February 2nd, 2020

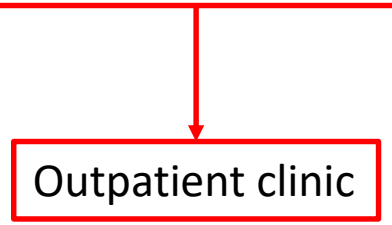
GIST STORIES

ALESSANDRO GRONCHI MD

Case 2

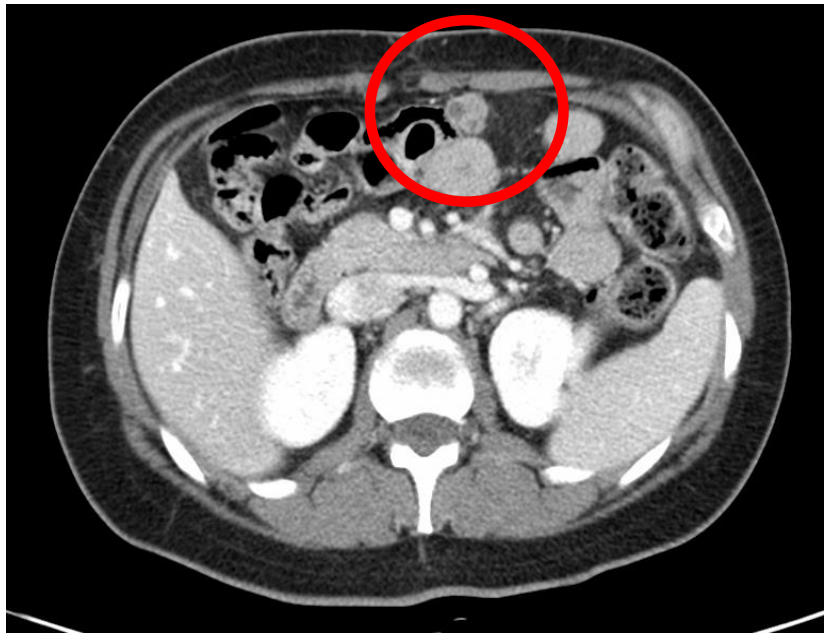
Case 2

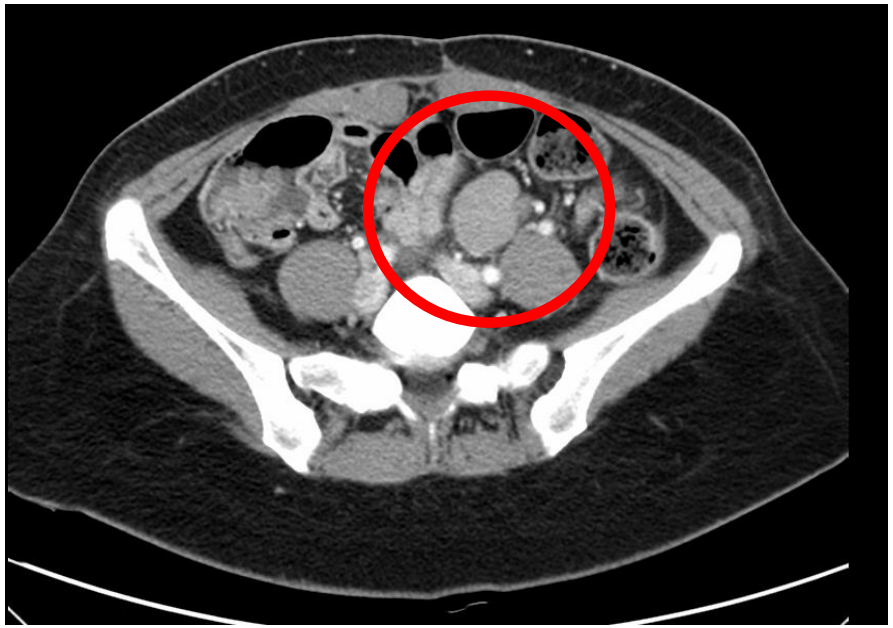
- 47F, ECOG PS 0
- 2011 (elsewhere): primary GIST of the colon treated with surgery (8cm, 80/50HPF, no tumor rupture). Mutation status: KIT and PDGFRA WT. IHC: DOG1 focal +.
- Jun 2011-Dec 2011: postoperative Imatinib 400mg
- Dec 2011: 2 peritoneal nodules (35mm + 22mm)
- Jan 2012-May 2012: Sunitinib, PRO



Case 2

May 2012 (Sunitinib: PRO)





What's next?

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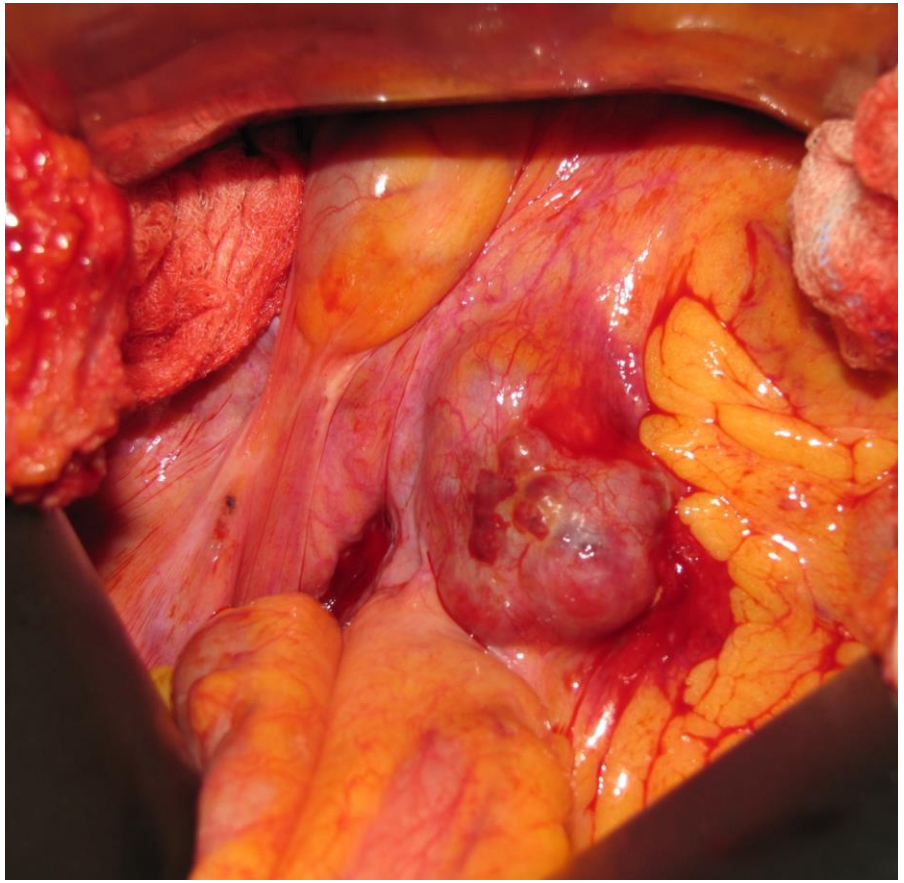
- May 2012: surgery



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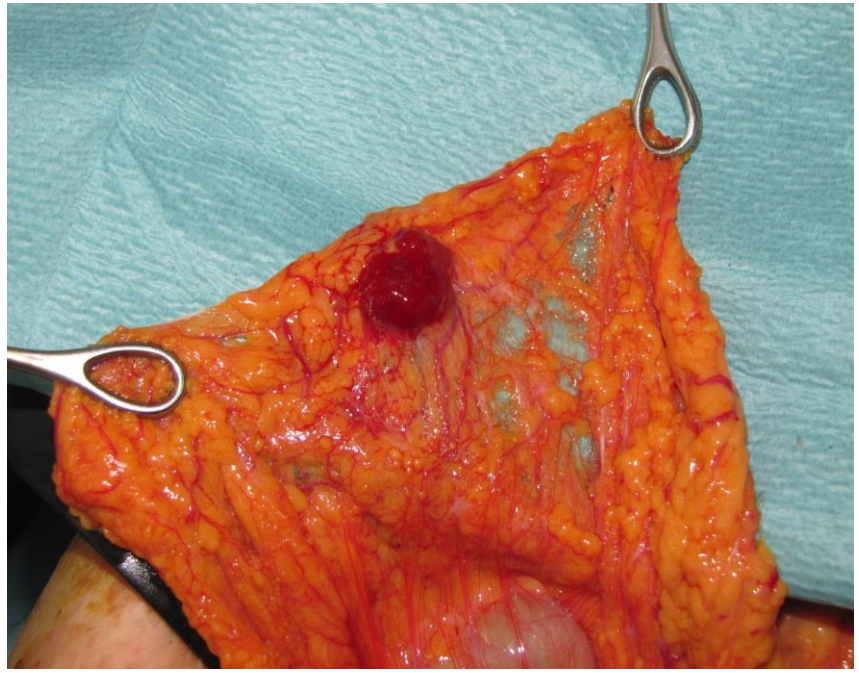

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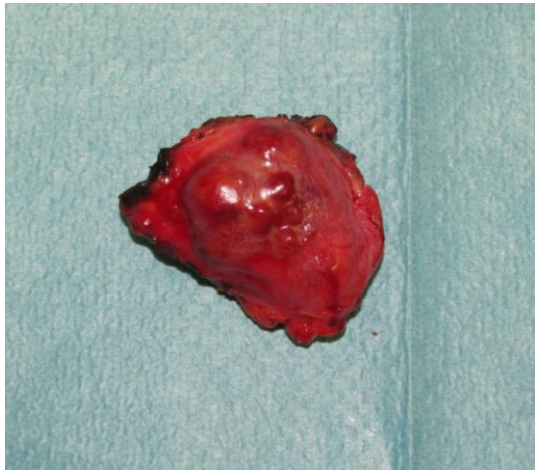
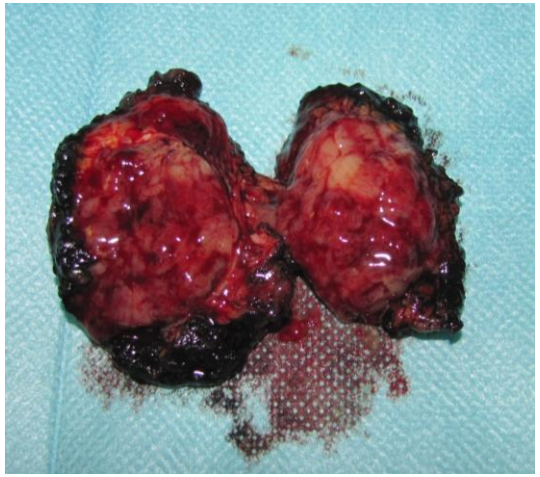
- May 2012: surgery
- Pathology: GIST SDHB+, DOG1-





What's next?

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- Sep 2012: hepatic and peritoneal relapse

What's next?

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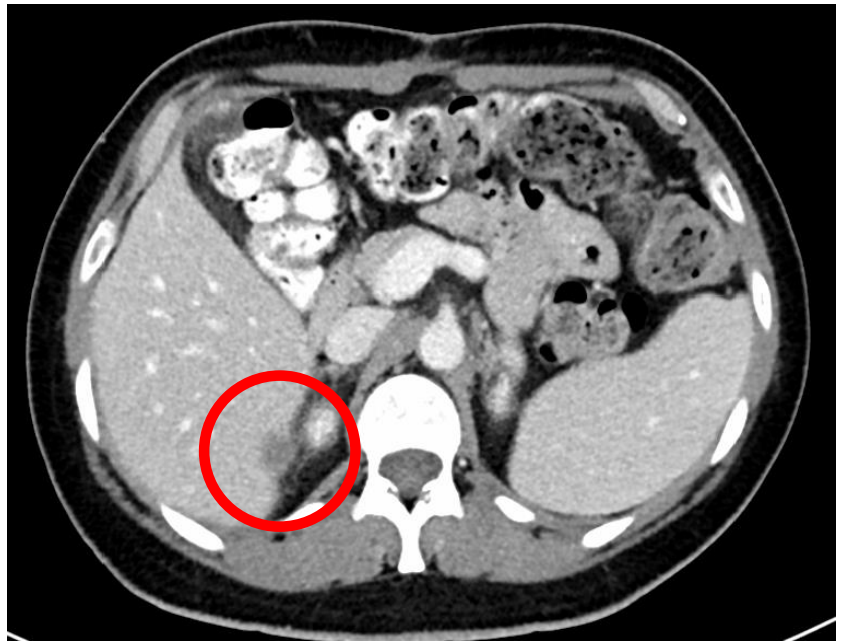
- Dec 2011: 2 peritoneal nodules (35mm + 22mm)
- Jan 2012-May 2012: Sunitinib, PRO
- May 2012: surgery
- Pathology: GIST SDHB+, DOG1-
- Sep 2012: hepatic and peritoneal relapse

Regorafenib 120mg
24 months: PR

Case 2

- Aug 2014: spontaneous bowel perforation → emergency surgery elsewhere
- Sep 2014: back to Regorafenib
- Dec 2014: SD

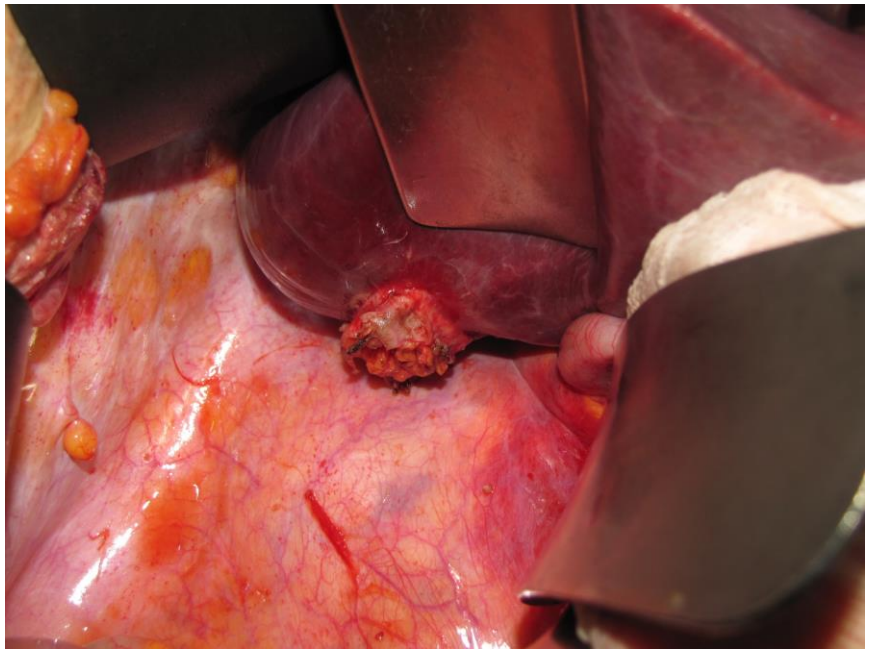
Dec 2014



What's next?

