# Three cases of GIST with comments

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# Case 1: A long story with new possibilities

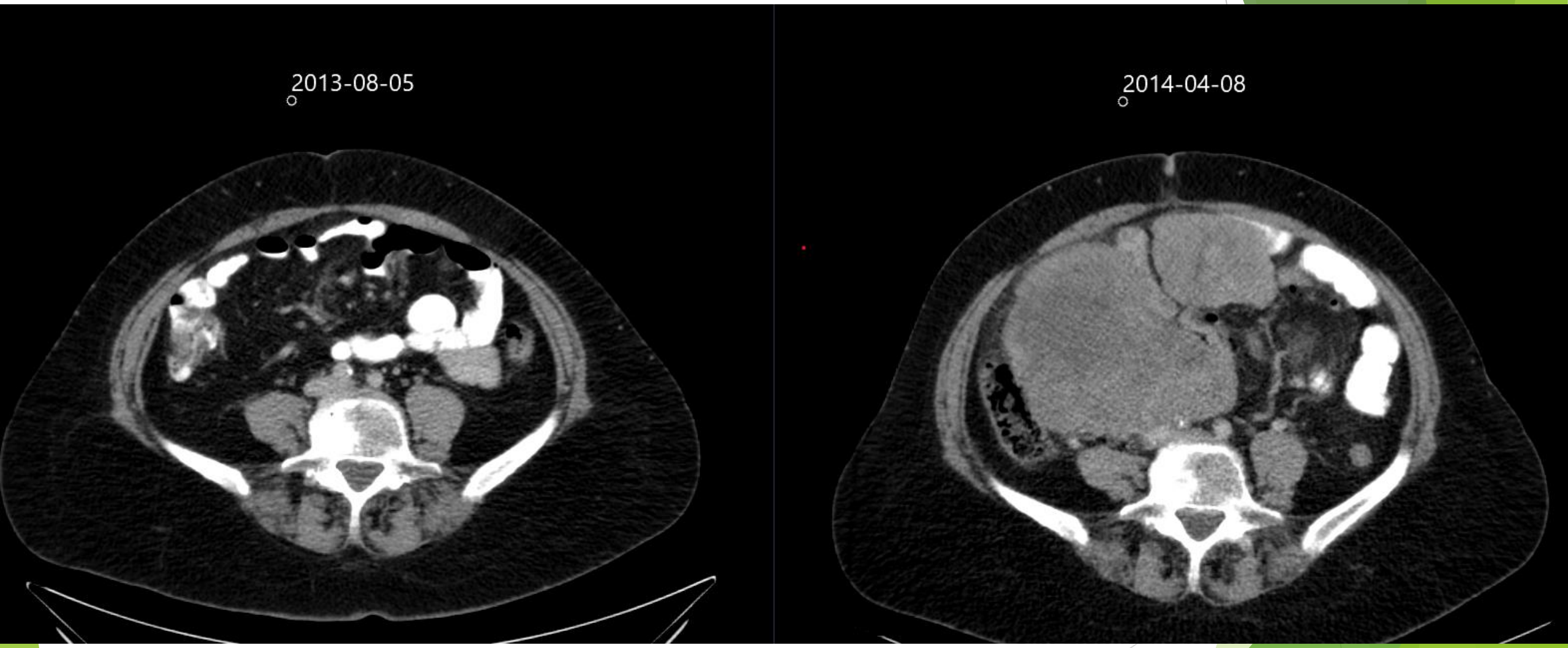
- 50-year old healthy female with increasing abdominal pain from autumn 2008, and during the spring 2009 also distension.
- Referred to the sarcoma centre to which she then belonged, and a CT scan showed a large tumour in the lower part of the abdomen. No metastases found.
- Biopsy $\rightarrow$ GIST
- Likely origin small bowel
- Mutation analysis showed a *KIT* exon 11 mutation
- To facilitate surgery preoperative imatinib was started in August -09.

- Rather poor tolerance, with dose reduction from 400 mg → 300 mg, but impressive tumour shrinkage.
- Surgery after 6 months of treatment in February 2010; radical but narrow margins.
- Planned for additional adjuvant imatinib for one year.

