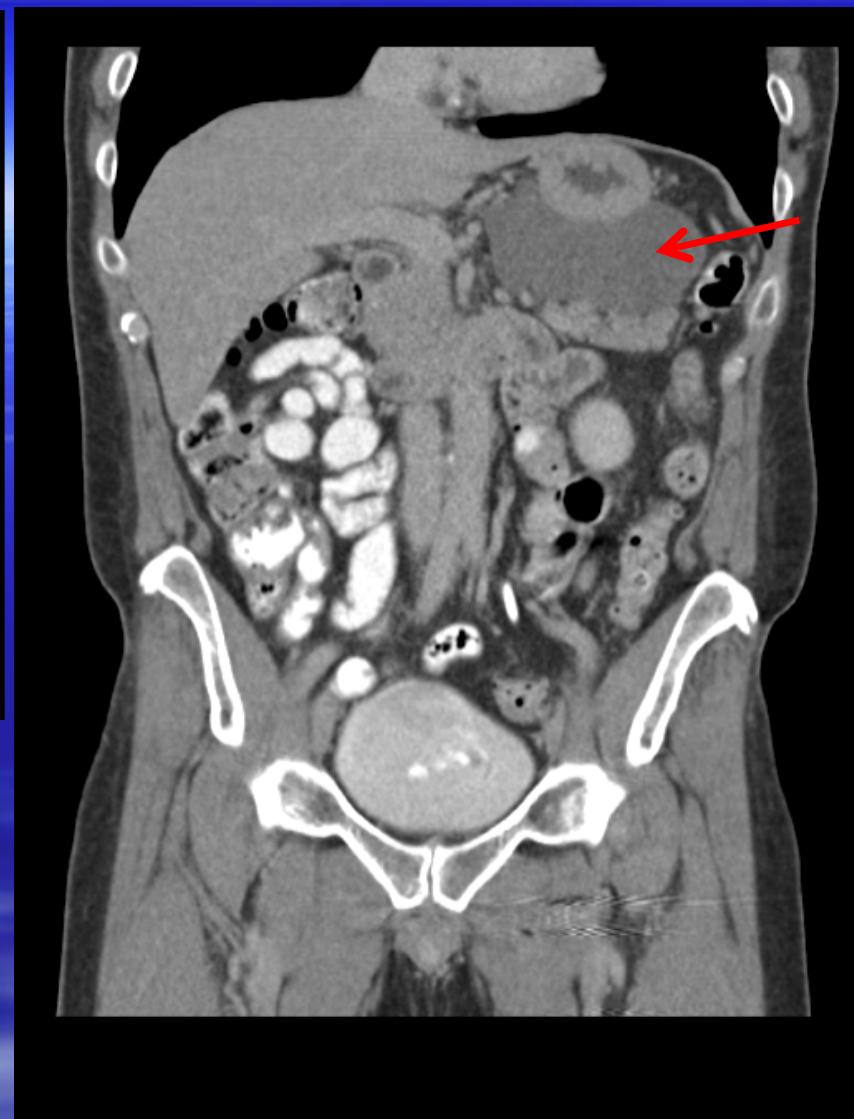
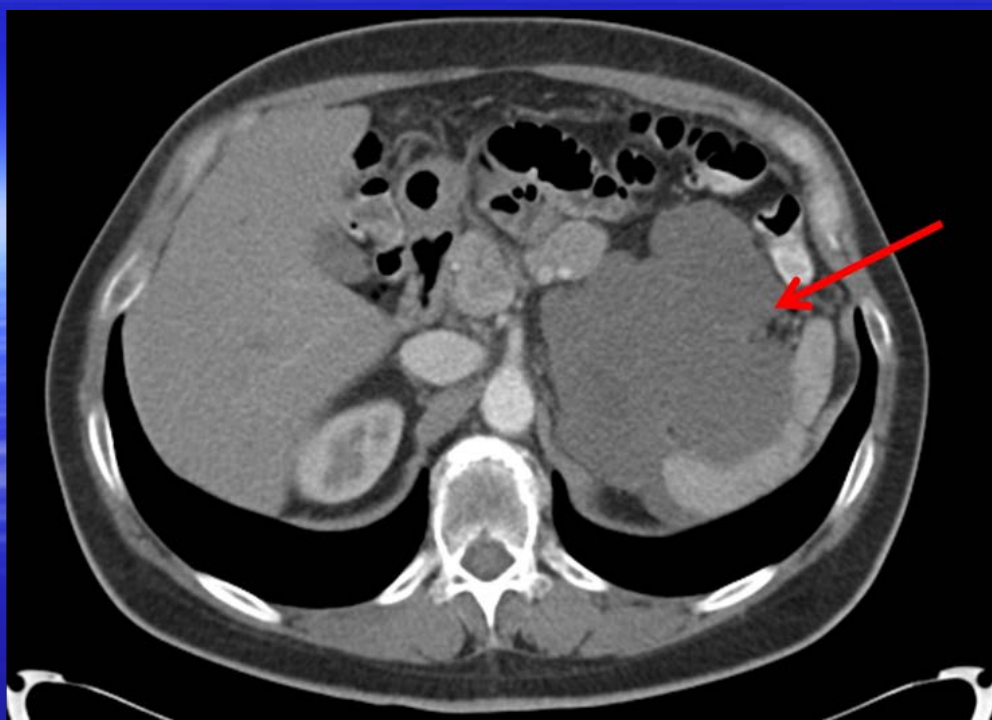
Difficult, or Inoperable ?