Case 2

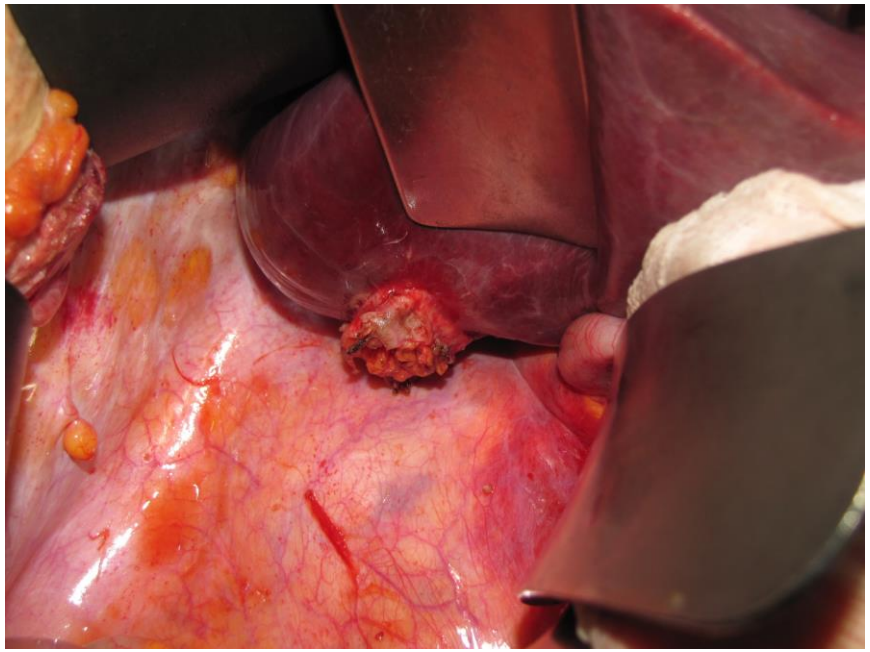
- Aug 2014: spontaneous bowel perforation → emergency surgery elsewhere
- Sep 2014: back to Regorafenib
- Dec 2014: SD
- Jan 2015: surgery (liver metastasectomy).
  Pathology: residual viable tumor <1%, 3cm, R0.



What's next?

Case 2

- Aug 2014: spontaneous bowel perforation → emergency surgery elsewhere
- Sep 2014: back to Regorafenib
- Dec 2014: SD
- Jan 2015: surgery (liver metastasectomy).
  Pathology: residual viable tumor <1%, 3cm, R0.
- Feb 2015: back to Regorafenib
- Dec 2019: NED



Clinical Cancer Research

Quadruple-Negative GIST Is a Sentinel for Unrecognized Neurofibromatosis Type 1 Syndrome

Daniela Gasparotto[1], Sabrina Rossi[2], Maurizio Polano[1], Elena Tamborini[3], Erica Lorenzetto[1], Marta Sbaraglia[2], Alessia Mondello[1], Marco Massani[4], Stefano Lamon[5], Raffaella Bracci[6], Alessandra Mandolesi[6], Elisabetta Frate[7], Franco Stanzial[8], Jerin Agaj[9], Guido Mazzoleni[10], Silvana Pilotti[3], Alessandro Gronchi[11], Angelo Paolo Dei Tos[2], and Roberta Maestro[1]

Abstract

Purpose: The majority of gastrointestinal stromal tumors (GIST) are driven by *KIT*, *PDGFRA*, or, less commonly, *BRAF* mutations, and *SDH* gene inactivation is involved in a limited fraction of gastric lesions. However, about 10% of GISTs are devoid of any of such alterations and are poorly responsive to standard treatments. This study aims to shed light on the molecular drivers of quadruple-negative GISTs.

Experimental Design: Twenty-two sporadic quadruple-negative GISTs with no prior association with Neurofibromatosis Type 1 syndrome were molecularly profiled for a panel of genes belonging to tyrosine kinase pathways or previously implicated in GISTs. For comparison purposes, 24 GISTs carrying *KIT*, *PDGFRA*, or *SDH* gene mutations were also analyzed. Molecular findings were correlated to clinicopathologic features.

Results: Most quadruple-negative GISTs featured intestinal localization, with a female predilection. About 60% (13/22) of quadruple-negative tumors carried *NF1* pathogenic mutations, often associated with biallelic inactivation. The analysis of normal tissues, available in 11 cases, indicated the constitutional nature of the *NF1* mutation in 7 of 11 cases, unveiling an unrecognized Neurofibromatosis Type 1 syndromic condition. Multifocality and a multinodular pattern of growth were common findings in *NF1*-mutated quadruple-negative GISTs.

Conclusions: *NF1* gene mutations are frequent in quadruple-negative GISTs and are often constitutional, indicating that a significant fraction of patients with apparently sporadic quadruple-negative GISTs are affected by unrecognized Neurofibromatosis Type 1 syndrome. Hence, a diagnosis of quadruple-negative GIST, especially if multifocal or with a multinodular growth pattern and a nongastric location, should alert the clinician to a possible Neurofibromatosis Type 1 syndromic condition. *Clin Cancer Res; 23(1); 273–82. ©2016 AACR.*

Introduction

Gastrointestinal stromal tumors (GISTs) are the most frequent mesenchymal neoplasm of the digestive tract, with an incidence of around 1.5 per 100,000/year. GISTs are thought to arise from the interstitial Cajal cells and are typically considered to be KIT/PDGFRA-driven tumors (1). In fact, about 85% of sporadic GISTs are characterized by activating mutations of either *KIT* or *PDGFRA* tyrosine kinase receptor genes, which account for their sensitivity to the kinase inhibitor imatinib. *KIT* and *PDGFRA* mutations result in constitutive activation of the RAS–RAF–MAPK pathway. In about 1% of *KIT*/*PDGFRA* wild-type cases, the same pathway is activated as a result of *BRAF* mutations (1, 2), and we have recently reported the involvement of the *ETV6-NTRK3* gene fusion (3). About 15% of sporadic GISTs are devoid of *KIT*/*PDGFRA*/*BRAF* mutations and are sometimes referred to as triple-negative GISTs. Triple-negative GISTs can be observed in the context of rare hereditary syndromes, including succinate dehydrogenase (SDH) protein complex-related syndromes (4), and, although not comprised in the diagnostic criteria, also in the context of Neurofibromatosis Type 1 (NF-Type 1; refs. 5, 6). Recent studies indicate that SDH-deficient GISTs represent about one third of triple-negative GISTs (7). SDH-associated GISTs are typically gastric, often multifocal, and affect young people, especially females (1, 7–9). They frequently arise in the context of the Carney–Stratakis Syndrome (GIST and paraganglioma dyad), characterized by germline inactivating mutations in any of the four genes encoding the SDH complex (*SDHA-D*; refs. 10, 11), or in the Carney Triad (GIST, paraganglioma, chondroma), associated with *SDHC* promoter hypermethylation (12, 13).

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

D. Gasparotto and S. Rossi share first authorship.

A.P. Dei Tos and R. Maestro share last authorship.

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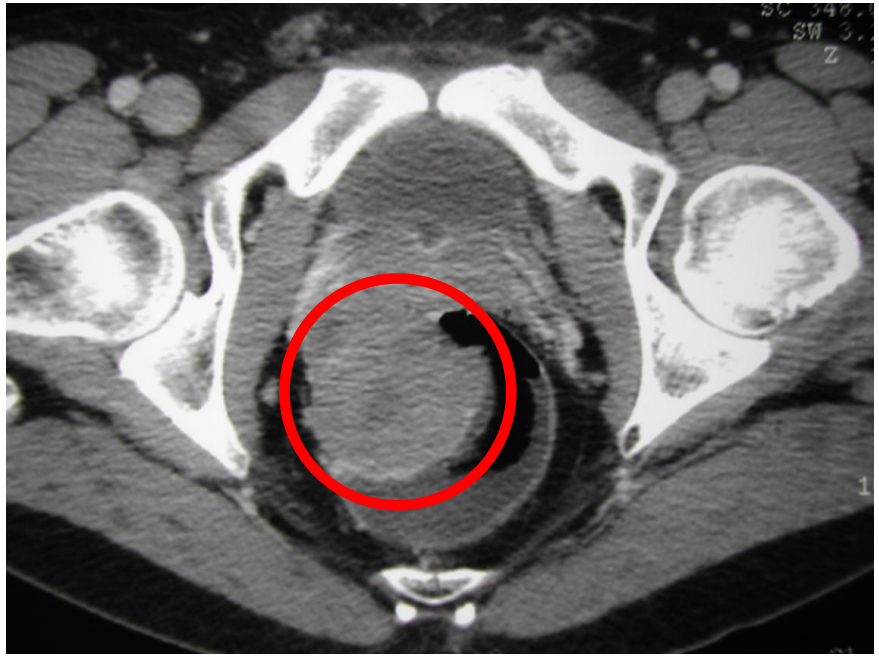
Case 3

Case 3

- 58 M, ECOG PS 0
- Dec 2002: 6 cm rectal mass

- Biopsy
  - GIST
  - *No mutational analysis available*

- CT scan: no distant metastases



What's next?

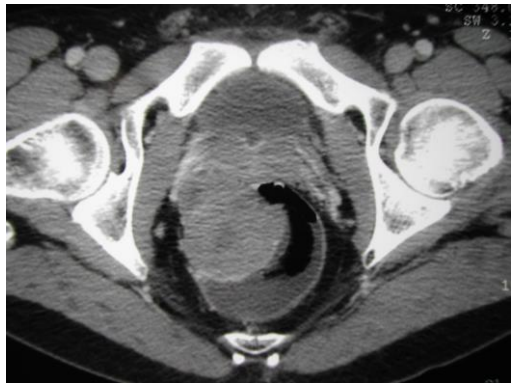
Case 3

- 58 M, ECOG PS 0
- Dec 2002: 6 cm rectal mass

- Biopsy
  - GIST
  - *No mutational analysis available*

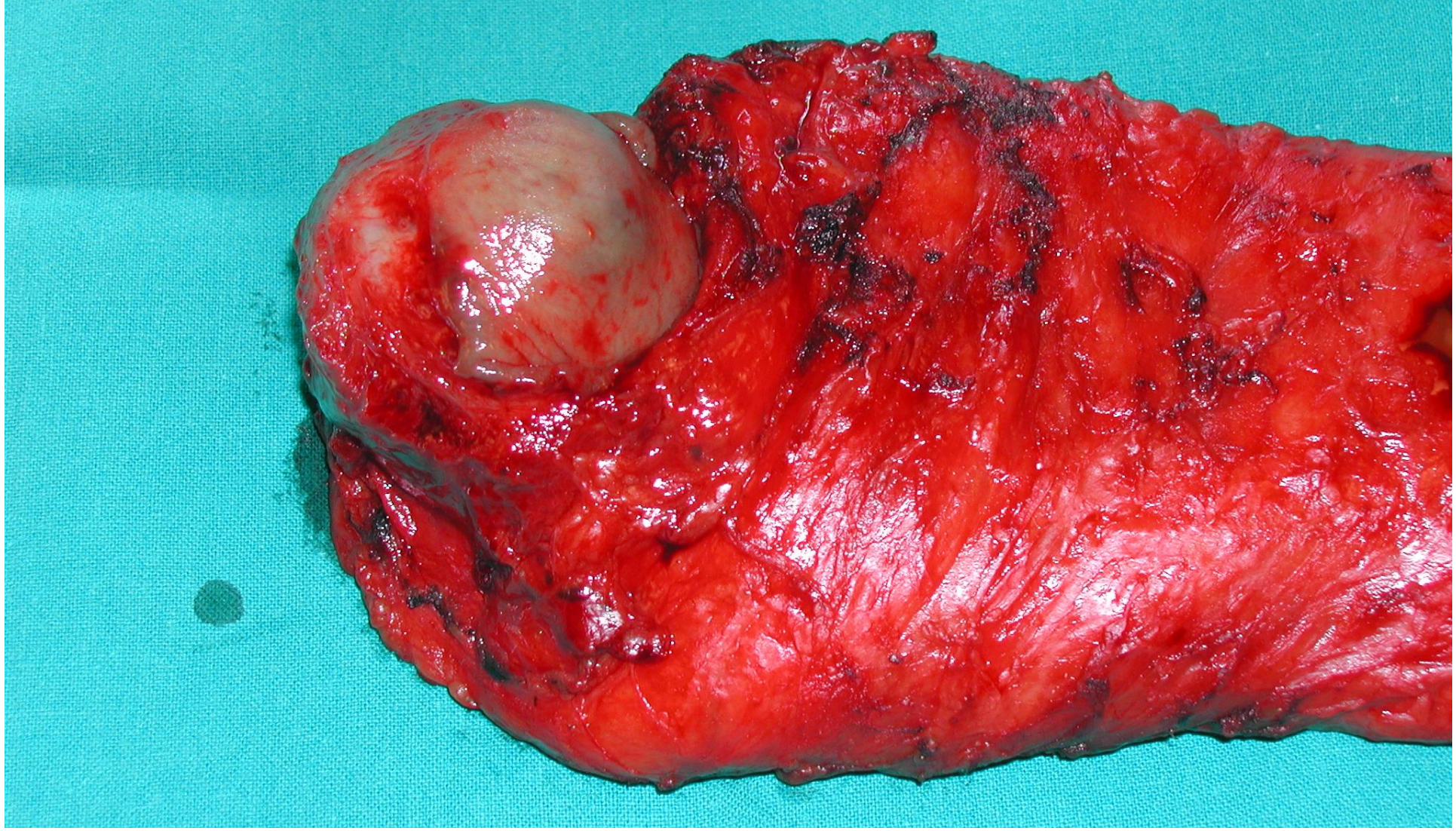
- CT scan: no distant metastases

- Im 400mg 9 months:
  PR (6cm → 4cm)