*Comments:*

- *Surgery usually 6-12 months after start of "neo-adjuvant" imatinib*
- *A large non-gastric GIST always high risk → adjuvant imatinib*
- *Recommended treatment length now is 3 years*

- During the adjuvant treatment she moved to our region.
- Imatinib was ended in February 2011, and follow-up with frequent CT scans did not show any sign of recurrence during the next 2-3 years.
- In March 2014, however, she experienced a feeling of heaviness in her abdomen.
- A new CT scan in April disclosed a large tumour recurrence of 20 x 18 cm at the site of her original GIST, which was not seen in August 2013.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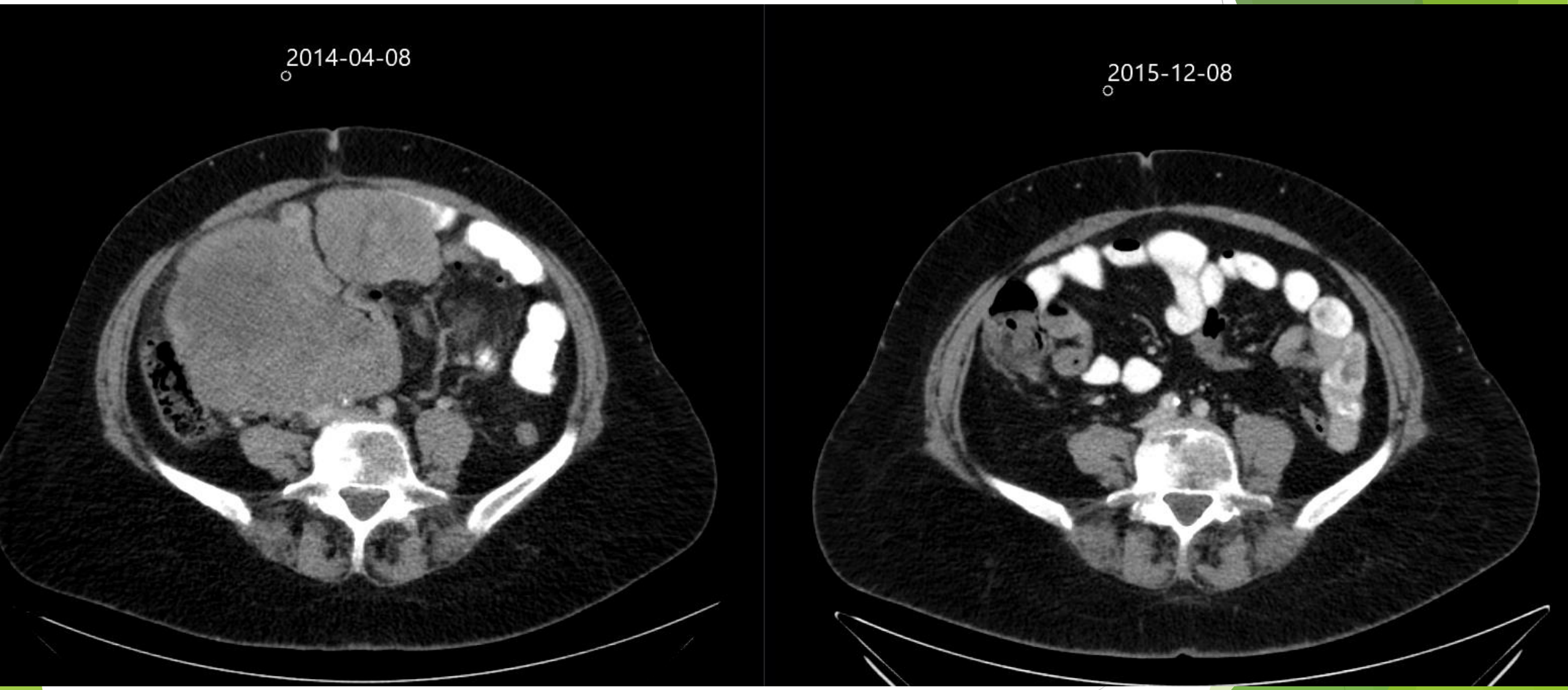
- Imatinib was re-started at 300 mg daily in April, and in end of May a CT showed a good regression to 14 x 13 cm.
- Imatinib was even less tolerable than during the adjuvant therapy with painful cramps and massive oedema which claimed diuretics.
- The dose was stepwise reduced to 200 mg → 100 mg → 100 mg every other day, but despite that, the tumour decreased in size successively until December 2015, during more than 1.5 years.

*Comment:*

- *The dose needed to control GIST may vary individually so treatment shall not be changed before progression on tolerable dose!*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- During the slow regression the possibility to do a new surgery was discussed within our multidisciplinary board at several occasions, but we refrained since the disease was well controlled by imatinib.
- However, in April 2016 a slight progression was seen and the patient accepted the suggestion of a new surgery performed in June.