Stomach, Pancreas, Spleen, Adrenal, Diaphragm



**GIST arising from the back
of the stomach-prolonged
imatinib**



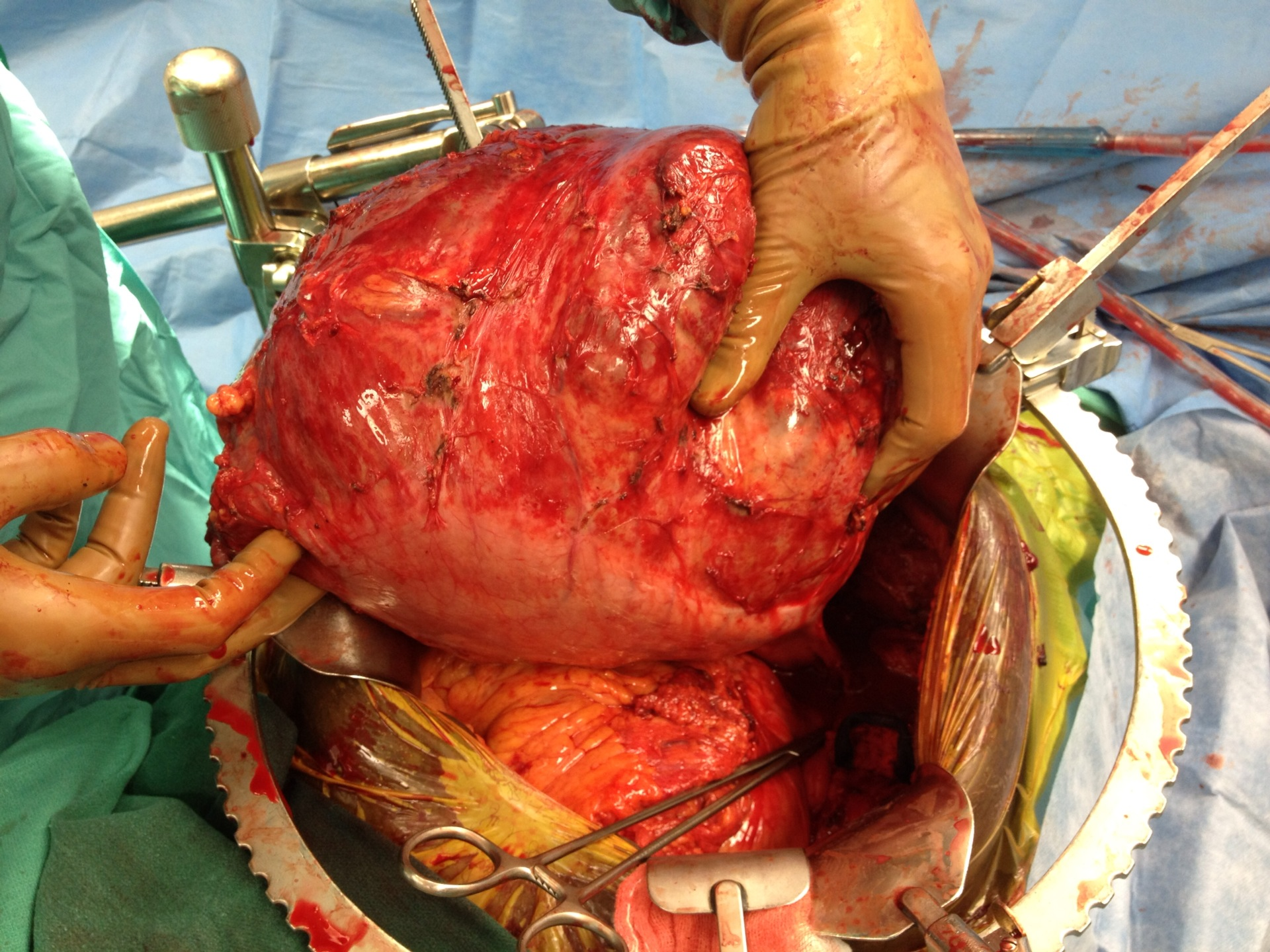


**R0 resection-
Partial gastrectomy,
distal pancreas,
spleen, left adrenal**

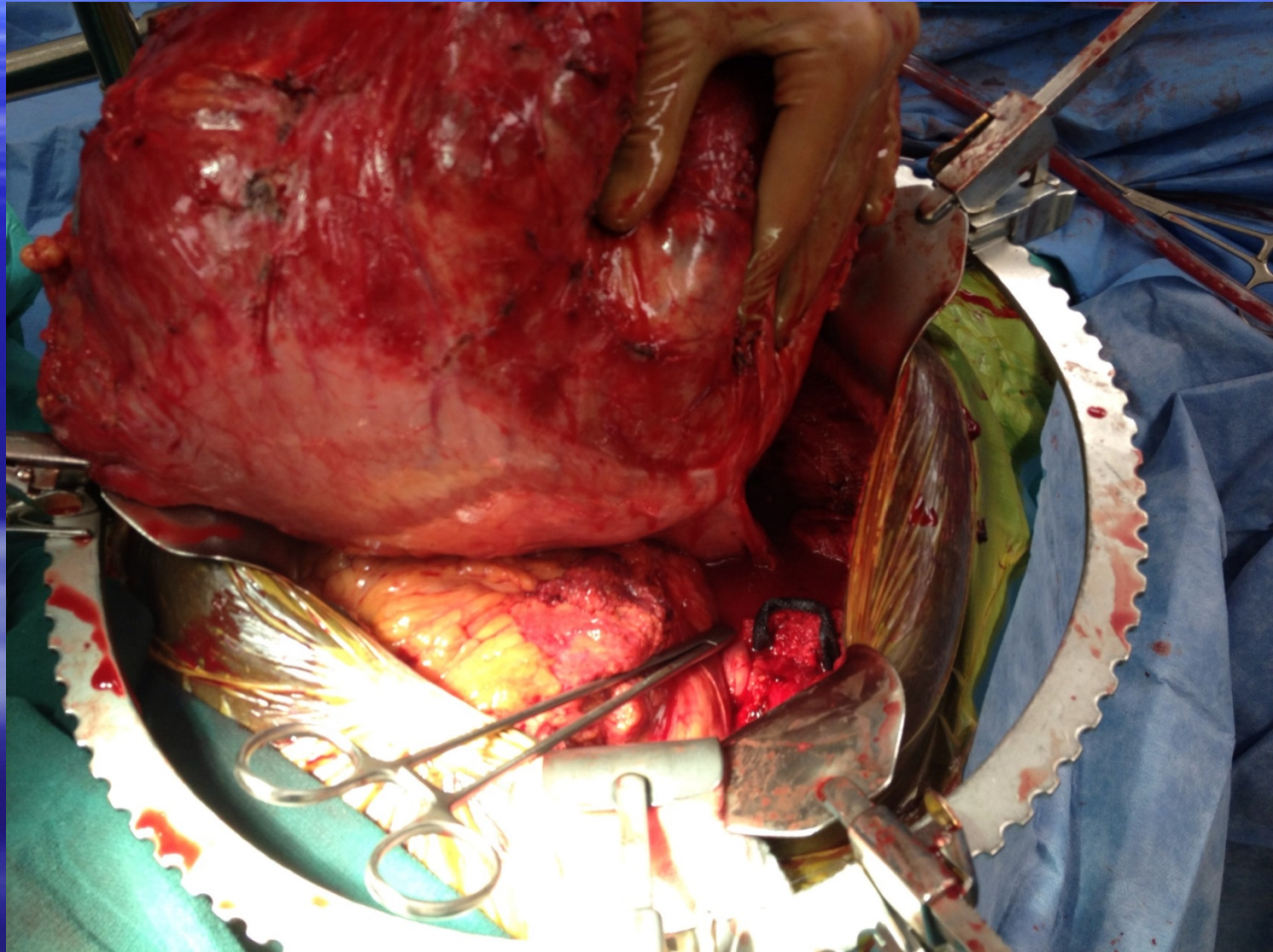
**Stomach, liver, spleen, and
transverse colon**