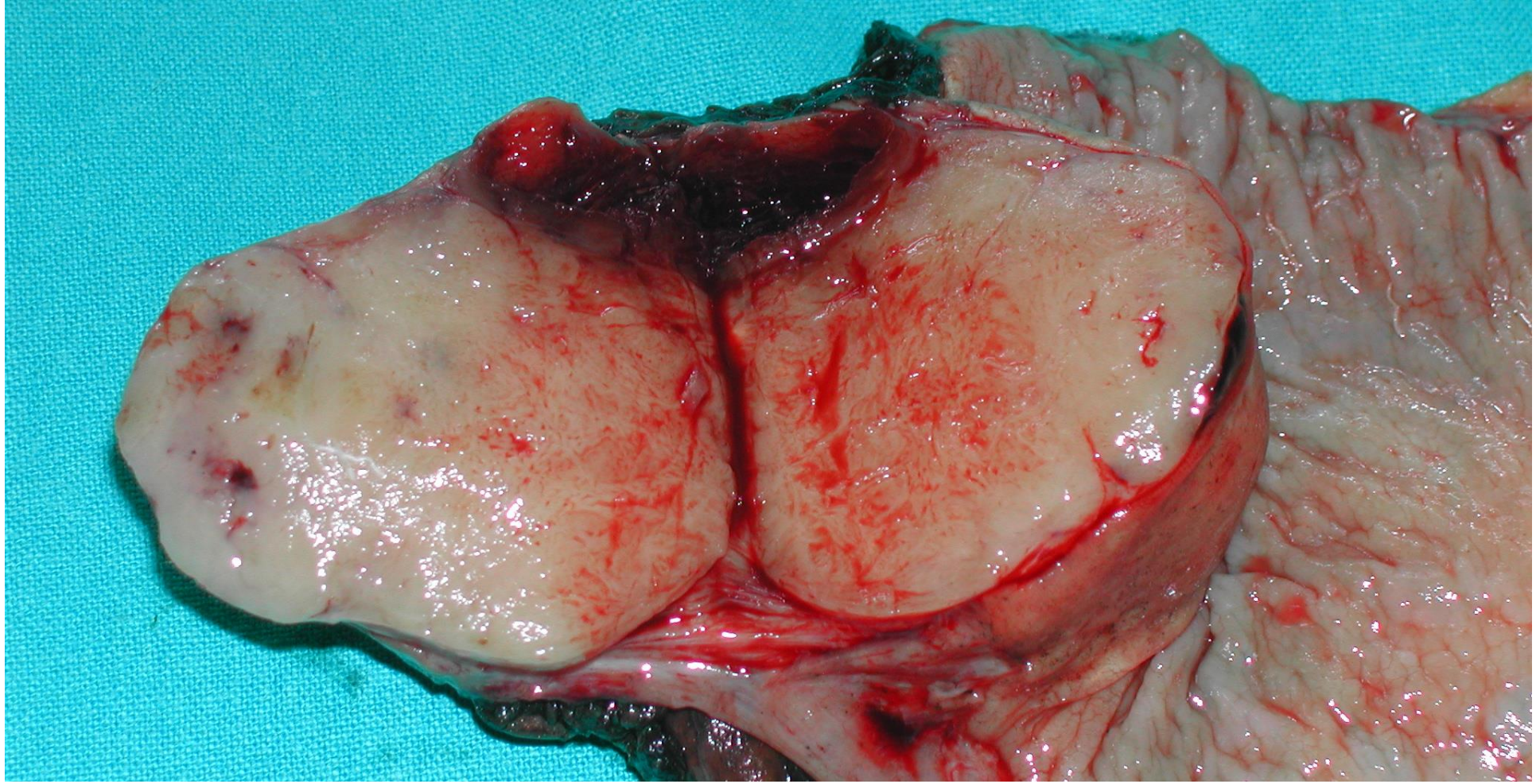


Im 400mg 9 mo

What's next?



Path report: GIST, residual viable tumor 90%



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What's next?

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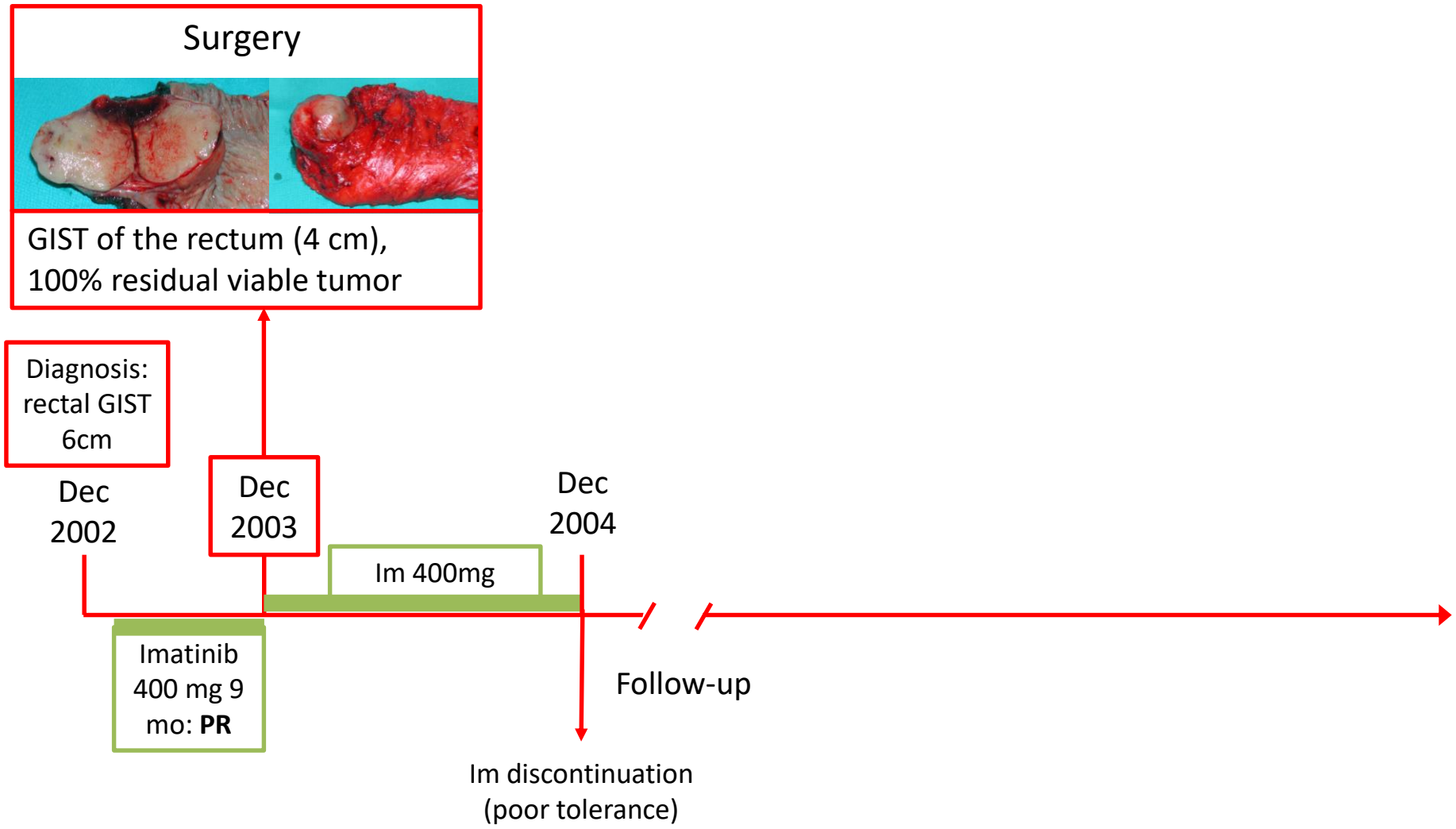
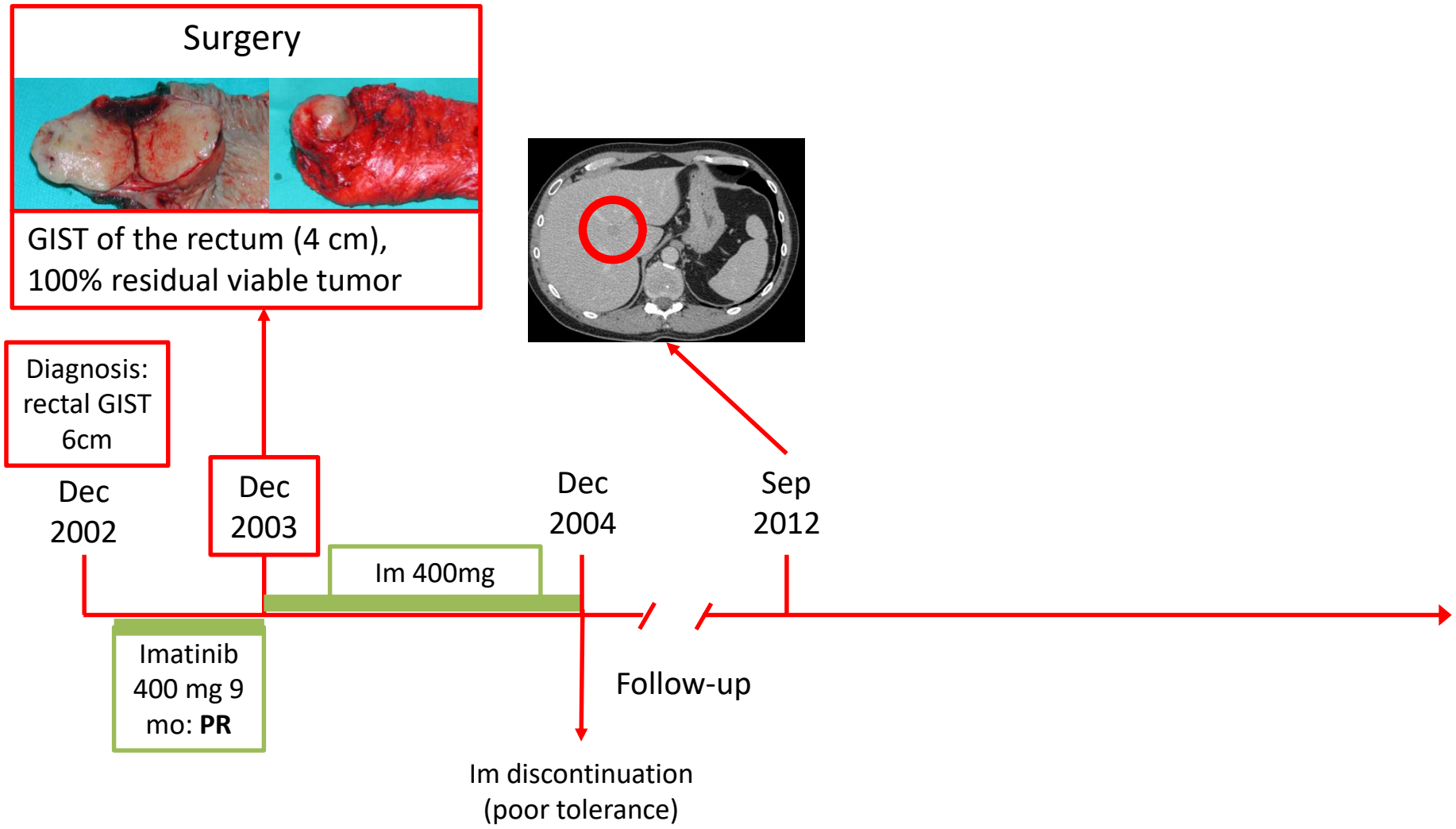

Surgery
GIST of the rectum (4 cm),
100% residual viable tumor
Diagnosis:
rectal GIST
6cm
Dec
2002
Dec
2003
Dec
2004
Im 400mg
Imatinib
400 mg 9
mo: PR
Follow-up
Im discontinuation
(poor tolerance)