*Comment:*

- *A GIST responding to TKI and becoming radically operable is a relative indication for surgery, and the indication here became strengthened by an early sign of progression.*
- *After a recurrence, however, there is a strong indication for life-long imatinib even after a radical surgery.*

- The tumour could be resected together with some smaller metastatic lesions in the surrounding.
- The pathology report showed a very high number of mitoses, 85/50 high power fields (HPFs). Mutational analysis showed the original exon 11 mutation and a secondary mutation in *KIT* exon 17.
- *Comment:*
- *In GISTs with primary KIT mutation, thus the large majority, a progression is commonly due to secondary mutations.*

- Imatinib was re-started at 100 mg daily, acceptably tolerated.
- High risk of new recurrences → frequent CT scans, which were normal without new metastases for more than a year.
- In July 2017, three small metastatic lesions were seen on CT.
- The treatment was changed to regorafenib (Stivarga) because the secondary mutation in exon 17 seen after last surgery.

*Comment:*

- *In most cases of advanced GISTs there are multiple secondary mutations, but since the only one shown in the mutational analysis was in exon 17 we did choose regorafenib rather than sunitinib.*

- Did not tolerate “standard dose” of 160 mg of regorafenib because of severe fatigue, hand/foot-syndrome and stomatitis → 120 mg.
- CT in October -17 showed some regression after two months, and in January -18 the situation was stable, but due to increased hand/foot-syndrome we had to reduce the dose to 80 mg and later to alternate 80/40 mg every other day.
- CT scans in March, May and July -18 demonstrated stable disease.

*Comment:*

- *Few patients tolerate the recommended dose of 160 mg of regorafenib, most often due to hand-foot syndrome*

- In October -18 a slow progression was shown of the three known metastases but no new lesions, so we continued regorafenib.
- In March -19 further progression and now also two new lesions.
- Treatment changed to sunitinib 37.5 mg daily, soon reduced to 25 mg.
- At first evaluation marked progression.
- Since regorafenib had worked well for 1.5 years, she was shifted back to this drug in May -19, but now in combination with the mTOR-inhibitor everolimus. mTOR-inhibitors have been reported useful in combination with TKI in GIST, but are not much used.

- In June and August -19 new scans showed mixed response, some lesions shrinking and some growing, but regression dominated.
- In November, however, the progression dominated the mixed picture.
- Treatment unchanged, but request for participation in CUP ("compassionate use program") for avapritinib.

*Comments:*

- *mTOR-inhibitors may be helpful in GIST in combination with TKIs*
- *Mixed responses common since different metastases often have different mutations, some sensitive and some resistant for the on-going treatment*

- Started with avapritinib in February -20, 300 mg daily, which was reduced to 200 mg due to nausea, vomiting and facial oedema.
- In April mixed response but in May progression and she stopped this treatment too, and started sorafenib + everolimus.
- She had increasing pain from two rather big lesions, and we also gave palliative radiotherapy towards these in August during four weeks.
- In October CT showed that one of these two lesions were somewhat reduced, the other stable. Her pain decreased.

*Comment:*

- *Radiotherapy may be active in growing or symptomatic GIST metastases when the medical treatment is not enough to control the disease*

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Radiotherapy for GIST

# Radiotherapy for GIST progressing during or after tyrosine kinase inhibitor therapy: A prospective study

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ABSTRACT

*Purpose:* Gastrointestinal stromal tumor (GIST) has been considered radiation-resistant, and radiotherapy is recommended only for palliation of bone metastases in current treatment guidelines. No registered prospective trial has evaluated GIST responsiveness to radiotherapy.

*Patients and methods:* Patients with GIST progressing at intra-abdominal sites or the liver were entered to this prospective Phase II multicenter study (identifier NCT00515931). Metastases were treated with external beam radiotherapy using either conformal 3D planning or intensity modulated radiotherapy and conventional fractionation to a cumulative planning target volume dose of approximately 40 Gy. Systemic therapy was maintained unaltered during the study.

*Results:* Of the 25 patients entered, 19 were on concomitant tyrosine kinase inhibitor therapy, most often imatinib. Two (8%) patients achieved partial remission, 20 (80%) had stable target lesion size for ⩾3 months after radiotherapy with a median duration of stabilization of 16 months, and 3 (12%) progressed. The median time to radiotherapy target lesion progression was 4-fold longer than the median time to GIST progression at any site (16 versus 4 months). Radiotherapy was generally well tolerated.

*Conclusions:* Responses to radiotherapy were infrequent, but most patients had durable stabilization of the target lesions. GIST patients with soft tissue metastases benefit frequently from radiotherapy.

- The smaller lesions not given radiotherapy increased during four months with sorafenib, and she was switched to pazopanib, which she tolerated much better than the earlier TKIs given.
- A new CT scan in January -21, however, showed progression of the three largest lesions with 3, 3 and 1 cm in diameter, respectively, whereas other were reduced.
- She went on with pazopanib, but we also applied for participation in an “early access” program for ripretinib, and when this was approved she started ripretinib in mid-February.