Eight Months of Imatinib



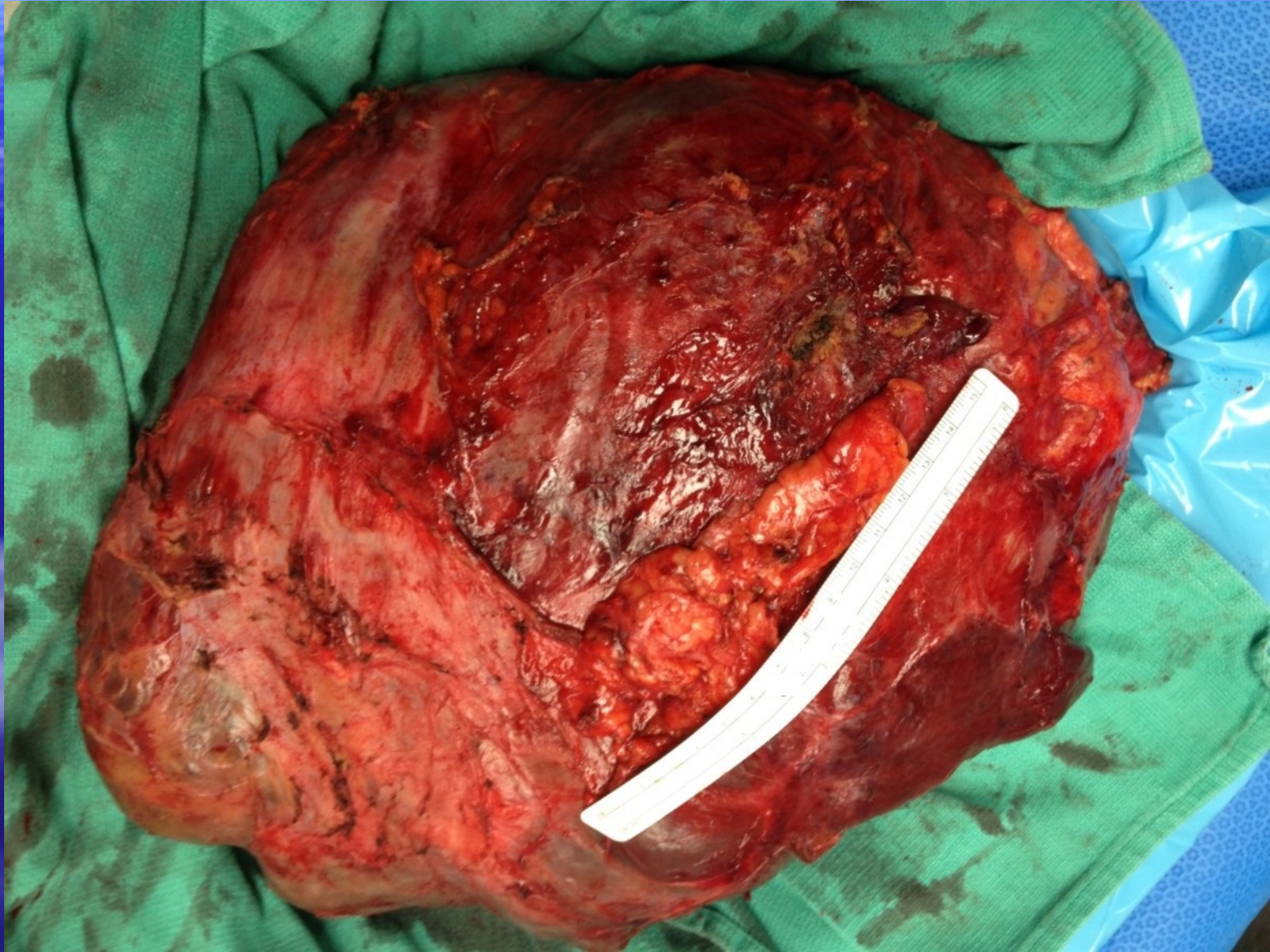


En Bloc Resection of Stomach, Left Lobe of Liver, Colon, Spleen





R0 Resection-indefinite Imatinib



**Obstructed for 8 Months on
Hyperalimentation-Previous
Resections including Right
Hepatic Lobectomy-Flew
down to our Hospital**

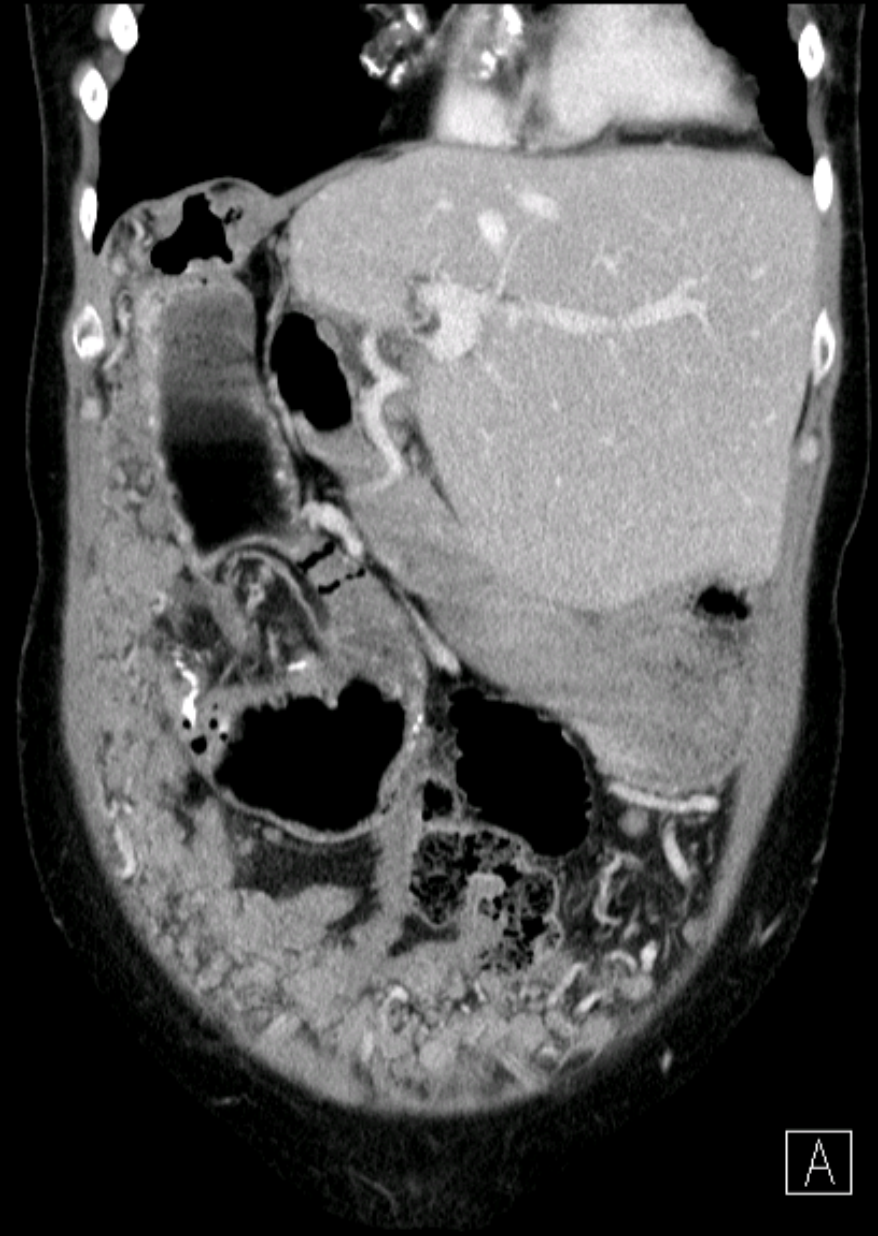
Metastatic GIST but
Non-malignant SBO

Don't give up too soon!