Case 3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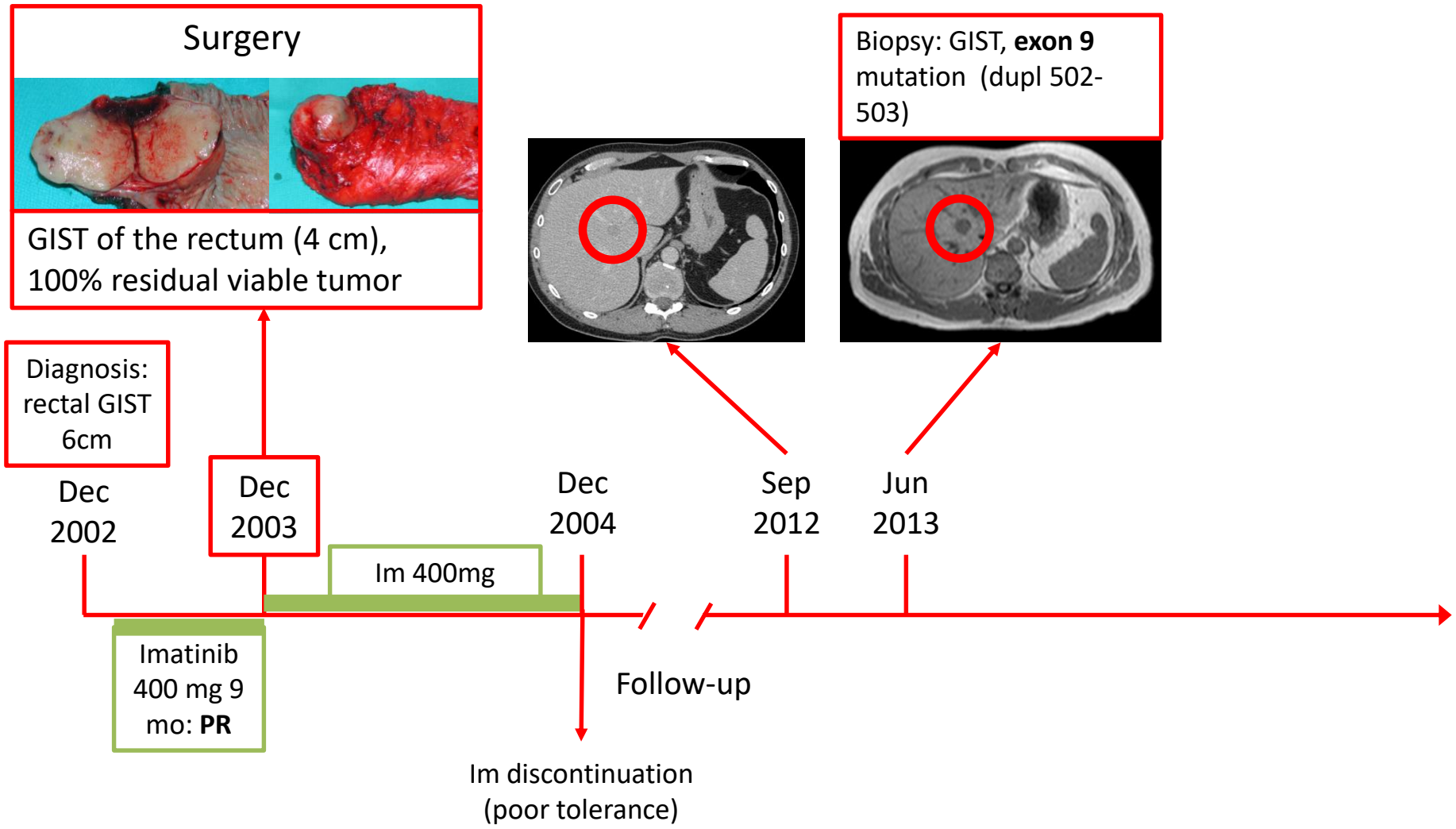
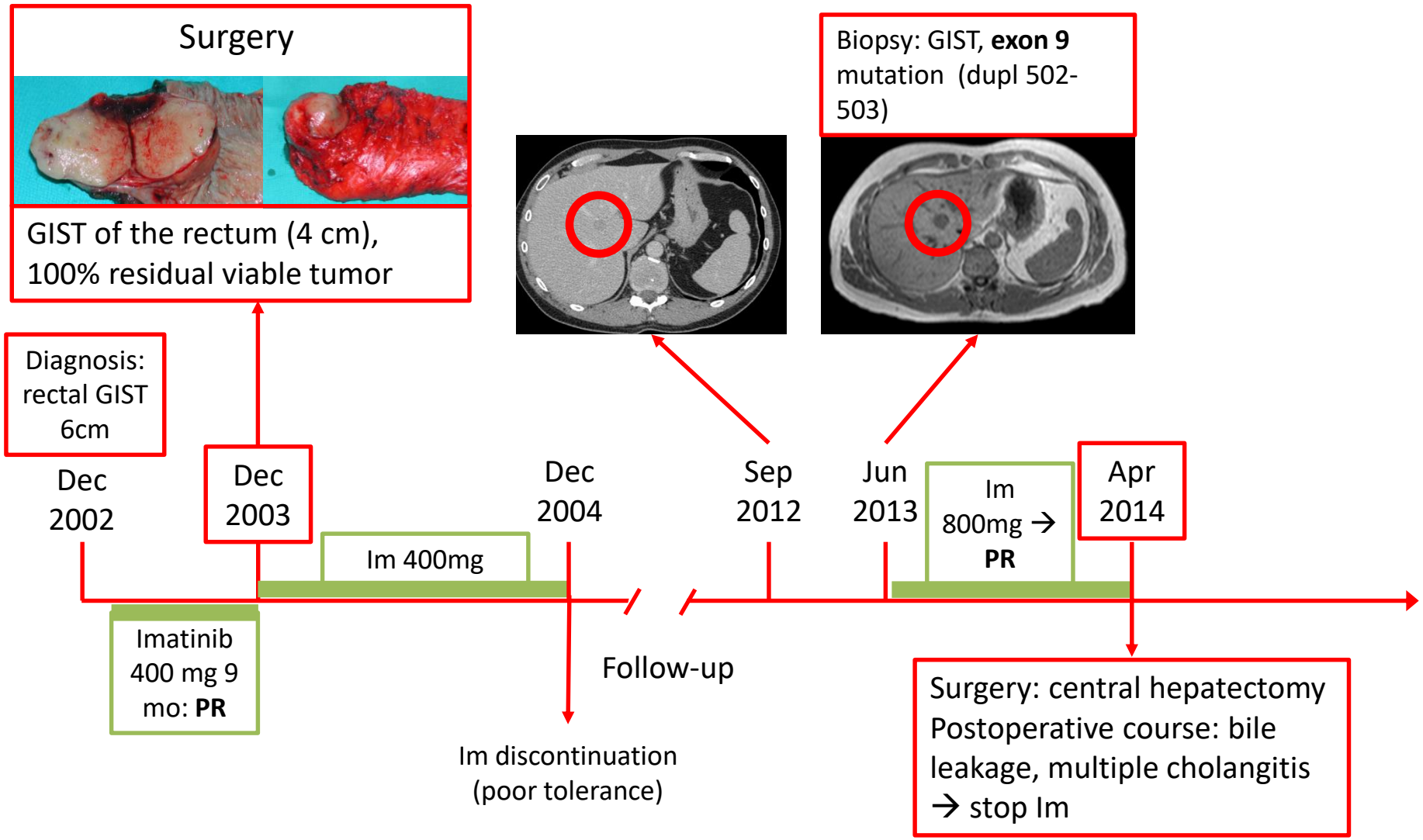

Surgery
GIST of the rectum (4 cm), 100% residual viable tumor
Biopsy: GIST, **exon 9** mutation (dupl 502-503)
Diagnosis: rectal GIST 6cm
Dec 2002
Dec 2003
Dec 2004
Sep 2012
Jun 2013
Im 400mg
Imatinib 400 mg 9 mo: **PR**
Follow-up
Im discontinuation (poor tolerance)

Case 3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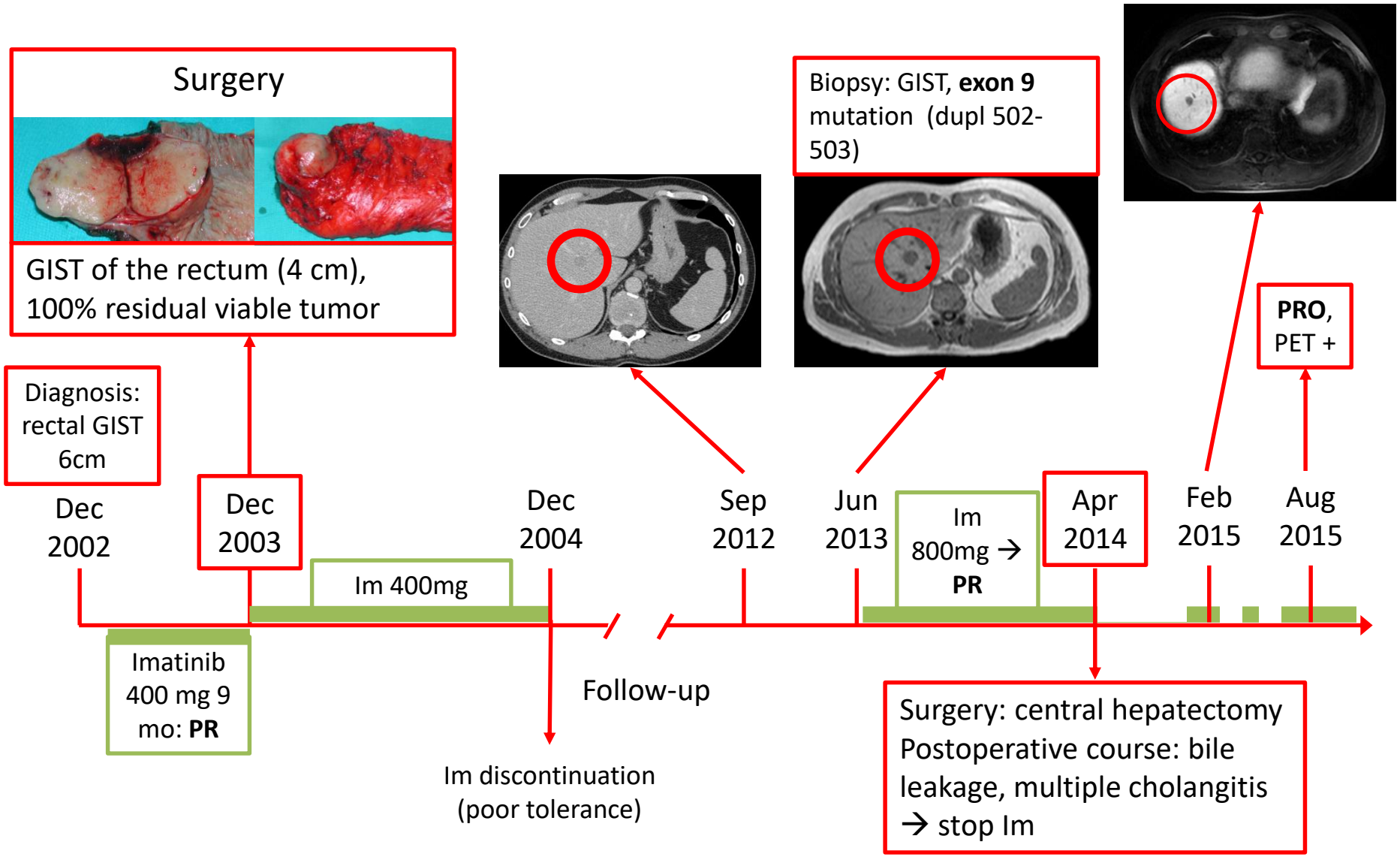
Diagnosis: rectal GIST 6cm
Dec 2002
Dec 2003
Im 400mg
Imatinib 400 mg 9 mo: **PR**
Dec 2004
Follow-up
Im discontinuation (poor tolerance)
Sep 2012
Jun 2013
Im 800mg → **PR**
Apr 2014
Surgery: central hepatectomy
Postoperative course: bile leakage, multiple cholangitis
→ stop Im

Case 3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Dec 2002
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Imatinib 400 mg 9 mo: **PR**
Im 400mg
Dec 2004
Follow-up
Im discontinuation (poor tolerance)
Sep 2012
Jun 2013
Biopsy: GIST, **exon 9** mutation (dupl 502-503)
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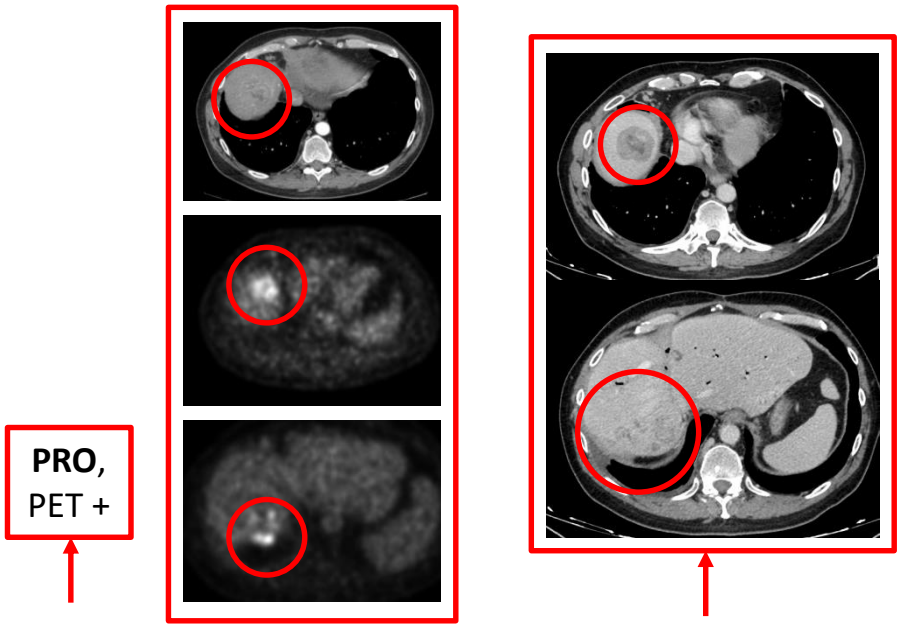
Apr 2014
Surgery: central hepatectomy
Postoperative course: bile leakage, multiple cholangitis → stop Im
Feb 2015
Aug 2015
PRO, PET +