*Comments:*

- *Beside the three approved TKIs for GIST in general in Europe, imatinib, sunitinib and regorafenib, several other drugs have been tested in smaller trials or case series with promising results, e.g., sorafenib and pazopanib, and all may be worth trying (if available) since you can not predict which GIST that may respond*
- *Avapritinib was evaluated in a large trial (VOYAGER) at the time this patient was approved for their CUP, but has been only really useful in the specific mutation called D842V in the PDGFRA exon 18 gene, where it is now approved.*

- She tolerates ripretinib well in recommended dose of 150 mg daily.
- New CT scan April 12 shows only a minor progression of 0.5, 1 and 1 cm, respectively when compared with the CT scan done one month before start of ripretinib.
- During that month, it is highly probable that the tumours grow further, and thus the disease is certainly at least stable since start of this drug.
- Furthermore, she is feeling better, increased appetite etc.

*Comment:*

- *Ripretinib is a very promising new TKI for GIST in late treatment lines*

# Case 2: The importance of a correct diagnosis

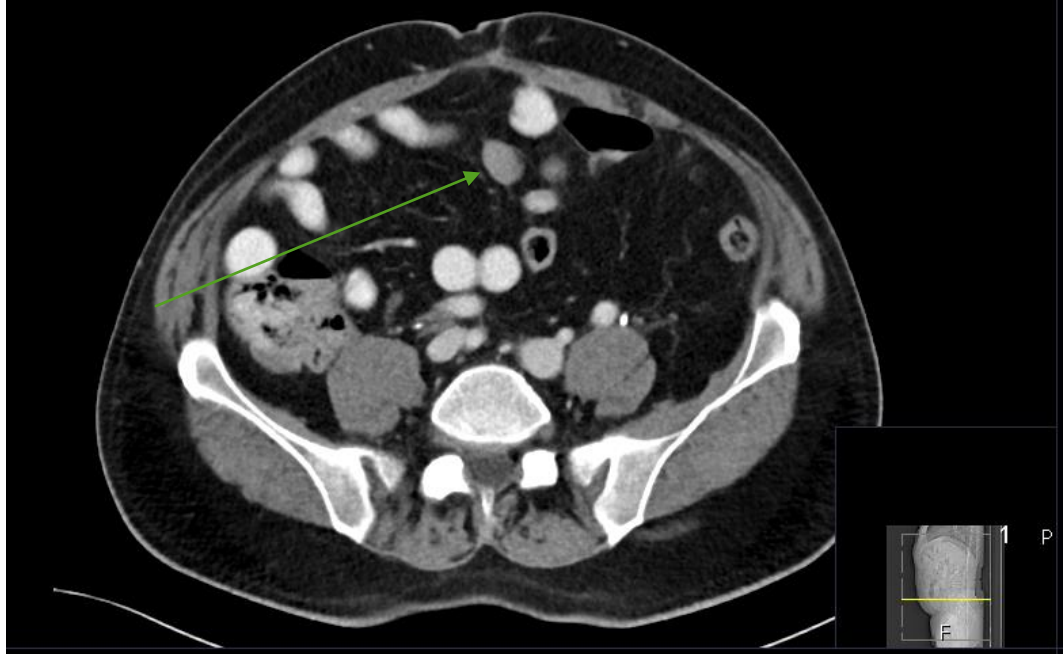
- 62-year old man with slight discomfort in his abdomen now and then since many years when he was hit by severe left-sided abdominal pain in September 2017 when being abroad
- Back home his primary health care unit suspected a diverticulitis, and he was treated with antibiotics and recovered completely
- The same symptoms recurred three months later, and he was almost fainting and was transported to the nearby hospital by ambulance