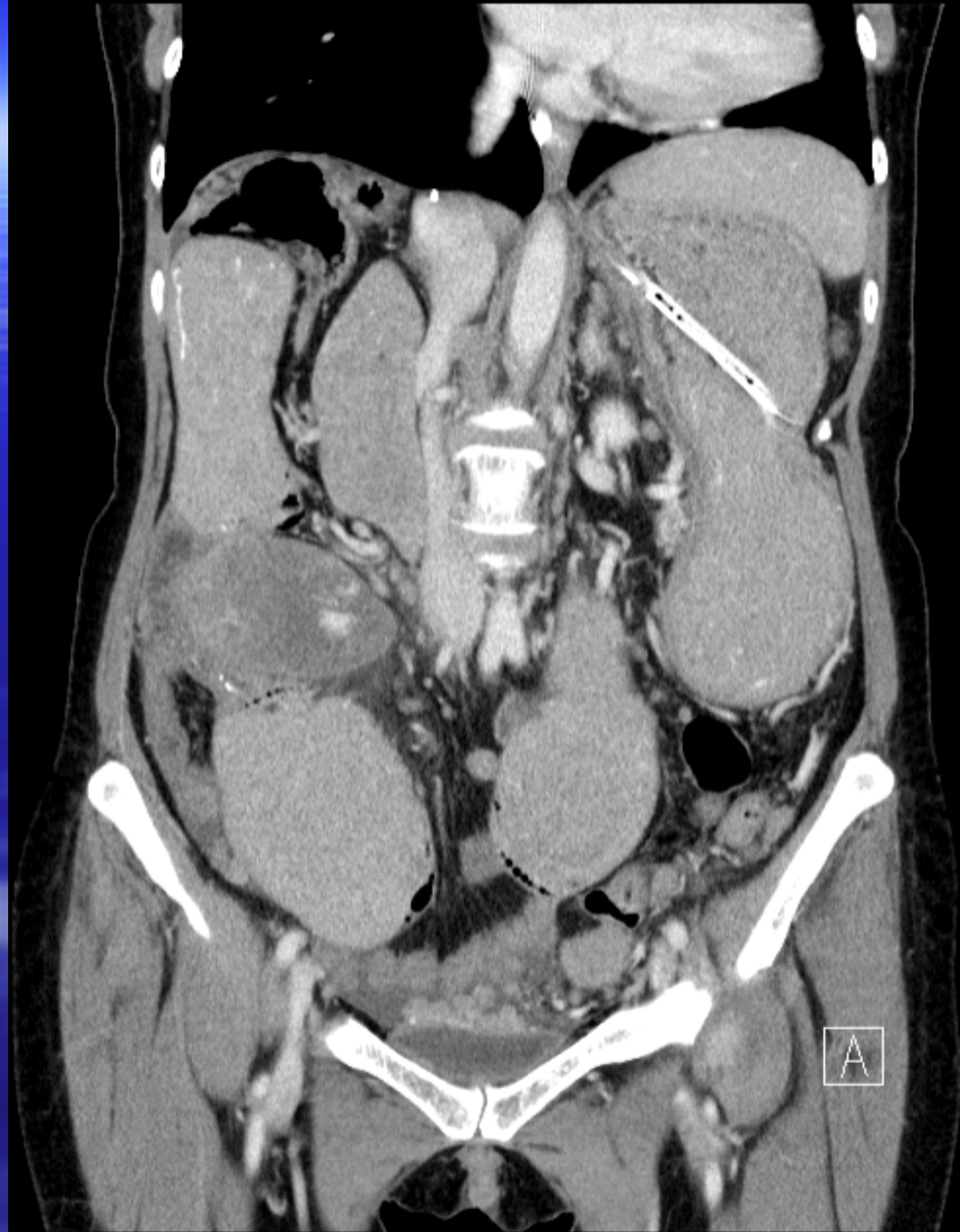
Dilated loop of Small Bowel

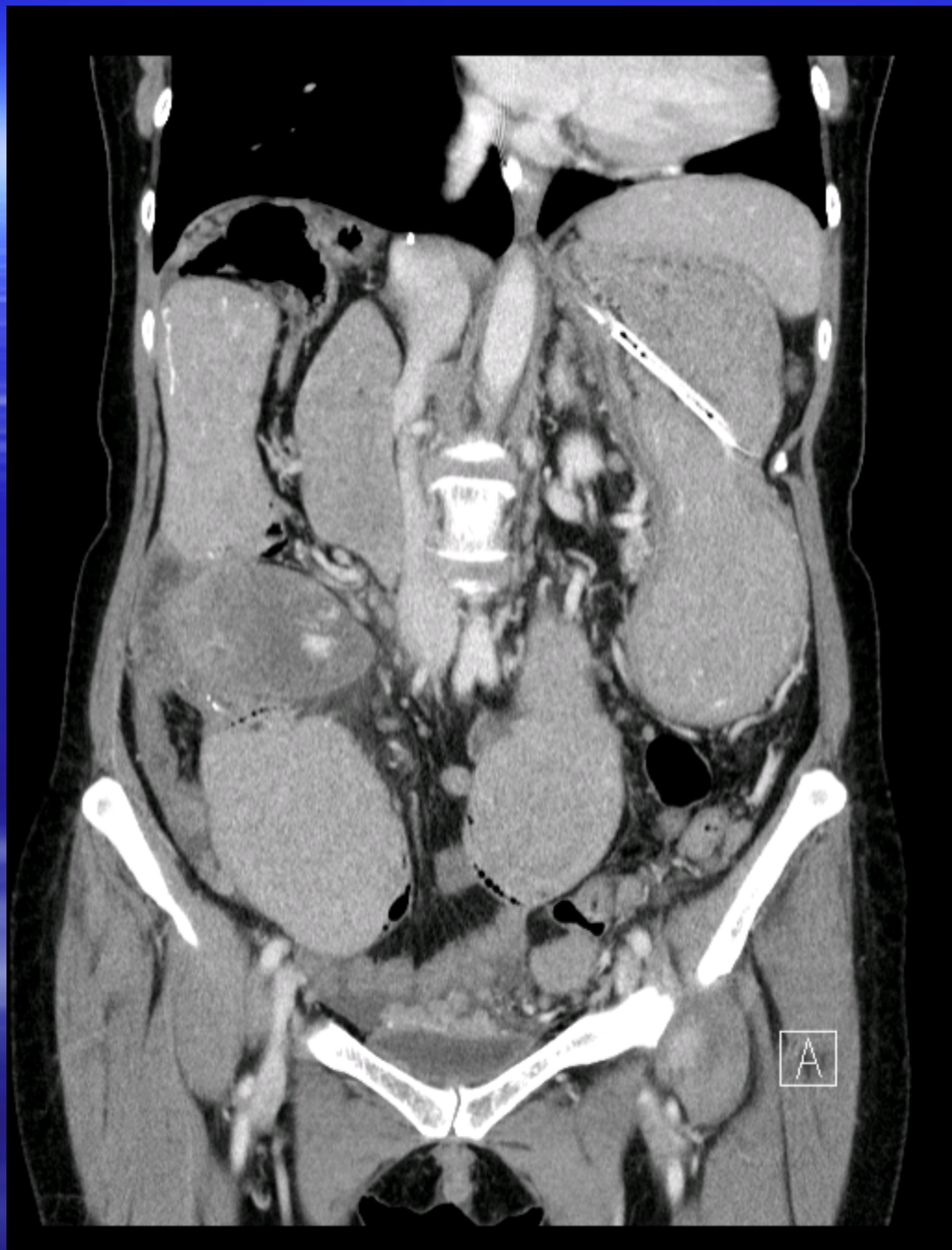


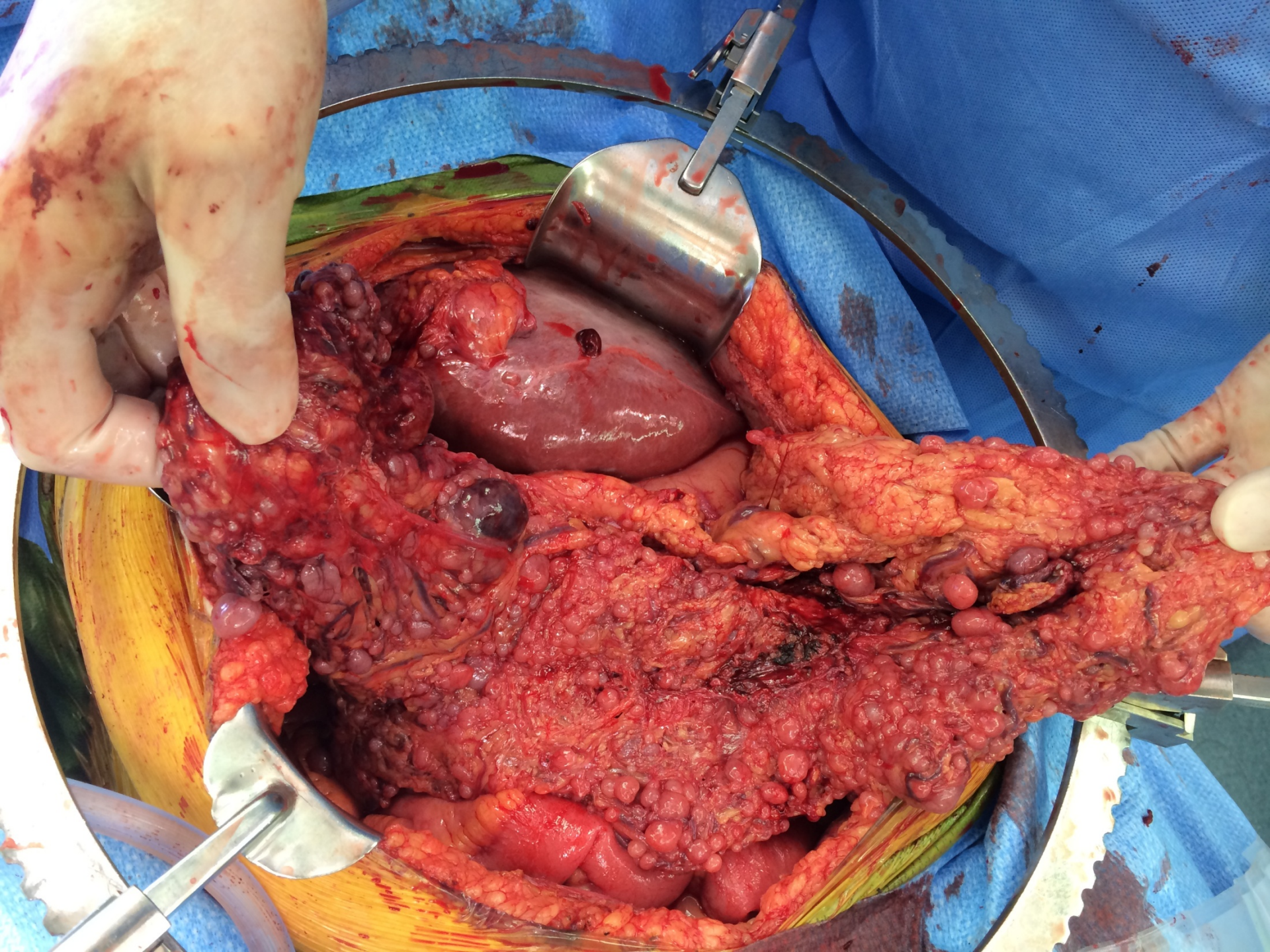
**Dilated jejunum
and collapsed
ileum- no
disease in liver**