Case 3



PRO, PET +

Aug 2015

Oct 2017

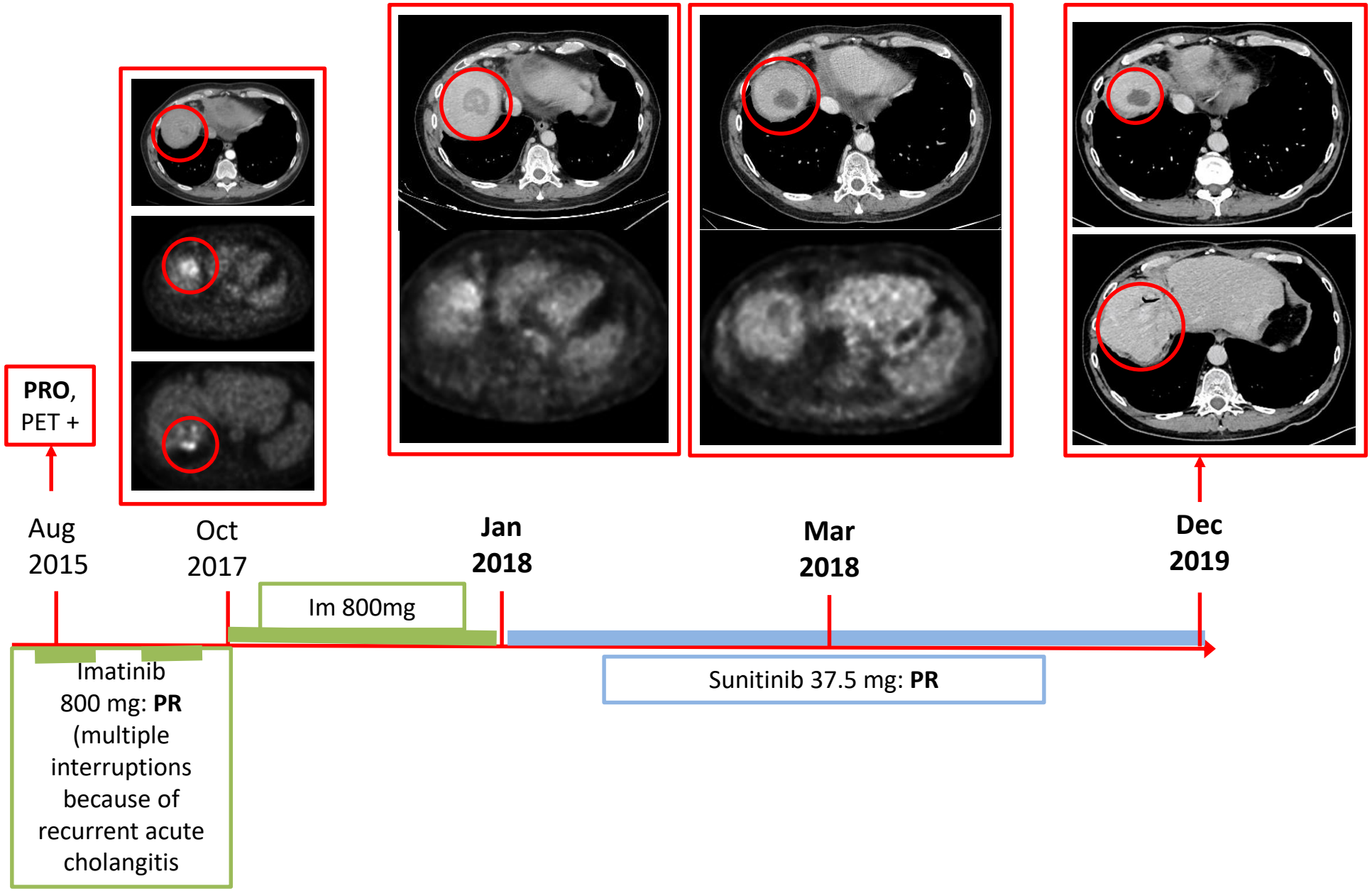
Jan 2018

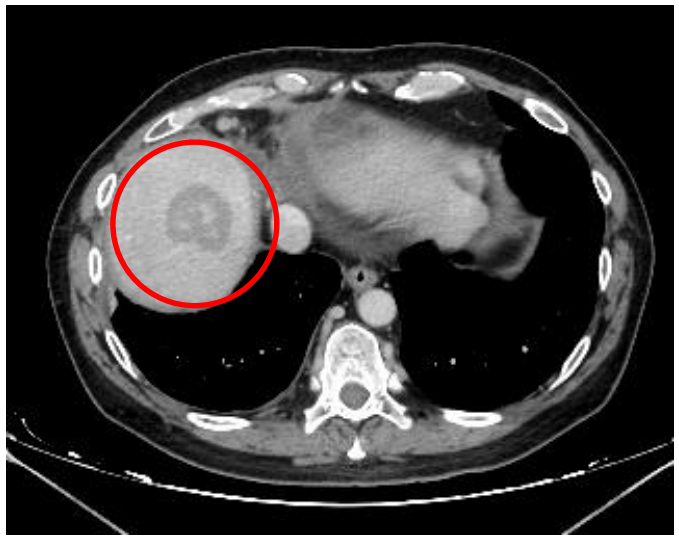
Im 800mg

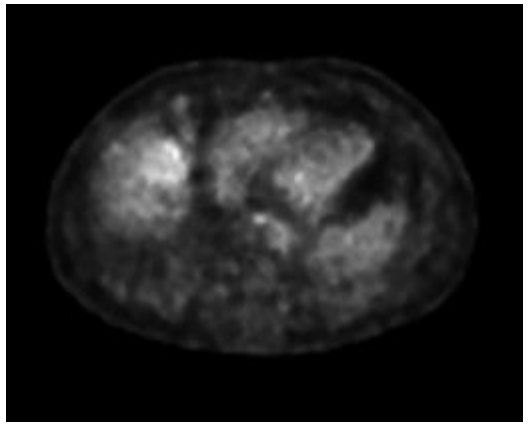
Imatinib 800 mg: **PR** (multiple interruptions because of recurrent acute cholangitis

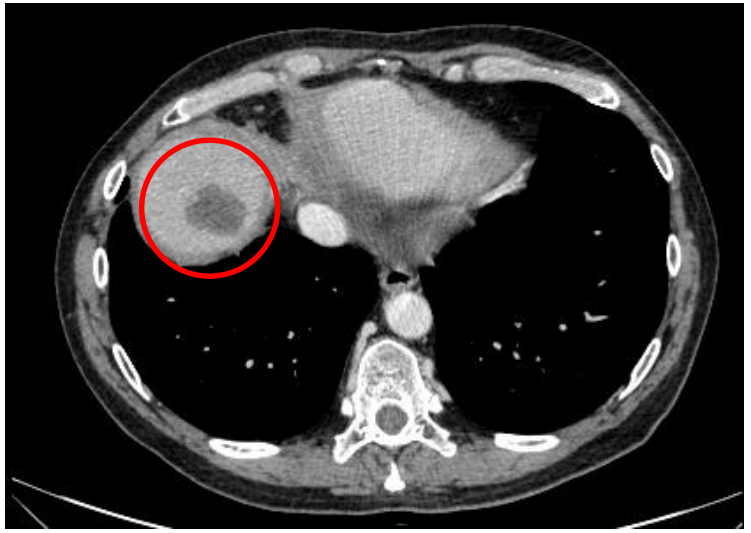
What's next?

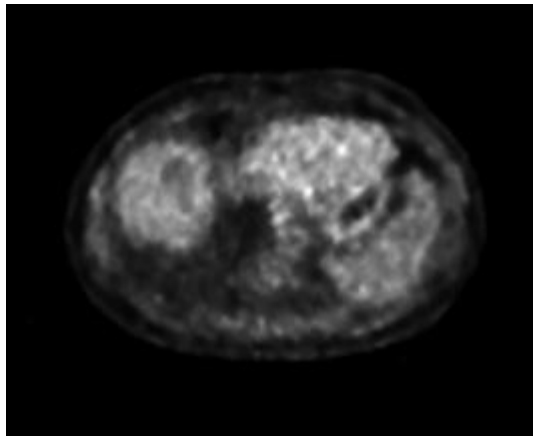
Case 3


PRO,
PET +
Aug
2015
Oct
2017
Jan
2018
Mar
2018
Dec
2019
Im 800mg
Imatinib
800 mg: PR
(multiple
interruptions
because of
recurrent acute
cholangitis
Sunitinib 37.5 mg: PR







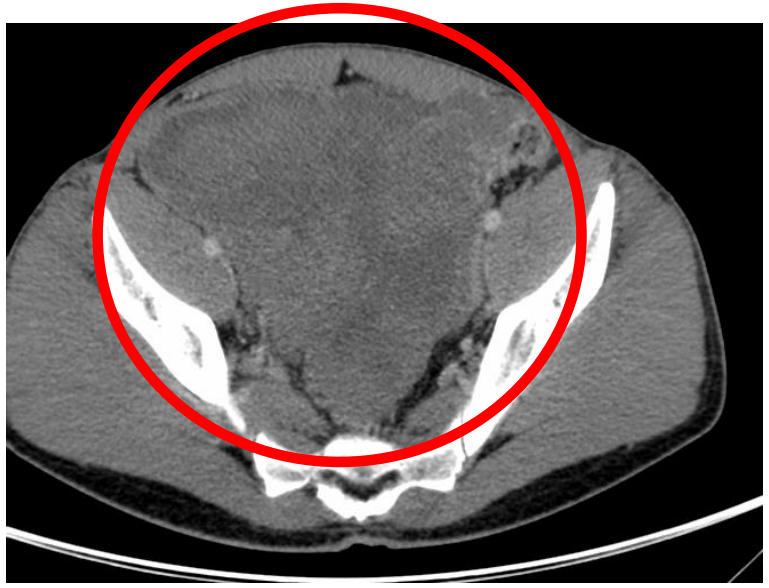


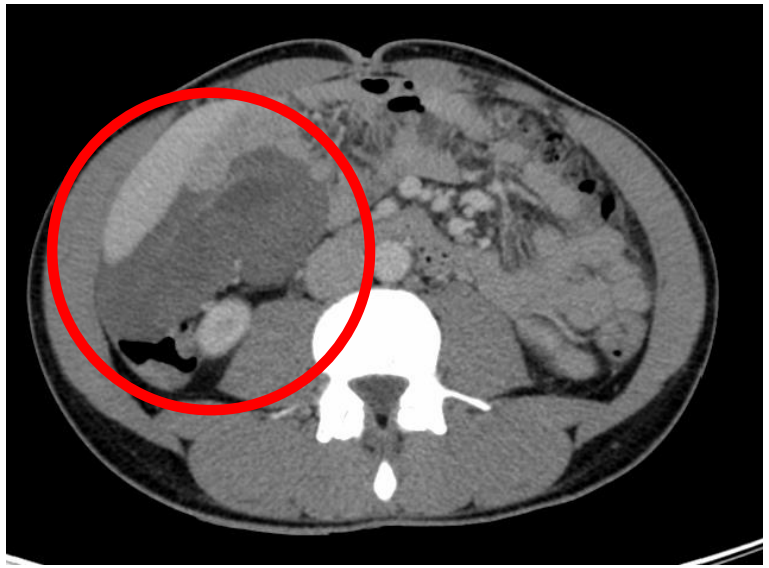
Case 5

Case 5

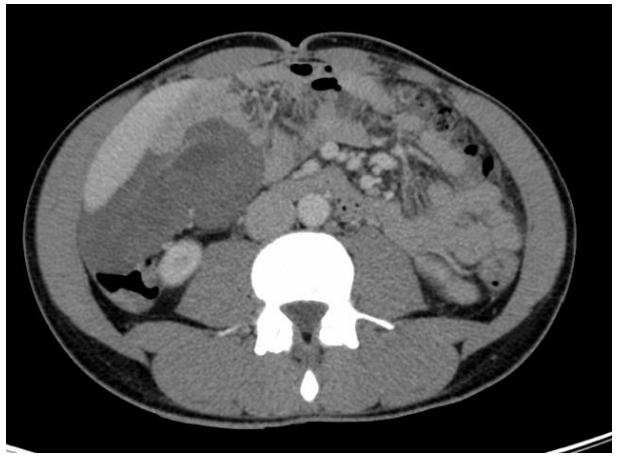
- 28 M, ECOG PS 0
- Aug 2016: abdominal pain + anemia
- CT scan: 15 cm pelvic mass + peritoneal nodules
- Percutaneous CT-guided biopsy: GIST, exon 11 mutation

What's next?





5. LD

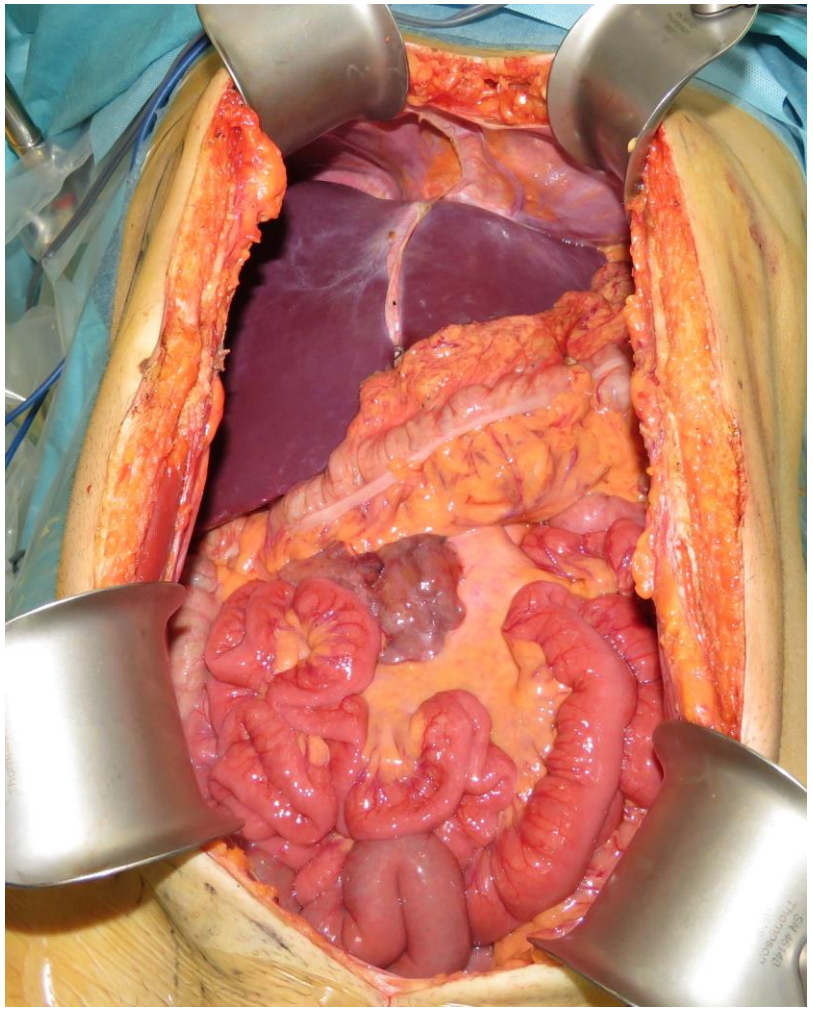


Im 400mg
12 months

What's next?