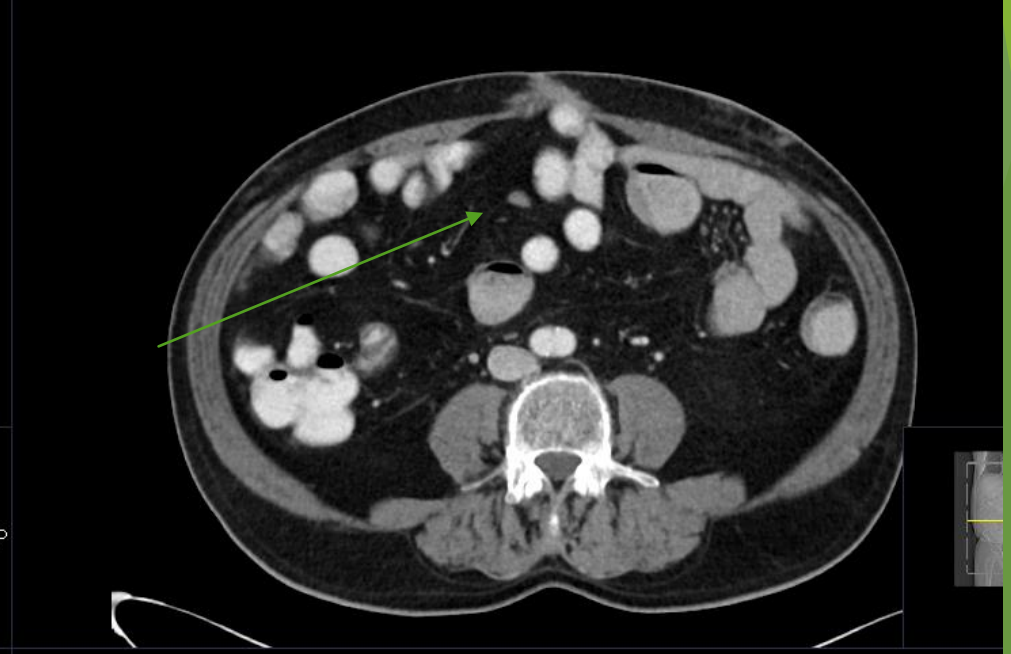
- A CT scan showed at least three tumours in the lower part of the abdomen measuring 12, 6 and 1.5 cm in longest diameters
- Retrospectively, the largest was found with a size of 5 cm in a CT performed back in 2014
- His condition called for an acute surgery where the three tumours were resected + some small metastases in the abdominal wall
- Pathology report: undifferentiated spindle cell sarcoma with 7 mitoses per 10 HPF, thus a type of soft tissue sarcoma in advanced stage

*Comment:*

- *A correct diagnosis is of utmost importance in oncology (which it was not here)*

- A new CT after surgery showed small suspected metastatic lesions, also in the liver
- Based on the given diagnosis he was treated with chemotherapy in two lines with further progression after each (doxo+ifo x 3; gem + doc x 3)
- In September -18 we switched to the tyrosine kinase inhibitor pazopanib, registered for common STS, but not for GIST
- A new evaluation in November showed a striking regression of the metastases, with exception of the largest which had clearly grown but showed much lower attenuation (less dense)





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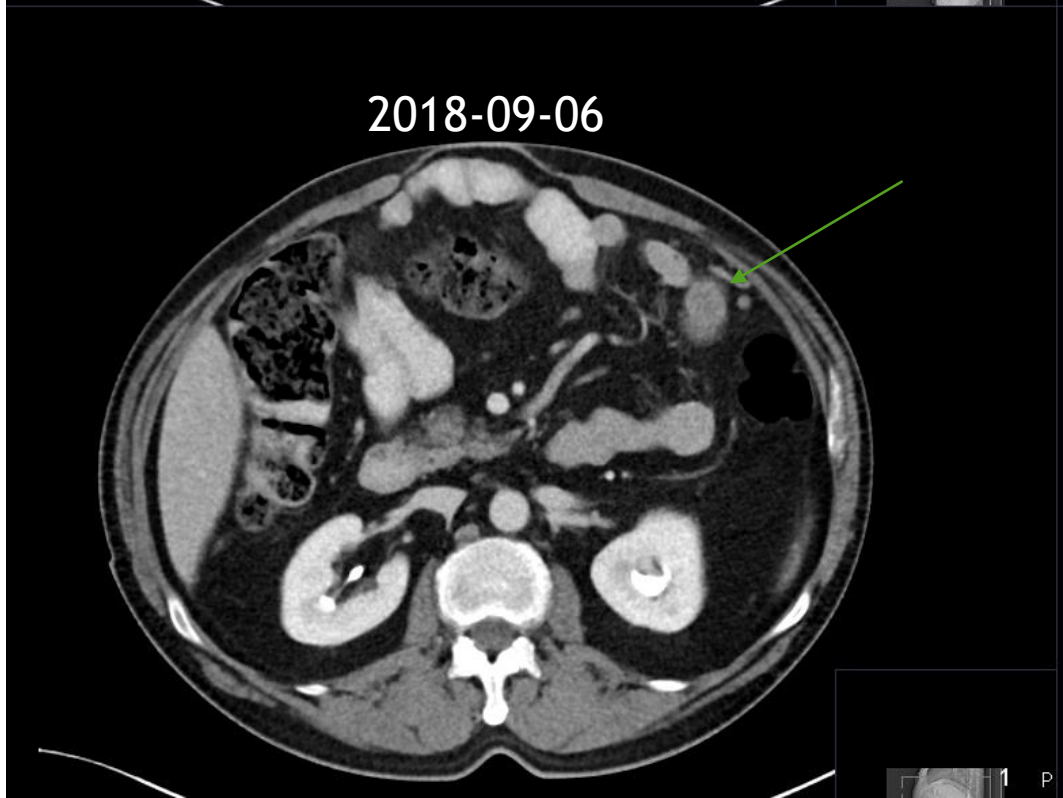