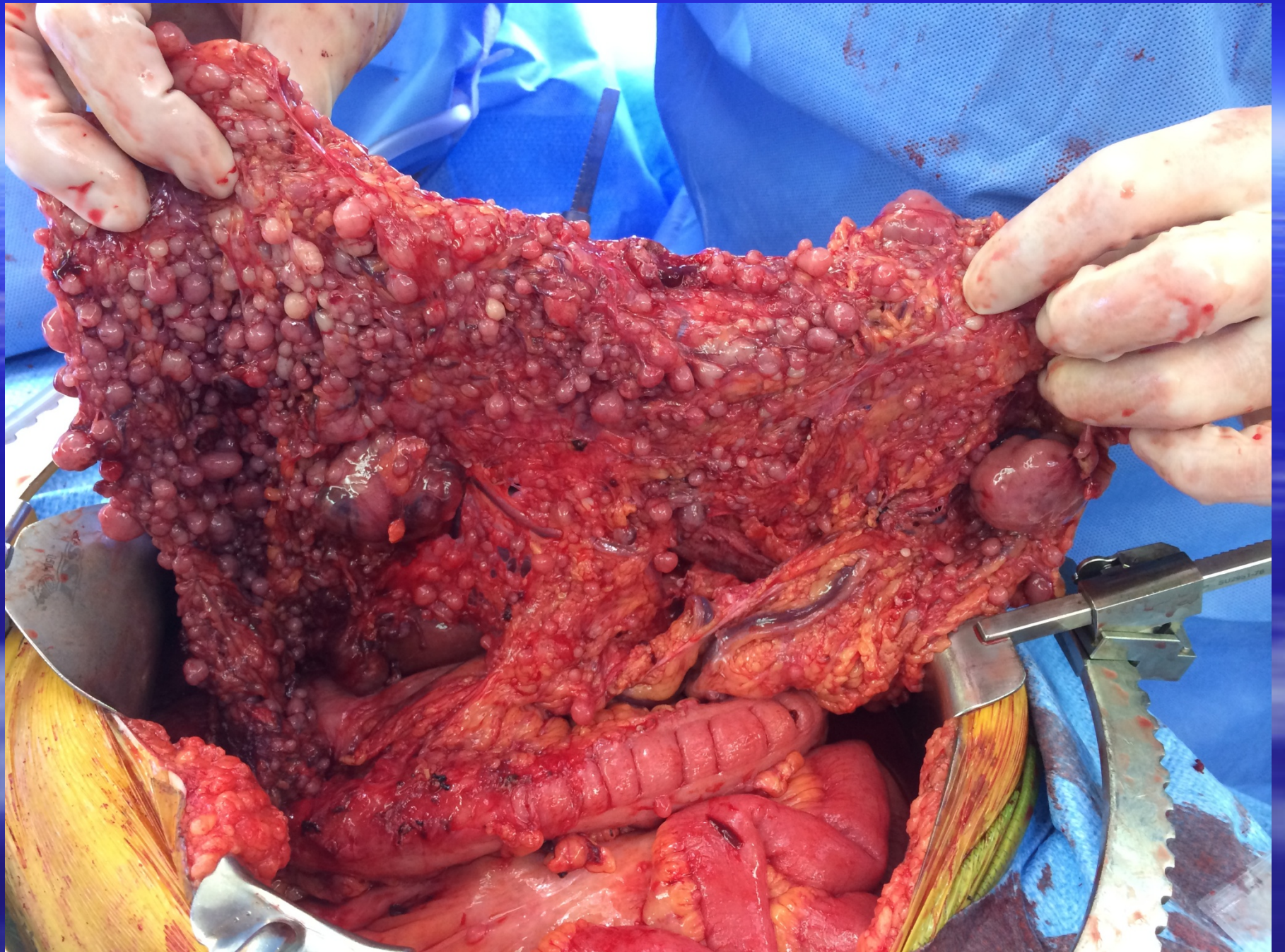


**Contrast in
massively
dilated jejunum
with 'hungry'
distal bowel**









**Omentectomy and R2
debulking-obstruction was
due to internal hernia
Indefinite TKIs**

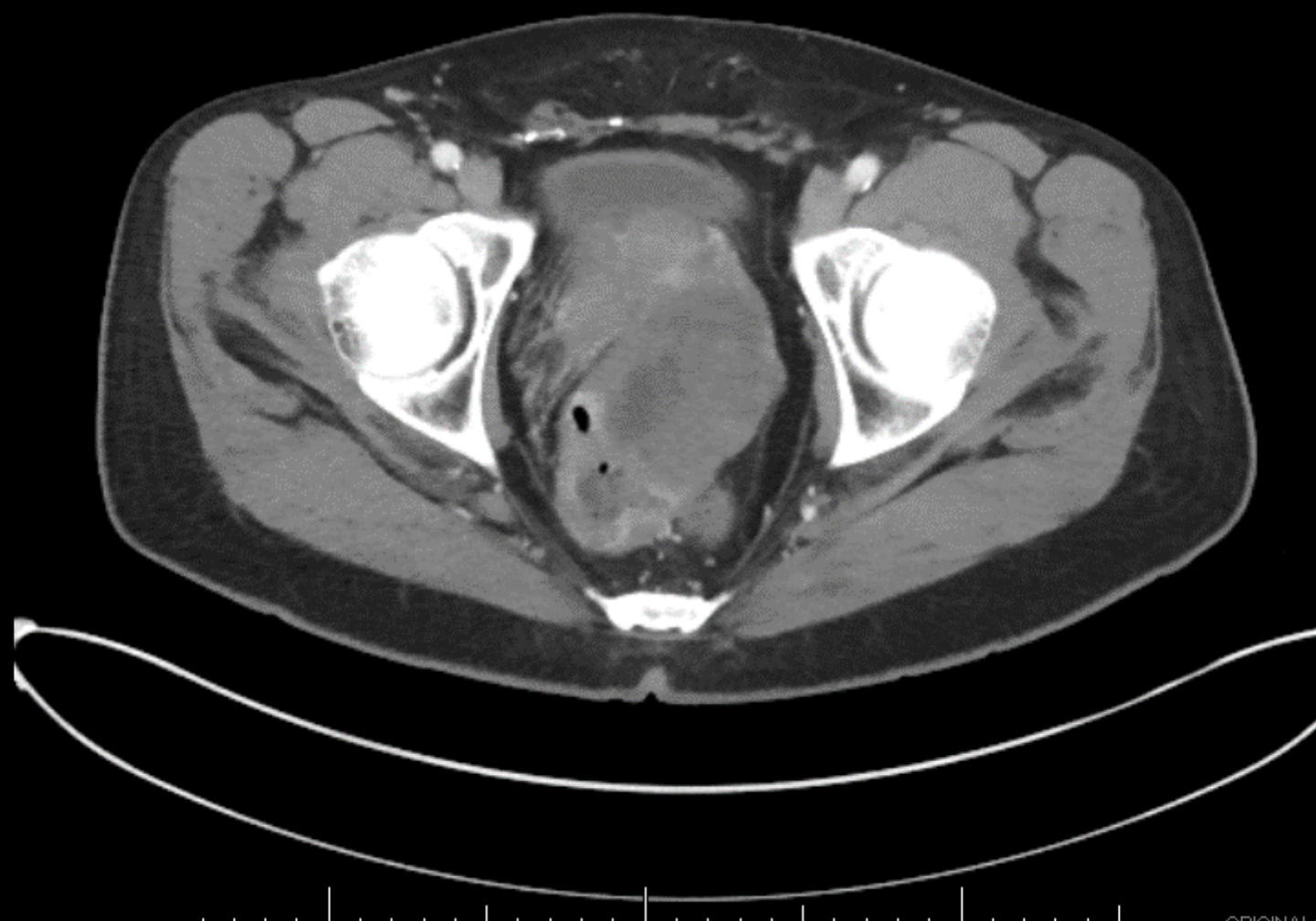
Rectal GISTs

- 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

R



KV 120
Effective mAs 276
Slice Location 22
Series #4
www/wwl 400/40