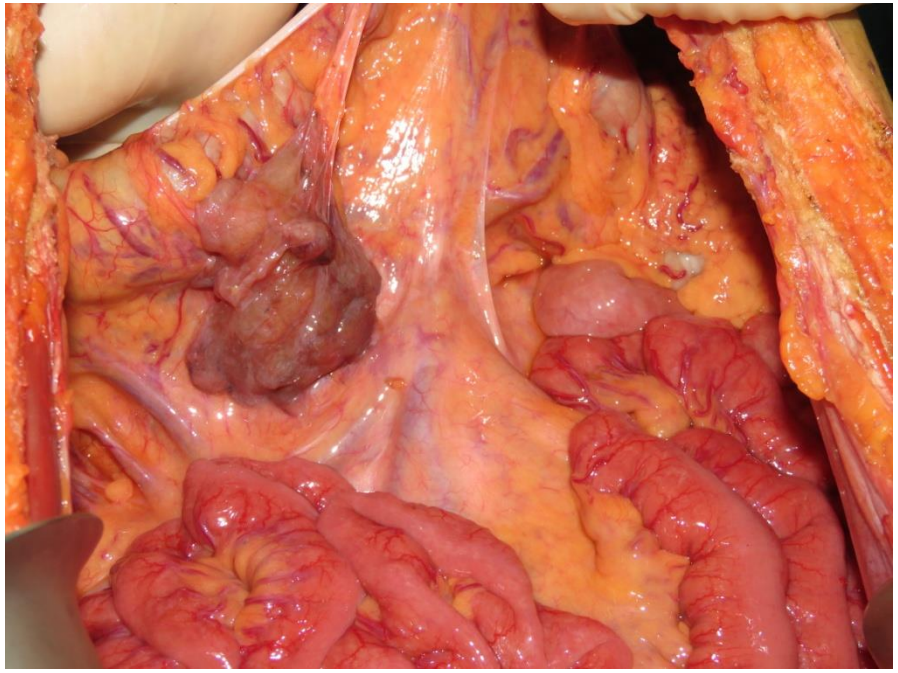
Case 5

- 28 M in good general conditions
- Aug 2016: abdominal pain + anemia
- CT scan: 15 cm pelvic mass + peritoneal nodules
- Percutaneous CT-guided biopsy: GIST, exon 11 mutation
- Im 400mg 12mo: PR
- Oct 2017 - surgery



Case 5

- 28 M in good general conditions
- Aug 2016: abdominal pain + anemia
- CT scan: 15 cm pelvic mass + peritoneal nodules
- Percutaneous CT-guided biopsy: GIST, exon 11 mutation
- Im 400mg 12mo: PR
- Oct 2017 - surgery



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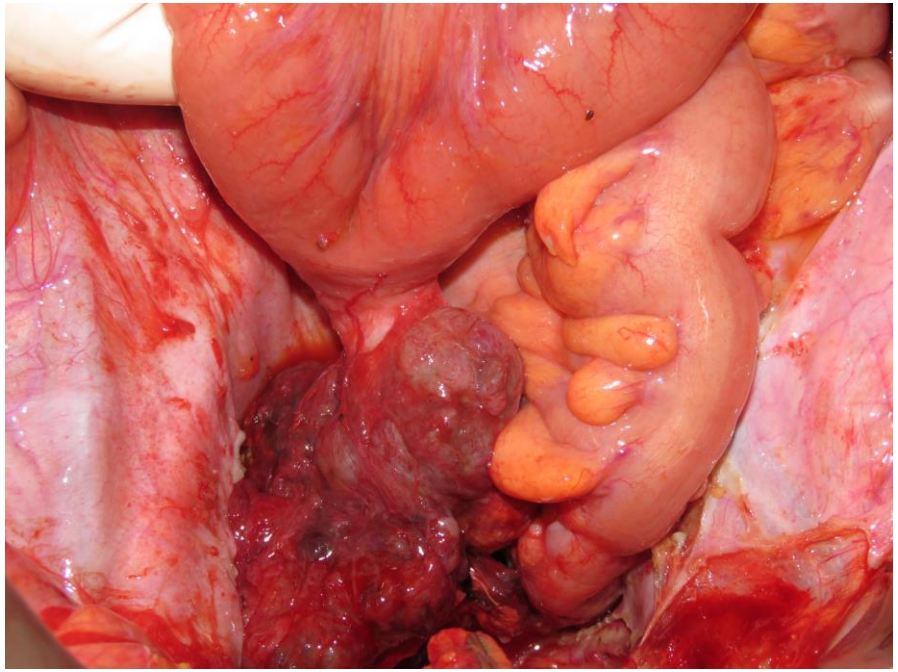
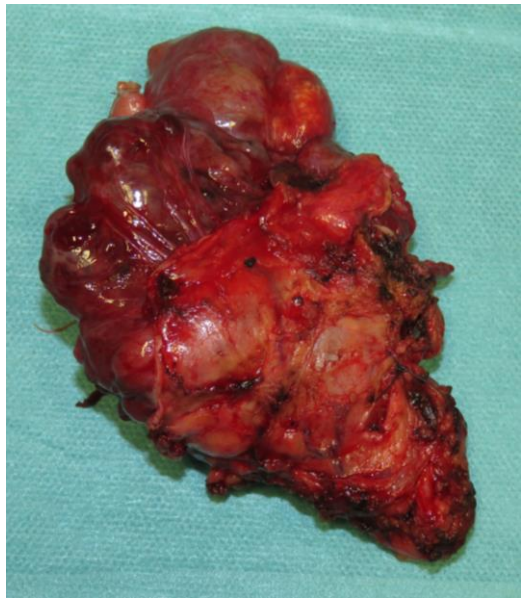
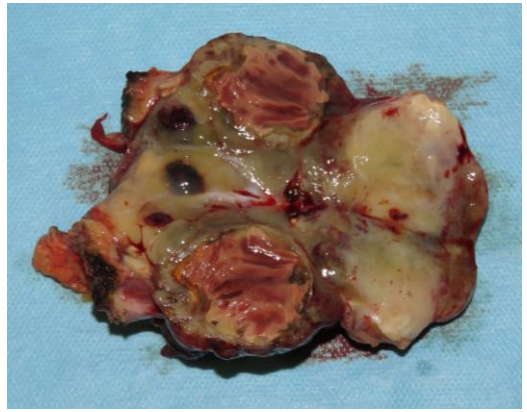
- Aug 2016: abdominal pain + anemia
- CT scan: 15 cm pelvic mass + peritoneal nodules
- Percutaneous CT-guided biopsy: GIST, exon 11 mutation
- Im 400mg 12mo: PR
- Oct 2017 - surgery



Case 5

- 28 M in good general conditions
- Aug 2016: abdominal pain + anemia
- CT scan: 15 cm pelvic mass + peritoneal nodules
- Percutaneous CT-guided biopsy: GIST, exon 11 mutation
- Im 400mg 12mo: PR
- Oct 2017 - surgery
- Pathology:
  - Residual viable tumor: from 1 to 30%
  - mitotic count: 7/50HPF
  - maximum diameter: 11cm
- FU: NED 4 months after surgery (Imatinib 400 mg)



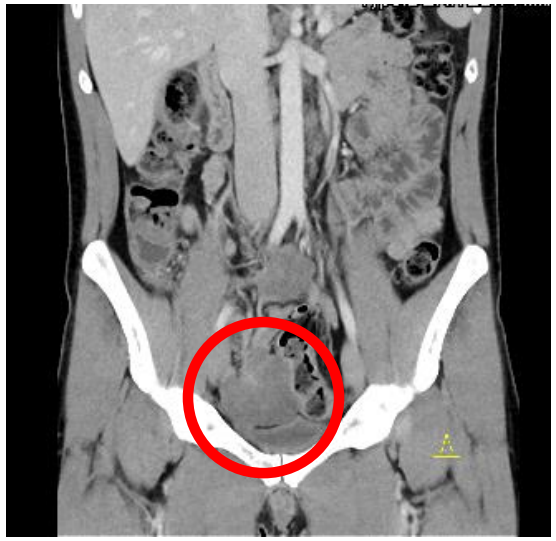


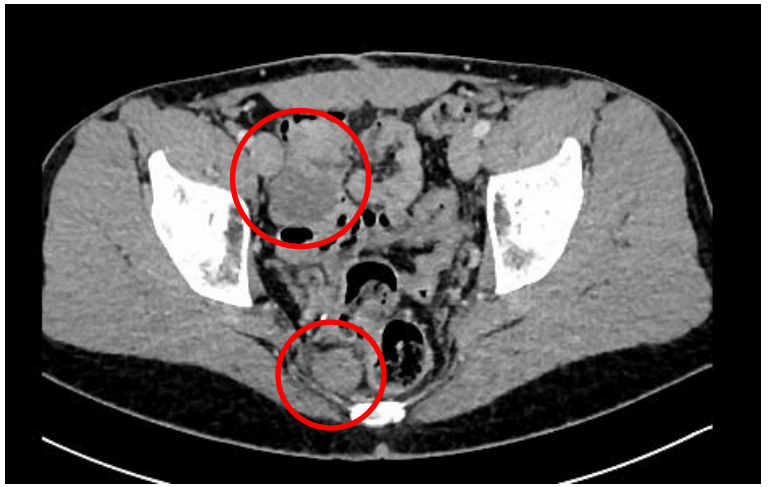
Case 5

- Jan 2019 – multifocal intra-abdominal recurrence

What's next?

Jan 2019

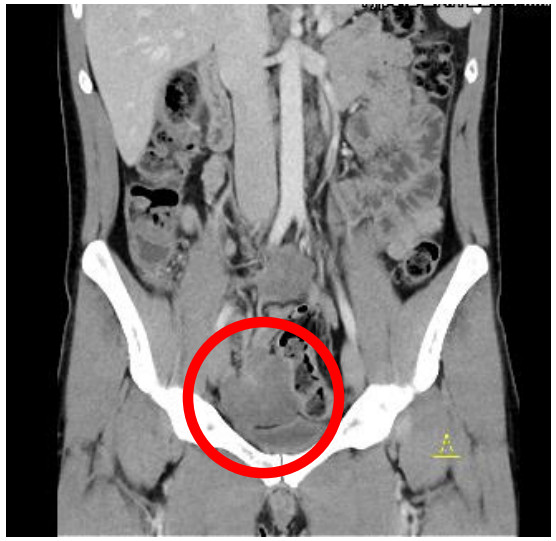


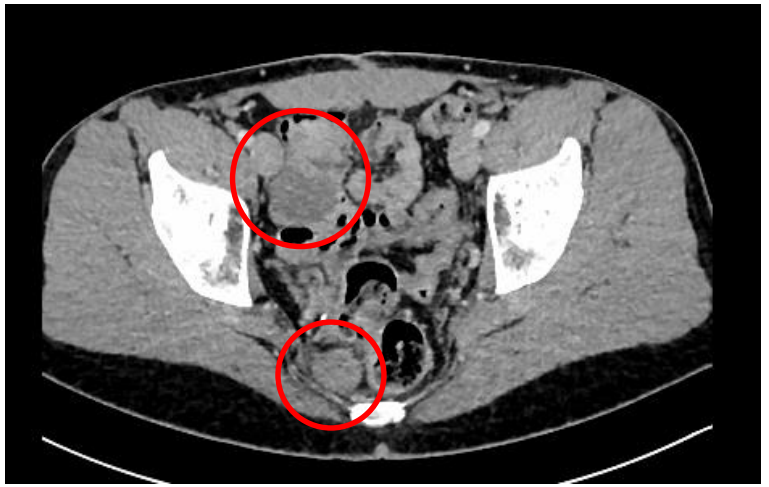


Case 5

- Jan 2019 – multifocal intra-abdominal recurrence
- ***Imatinib 800 mg***

Jan 2019





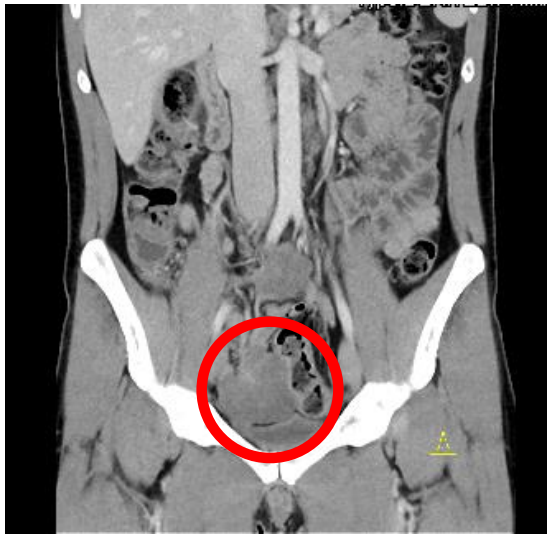
Case 5

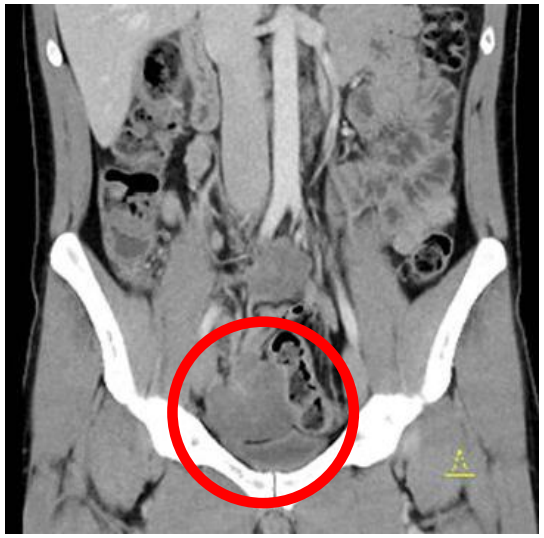
- Jan 2019 – multifocal intra-abdominal recurrence
- ***Imatinib 800 mg - > PD (May 2019)***

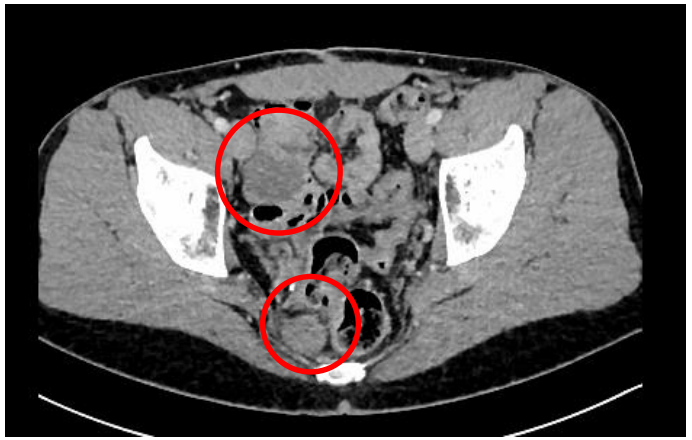
What's next?