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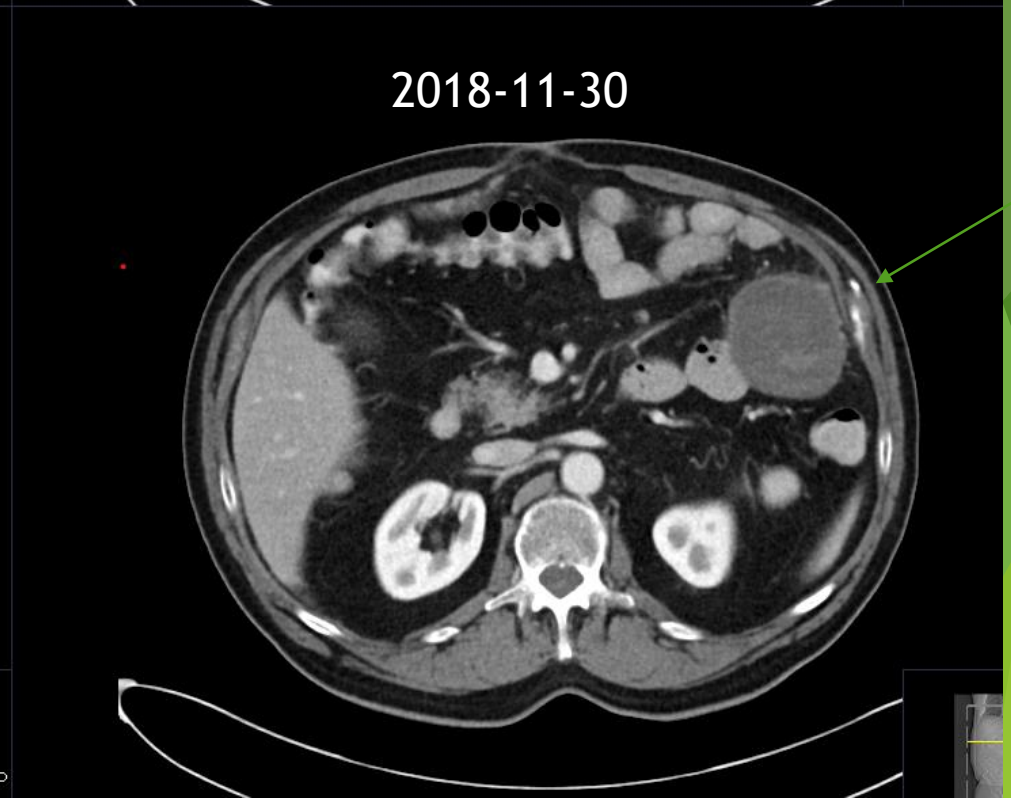


- Pazopanib was well tolerated except for some fatigue, but after reducing the dose from 800 to 600 mg daily he was able to do full time work
- The next CT scan in November showed the same trend – most lesions decreasing in size but the largest increased further
- Our multidisciplinary board decided to perform surgery to resect the only increasing tumour, which was performed in May -19
- The pathology report this time demonstrated a typical GIST, positive ICH for CD117 and DOG-1, with a *KIT* 11 mutation, 1 mitosis in 50 HPF