ORIGINAL/PRIMARY/AXIAL/CT

Abdomen^ONCO_TRIPLE_PHASE_ABD_PELVIS (Adult)
Series Abd/Pelvis 5.0 I31f 3
3/4/2013 10:41:26
5.00 mm
Image #70/87

A

R



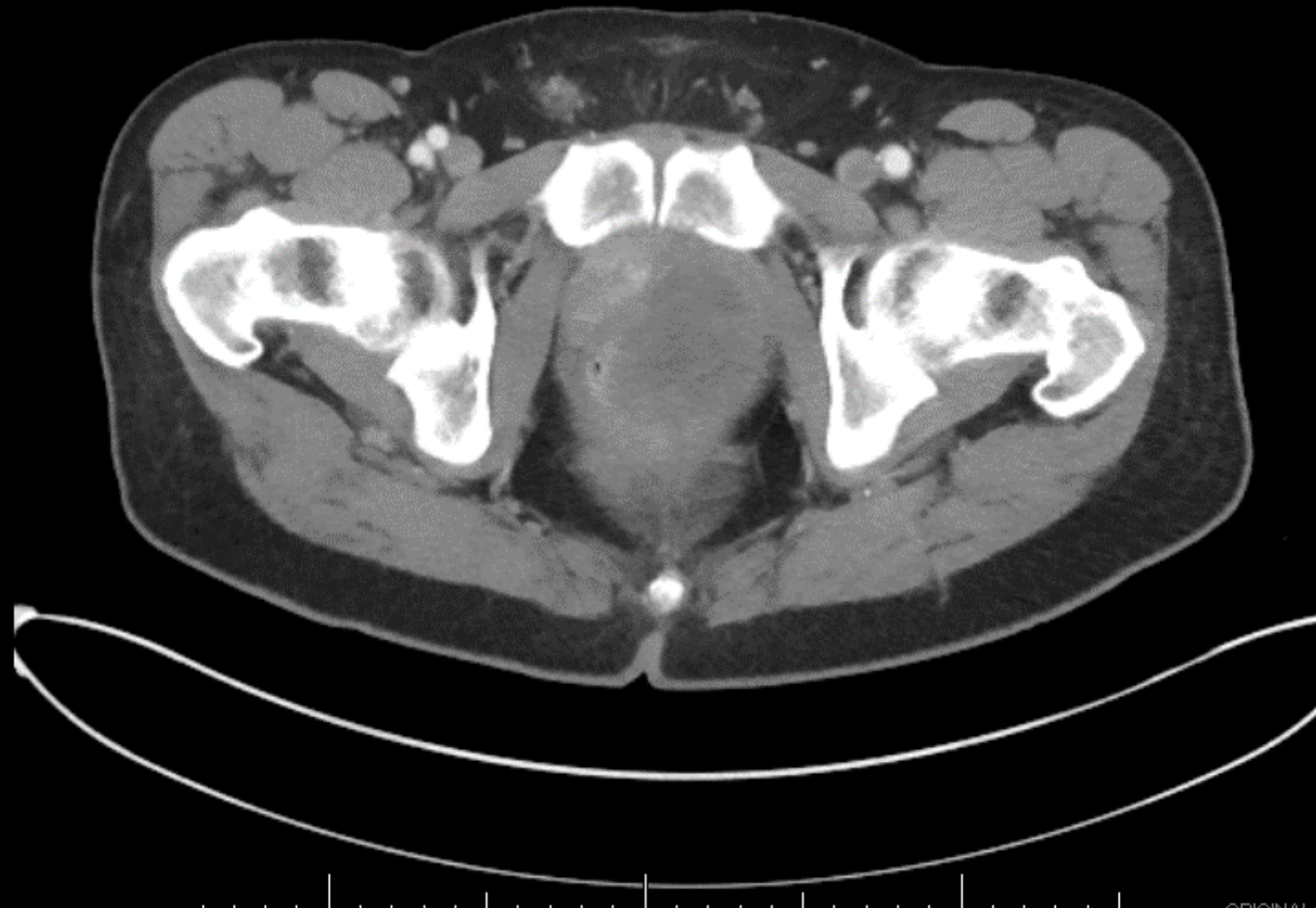
KV 120
Effective mAs 271
Slice Location 7
Series #4
www/wwl 400/40

ORIGINAL/PRIMARY/AXIAL/CT

Abdomen^ONCO_TRIPLE_PHASE_ABD_PELVIS (Adult)
Series Abd/Pelvis 5.0 I31f 3
3/4/2013 10:41:26
5.00 mm
Image #72/87