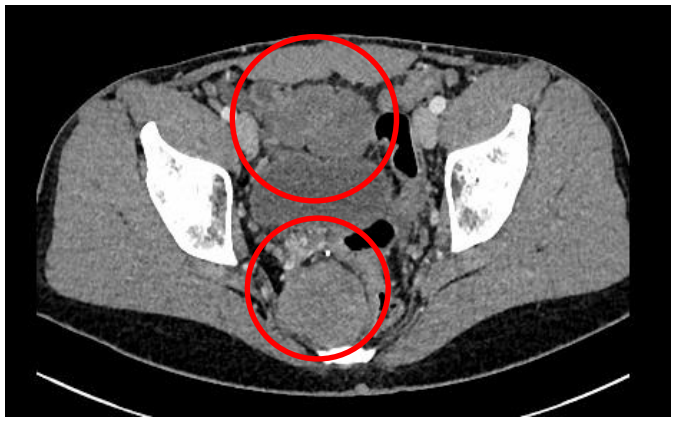
Jan 2019

May 2019





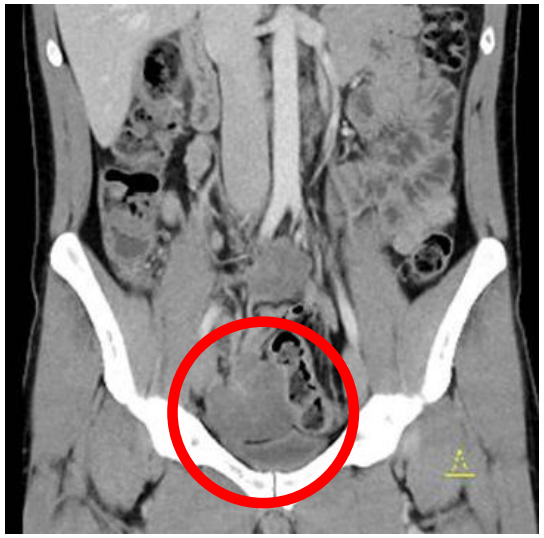


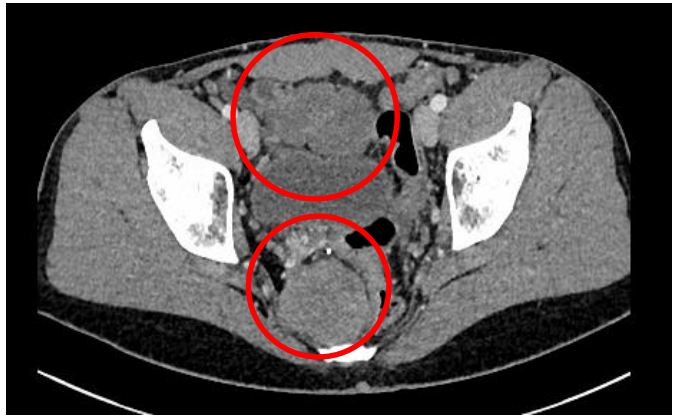


Case 5

- Jan 2019 – multifocal intra-abdominal recurrence
- Imatinib 800 mg - > PD (May 2019)
- ***Sunitinib 37.5 mg***

May 2019





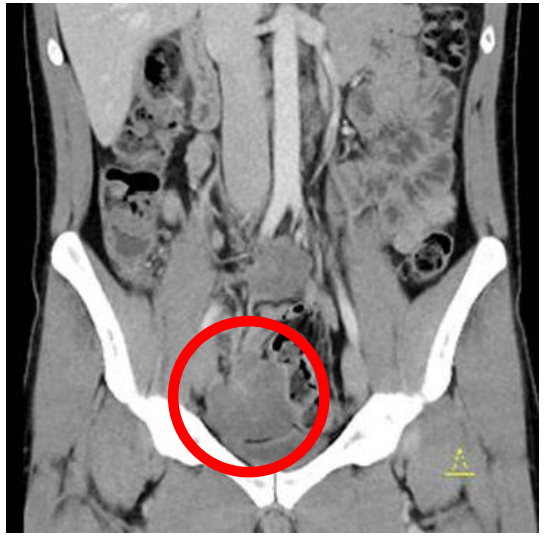
Case 5

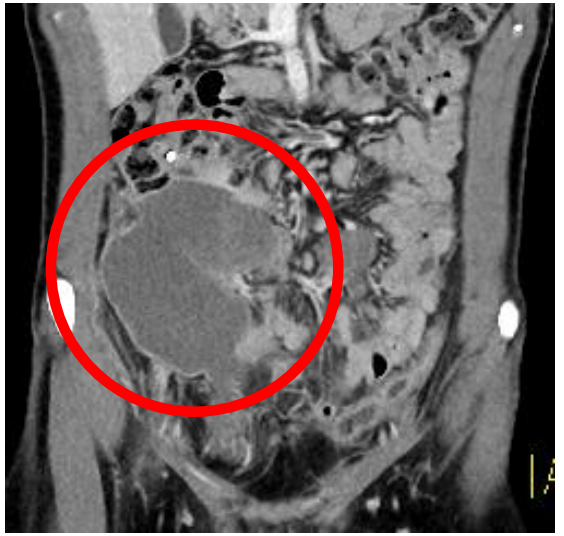
- Jan 2019 – multifocal intra-abdominal recurrence
- Imatinib 800 mg - > PD (May 2019)
- ***Sunitinib 37.5 mg -> PD (Aug 2019)***

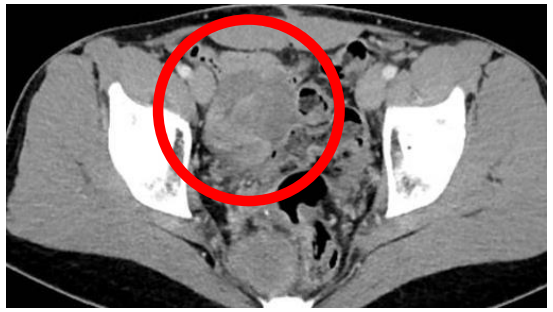
What's next?

May 2019

Aug 2019



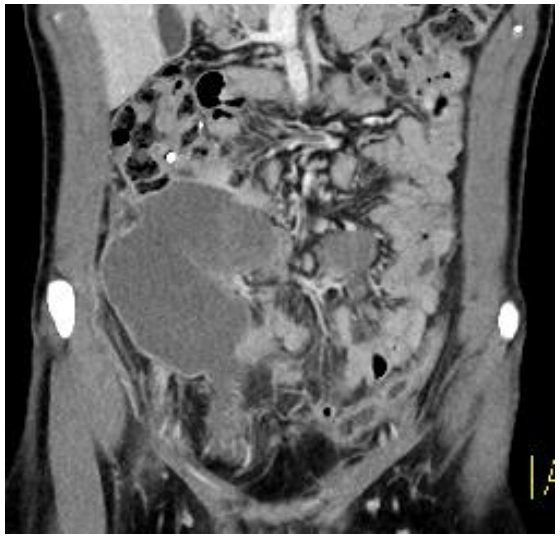


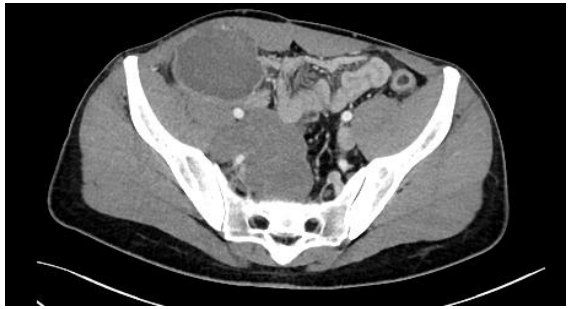


Case 5

- Jan 2019 – multifocal intra-abdominal recurrence
- Imatinib 800 mg - > PD (May 2019)
- Sunitinib 37.5 mg -> PD (Aug 2019)
- ***Avapritinib (Voyager study)***

Aug 2019

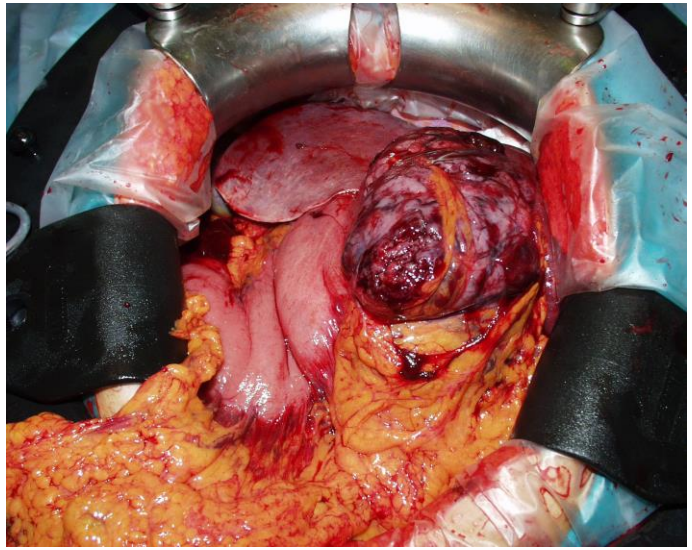


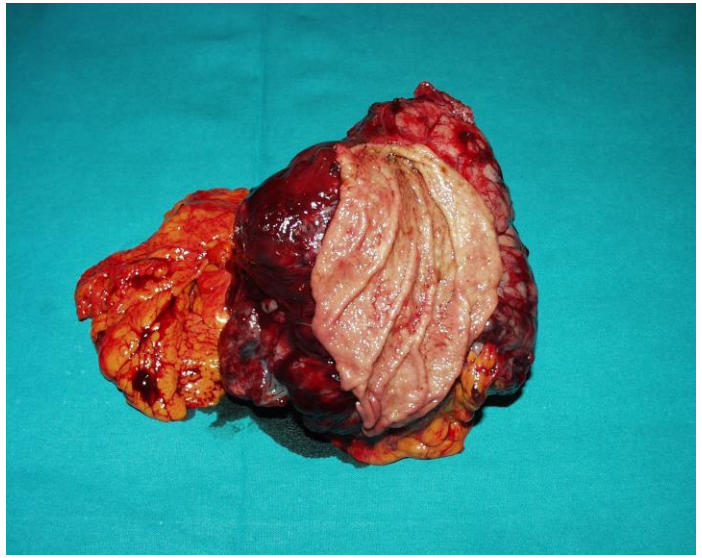


Case 1

Case 1

- 65 F, ECOG PS 0
- Jan 2007: primary GIST of the stomach - wedge resection + splenectomy. Path: 11cm, 112/50HPF, exon 11 mutation
- Feb 2007-Feb 2009: Imatinib 400 mg (EORTC 62024 trial)





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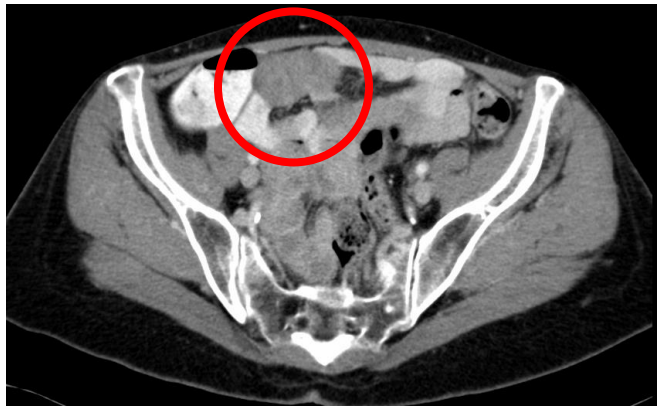
- Dec 2009: peritoneal relapse

Dec 2009



What's next?