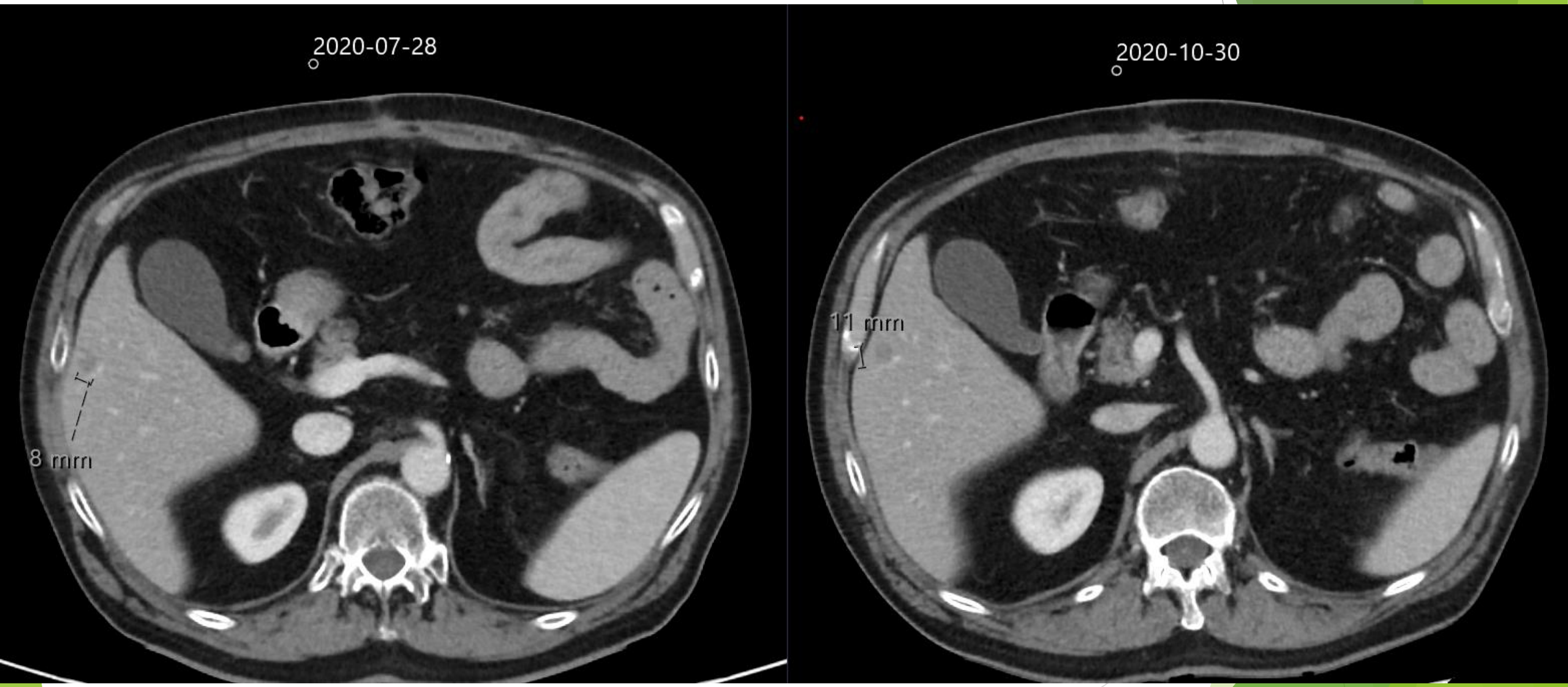
*Comment:*

- *Even if growing, this large lesion shows clear signs of response, not only by its appearance but also by the low mitotic rate compared to the initial tumour*

*Comments:*

- GIST is not responding at all to chemotherapy
- Pazopanib is a tyrosine kinase inhibitor, not registered for GIST but may be very active
- Mixed response is common in GIST due to different secondary mutations between and within tumour lesions
- Without heavy evidence of its usefulness surgery is sometimes performed in cases with just limited localized progress when the main part of the tumour is controlled by a tyrosine kinase inhibitor
- In cases with general progression surgery is contraindicated!

- Pazopanib controlled the rest of the disease for about a year with slow regression until July -20, but with clear progression in November with increased liver metastases and also one new lesion indicating new secondary mutations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- The patient had never received any other TKI than pazopanib, but imatinib is not effective against secondary mutations, so we shifted to sunitinib; 37.5 mg daily, later reduced to 25 mg due to severe diarrhoeas and medium severe hand-foot syndrome
- Evaluating CT after three months, in March -21, showed stable disease with a minor regression of some lesions

*Comment:*

- *Pazopanib and sunitinib are rather similar in their targets, but still all TKIs are individual, and you may always try a new one (if available) with some chance of benefit*

# Case 3: Specific solutions for specific mutations

## Follow-up from the SPAEN 2020 meeting

- 54-year old healthy woman with increasing distension of abdomen and a growing tumour on the left side in the autumn of 2009
- CT scan: 14 x 10 x 14 cm; small bowel origin; no metastases
- Biopsy showed GIST with a mutation in *PDGFRA* exon 18 (*not* D842V)
- Neo-adjuvant imatinib from January 2010 → very good response down to largest diameter of 4.5 cm
- Radical surgery in October 2010 and further imatinib adjuvant until April 2011

*Comment:*

- *Short adjuvant therapy standard by that time*
- *Some PDGFRA mutations may respond to imatinib (but not D842V)*

- In April 2012 she had a 10 cm large recurrence in lower part of abdomen
- Imatinib re-started with again very good response down to 3.5 cm
- Tinnitus and other side effects forced a dose reduction to 200 mg
- Radical surgery was performed in June 2013
- Continued with imatinib 200 mg daily
- Four years later, June 2017, a new smaller recurrence was diagnosed; surgery was performed in September, radical
- New mutation analysis found only the same primary mutation