A

R



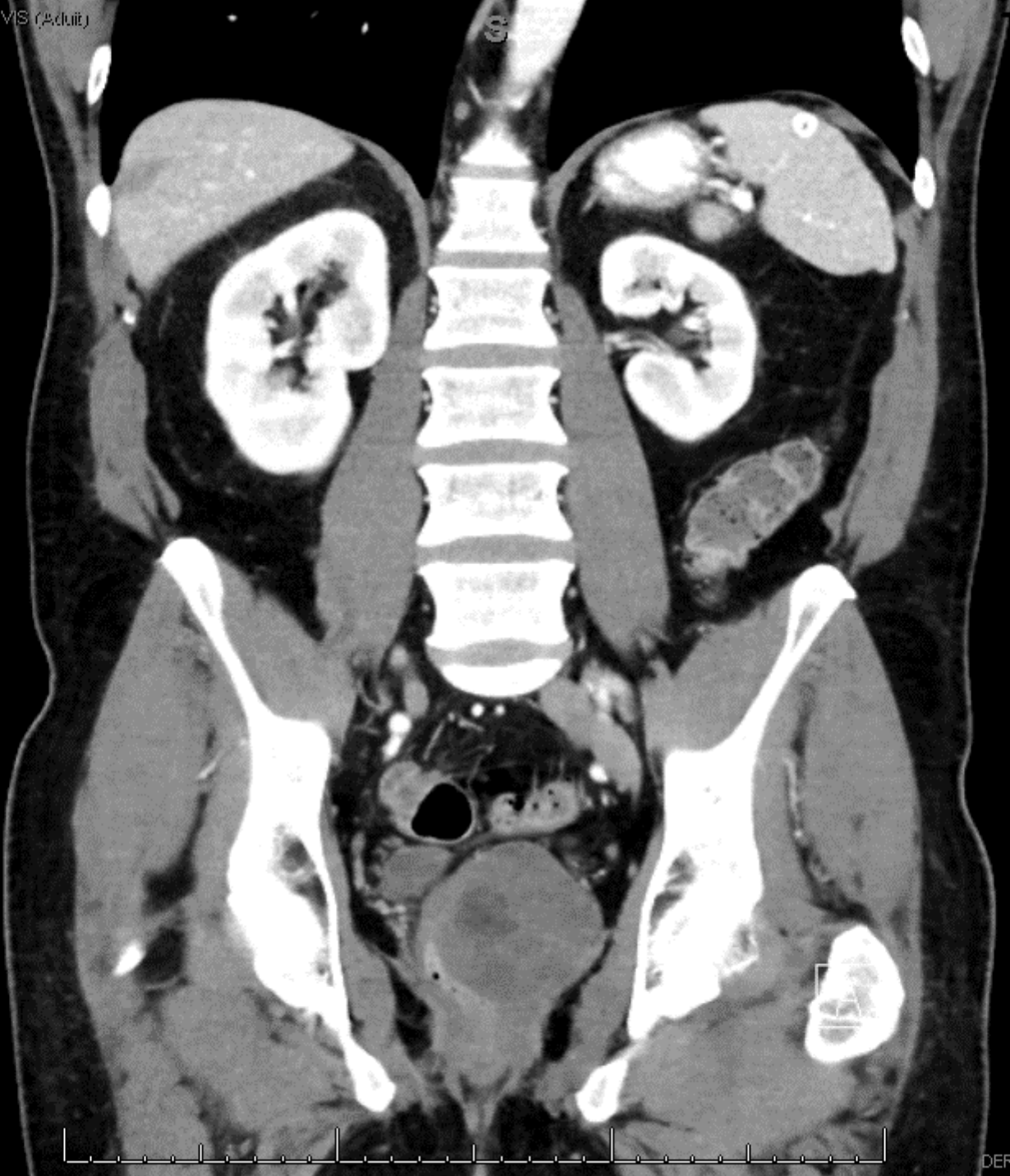
KV 120
Effective mAs 268
Slice Location -3
Series #4
www/wwl 400/40

ORIGINAL/PRIMARY/AXIAL/CT

Abdomen^ONCO_TRIPLE_PHASE_ABD_PELVIS (Avtiit)
Series Abd/Pelvis 3.0 MPR cor
3/4/2013 10:41:26
3.00 mm
Image #56/86

R

KV 120
Effective mAs 236
Slice Location
Series #7
www/wwl 300/40



DERIVED/PRIMARY/AXIAL/CT

Rectal GIST

- Treated with imatinib 10 months, tumor stable, symptoms resolved
- Transrectal US confirmed location of mass, unable to assess invasion prostate
- PET/CT decreased SUV uptake
- Localized to pelvis

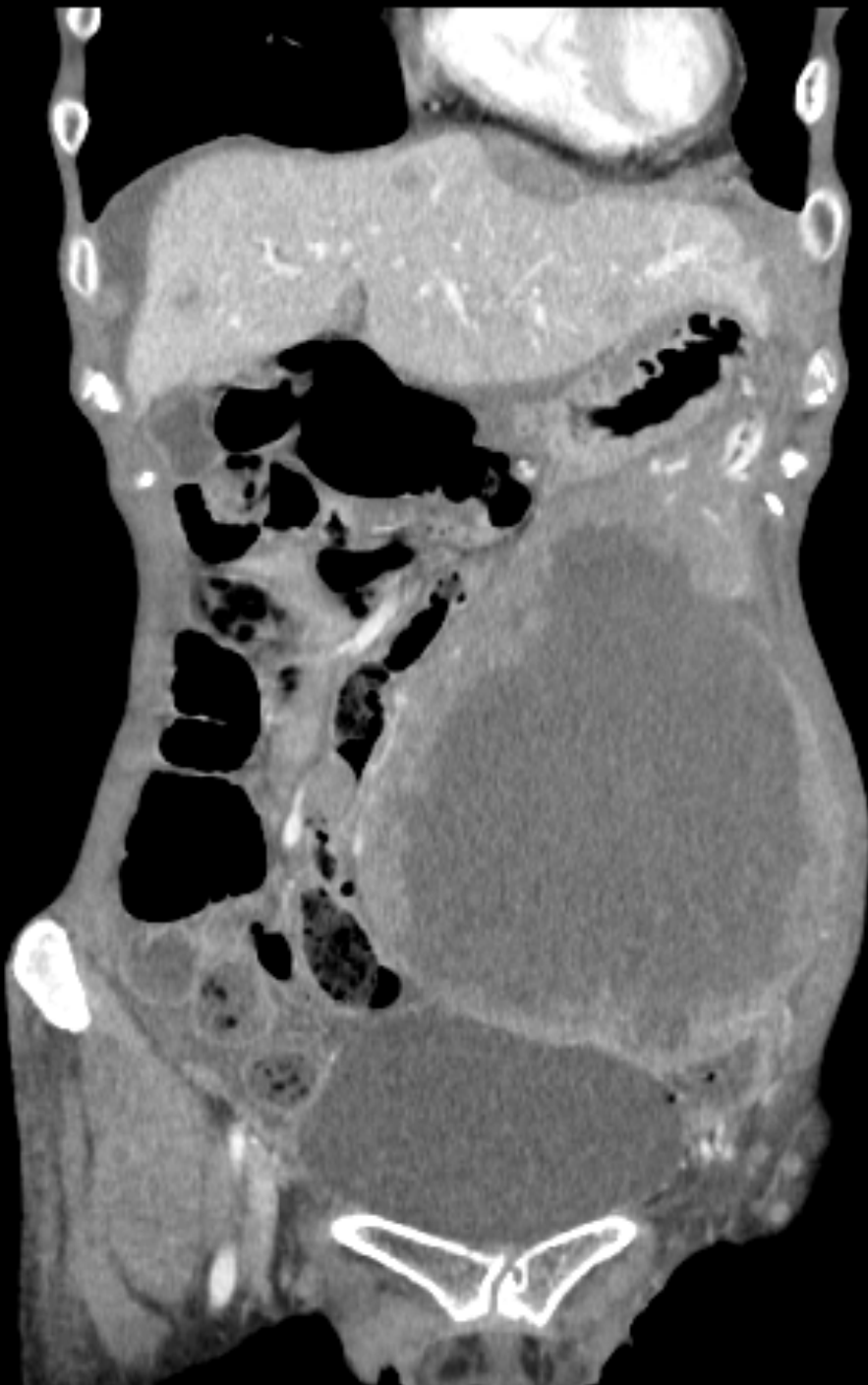
Rectal GIST

- Lower midline incision
- 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?**