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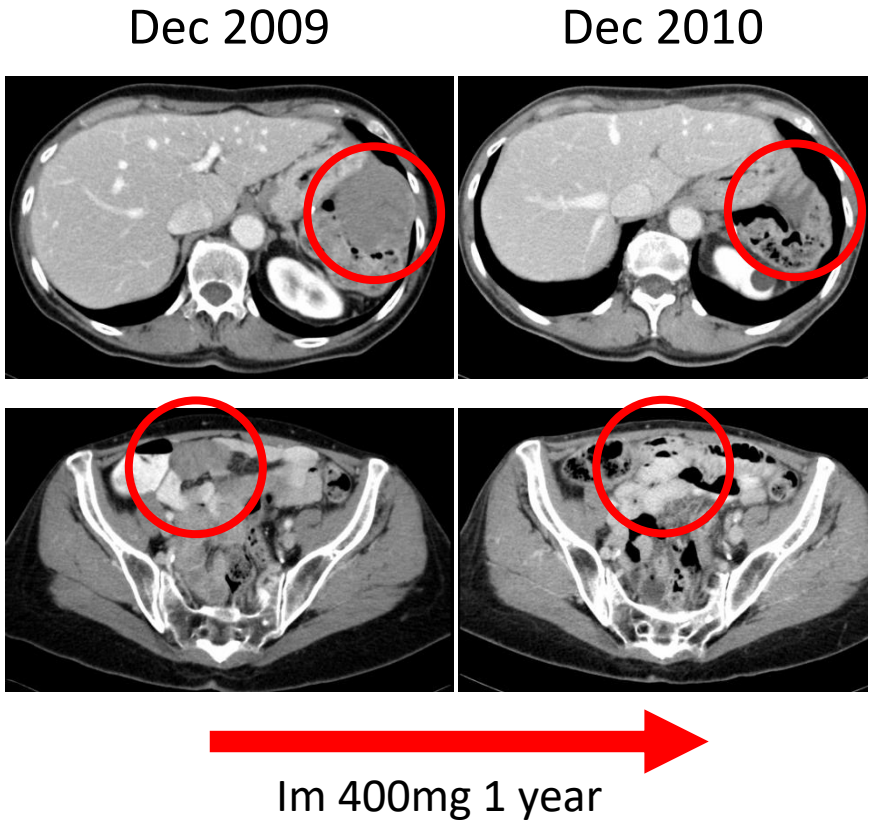
- Dec 2009: peritoneal relapse → Imatinib 400mg with **PR**



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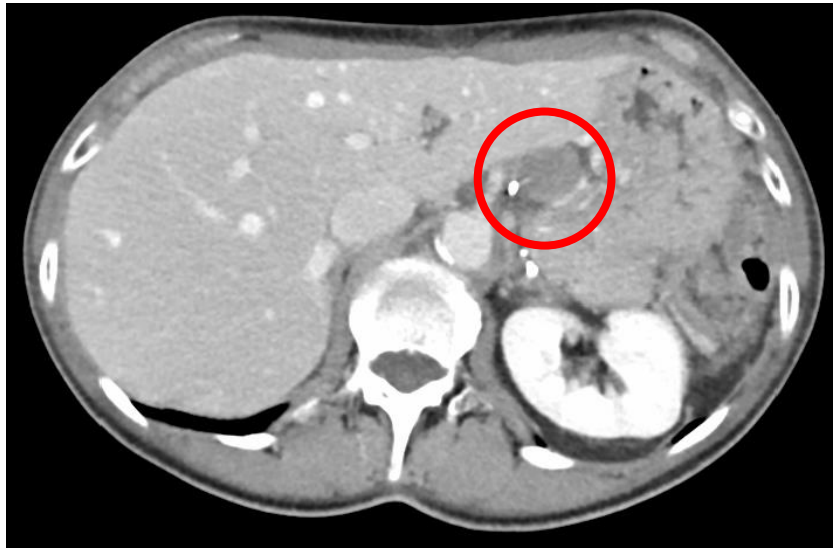
- Dec 2009: peritoneal relapse → Imatinib 400mg with PR
- Nov 2012: **PRO** of a single peritoneal nodule during Im 400mg

Nov 2012



What's next?

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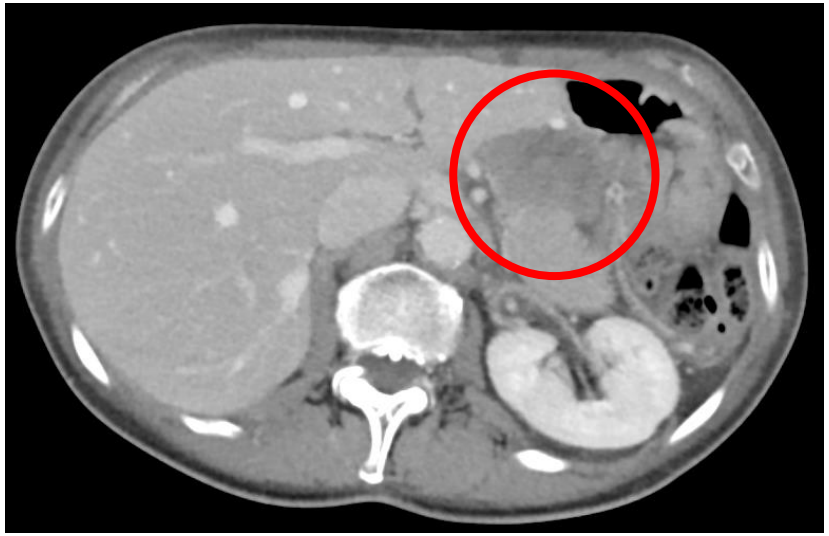
- Feb 2007-Feb 2009: Imatinib 400 mg (EORTC 62024 trial)
- Dec 2009: peritoneal relapse → Imatinib 400mg with PR
- Nov 2012: PRO of a single peritoneal nodule during Im 400mg → dose escalation to Im 600mg (800mg not tolerated) with **PRO**

Feb 2013: PRO (Im 600mg)



What's next?

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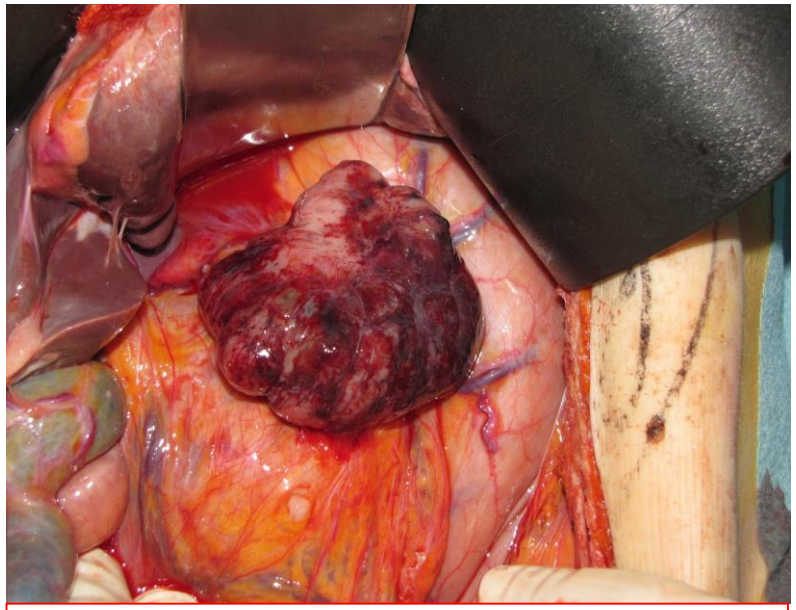
- Feb 2007-Feb 2009: Imatinib 400 mg (EORTC 62024 trial)
- Dec 2009: peritoneal relapse → Imatinib 400mg with PR
- Nov 2012: PRO of a single peritoneal nodule during Im 400mg → dose escalation to Im 600mg (800mg not tolerated) with PRO
- Mar 2013: surgery



Pathology: GIST, 55/10HPF, residual viable tumor from 0% to 85%, 3 peritoneal nodules

What's next?

Case 1

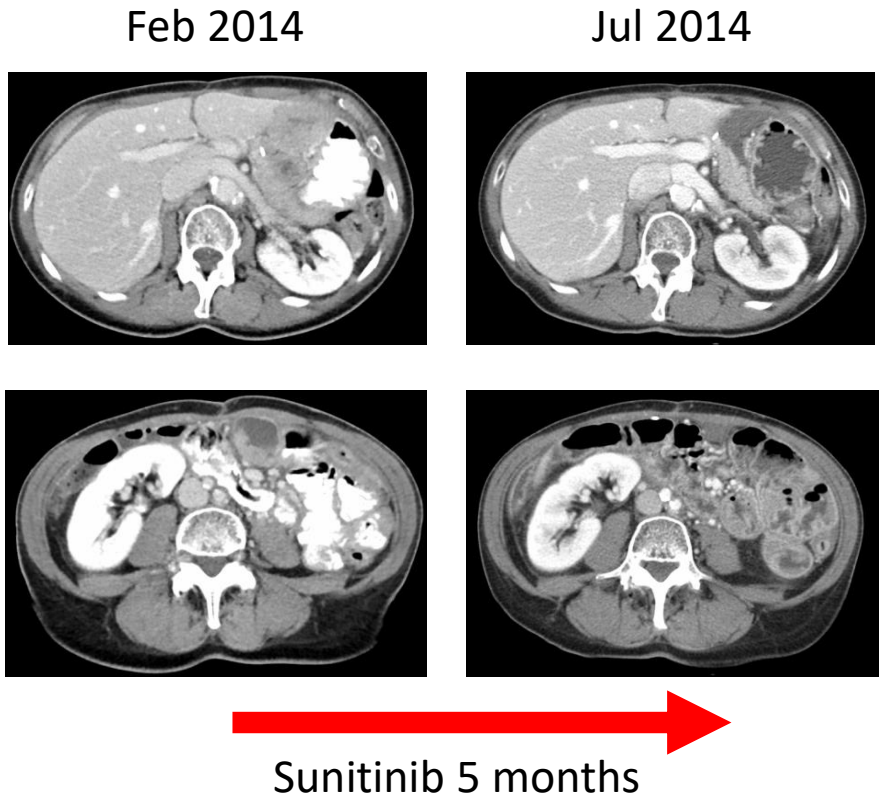
- 65 F, ECOG PS 0
- Jan 2007: primary GIST of the stomach - wedge resection + splenectomy. Path: 11cm, 112/50HPF, exon 11 mutation
- Feb 2007-Feb 2009: Imatinib 400 mg (EORTC 62024 trial)
- Dec 2009: peritoneal relapse → Imatinib 400mg with PR
- Nov 2012: PRO of a single peritoneal nodule during Im 400mg → dose escalation to Im 600mg (800mg not tolerated) with PRO
- Mar 2013: surgery
- Apr 2013: Im 400mg
- Feb 2014: multiple peritoneal nodules

Feb 2014 (Im 400mg)

What's next?

Case 1

- 65 F, ECOG PS 0
- Jan 2007: primary GIST of the stomach - wedge resection + splenectomy. Path: 11cm, 112/50HPF, exon 11 mutation
- Feb 2007-Feb 2009: Imatinib 400 mg (EORTC 62024 trial)
- Dec 2009: peritoneal relapse → Imatinib 400mg with PR
- Nov 2012: PRO of a single peritoneal nodule during Im 400mg → dose escalation to Im 600mg (800mg not tolerated) with PRO
- Mar 2013: surgery
- Apr 2013: Im 400mg
- Feb 2014: multiple peritoneal nodules → Sunitinib: PR



Case 1

- Aug 2015: new peritoneal nodules + nephrotic syndrome

Aug 2015

What's next?

Case 1

- Aug 2015: new peritoneal nodules + nephrotic syndrome
- Sep 2015: shift to Regorafenib
- Nov 2015: acute renal failure (nephrotic syndrome)

What's next?

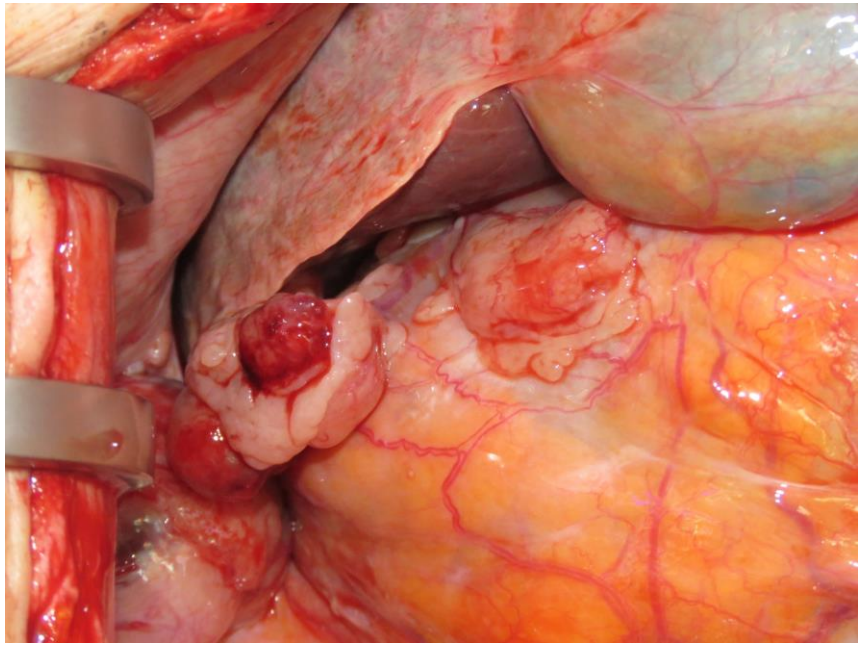
Case 1

- Aug 2015: new peritoneal nodules + nephrotic syndrome
- Sep 2015: shift to Regorafenib
- Nov 2015: acute renal failure (nephrotic syndrome) → rechallenge with Im 400mg
- Dec 2015: worsening of the renal function → stop Im

What's next?

Case 1

- Aug 2015: new peritoneal nodules + nephrotic syndrome
- Sep 2015: shift to Regorafenib
- Nov 2015: acute renal failure (nephrotic syndrome) → rechallenge with Im 400mg
- Dec 2015: worsening of the renal function → stop Im
- Jan 2016: surgery



Surgery: resection of multiple peritoneal nodules.

What's next?

Case 1

- Aug 2015: new peritoneal nodules + nephrotic syndrome
- Sep 2015: shift to Regorafenib
- Nov 2015: acute renal failure (nephrotic syndrome) → rechallenge with Im 400mg
- Dec 2015: worsening of the renal function → stop Im
- Jan 2016: surgery
- Feb 2016: rechallenge with Im 300mg/die (3 days ON, 5 days OFF), without renal side effects
- Nov 2016: SD → patient on a trip to Caribbean Sea, she will be back in a couple of weeks

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