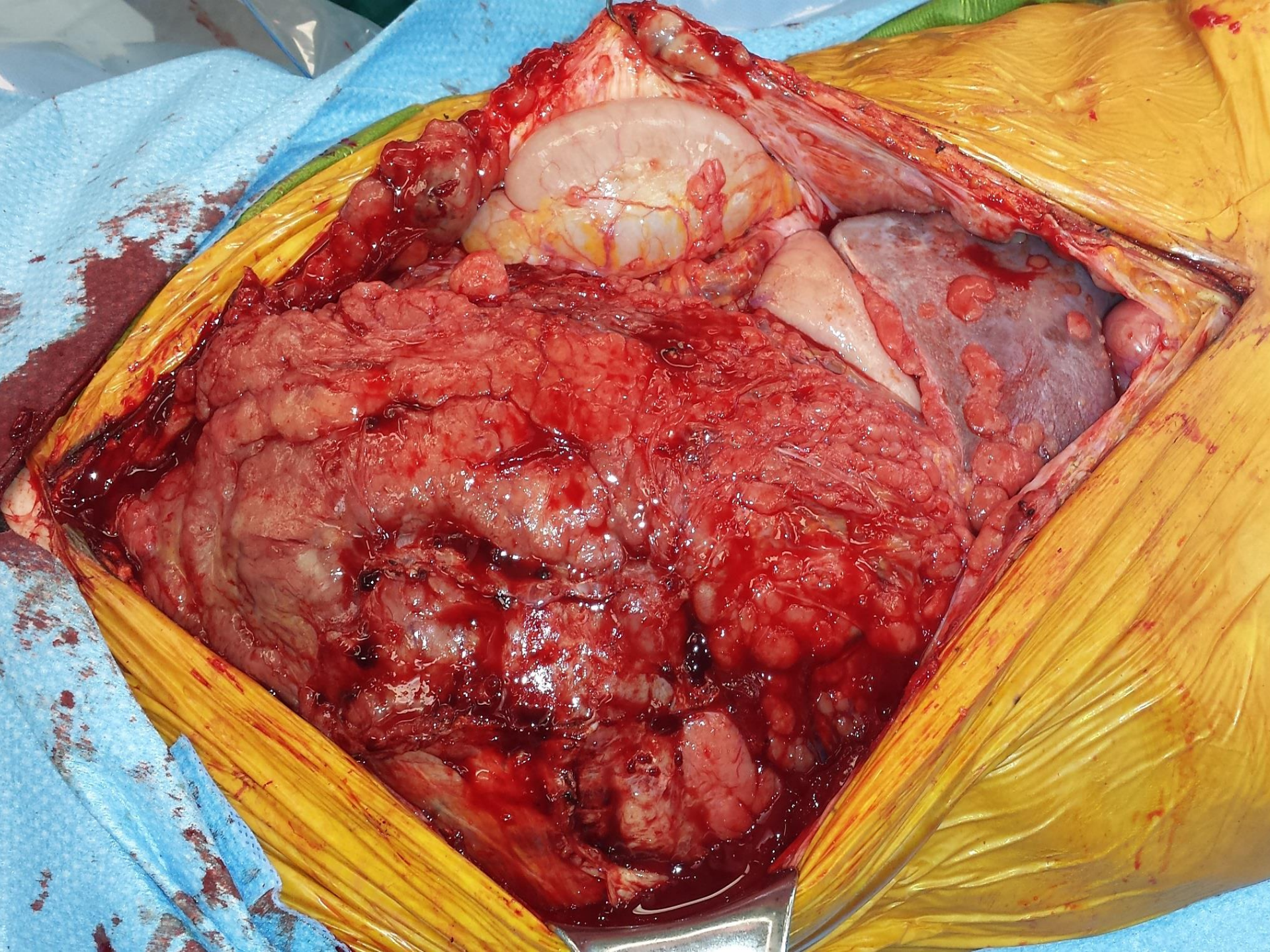






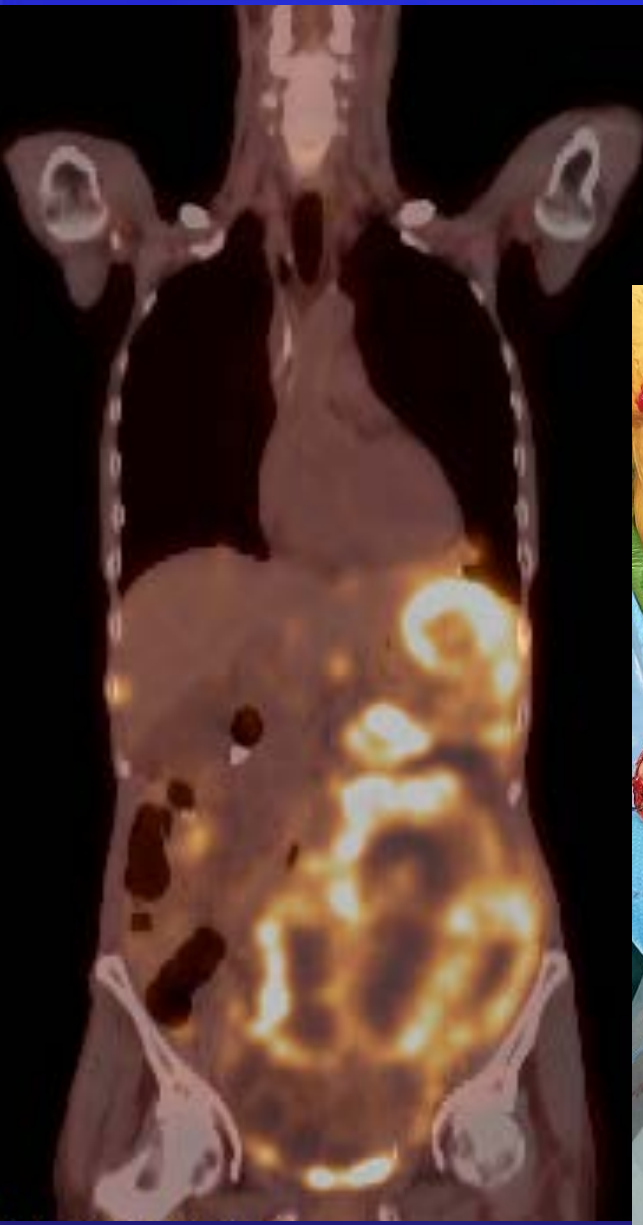








METRES
INCHES
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Devon OR Products & Safety Solutions
1 2 3 4 5 6
Measurement device is not calibrated. Use for approx. measurement only. MADE IN U.S.A.



Slice: 142

Who Should Receive Imatinib?

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