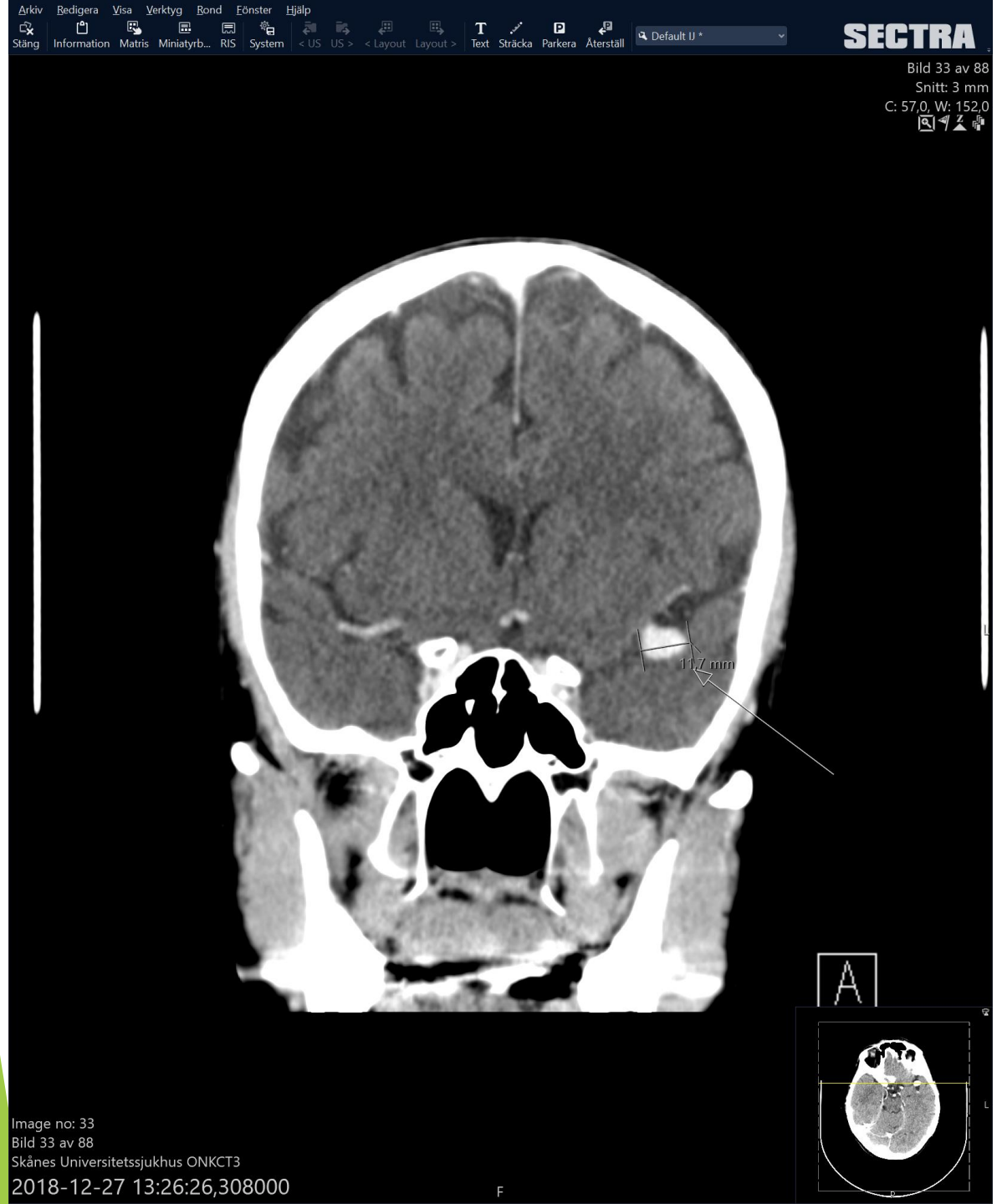
*Comment:*

- *The reduced dose may have caused the recurrence*

- She continued with imatinib 200 mg daily, could not tolerate a dose increase
- CT scan in October -17 showed two small suspected lesions in the pelvic region, 10 and 7 mm in size
- Next CT in December -17 showed increase to 13 and 8 mm
- Treatment was switched to sunitinib 37.5 mg daily which soon had to be decreased to 25 mg because of intolerance

- CT scan in April -18 showed only one remaining lesion of 8 mm, and in September no lesions at all → CR!
- However, severe fatigue, diarrhoeas and abdominal pain → dose down to 12.5 mg
- CT scan in December -18 then showed a dramatic GIST increase

- Information was given about the on-going international trial VOYAGER randomising between regorafenib and the new TKI avapritinib
- Avapritinib had shown very promising results in early trials, especially in the D842V mutation, but with problematic side effects as cognitive disturbances, and also an increased risk of intracranial bleedings
- The patient wanted to join, and according to the protocol a CT scan of the brain had to be done
- This showed a 12 mm large arterial aneurysm whit a high risk of rupture and severe brain bleeding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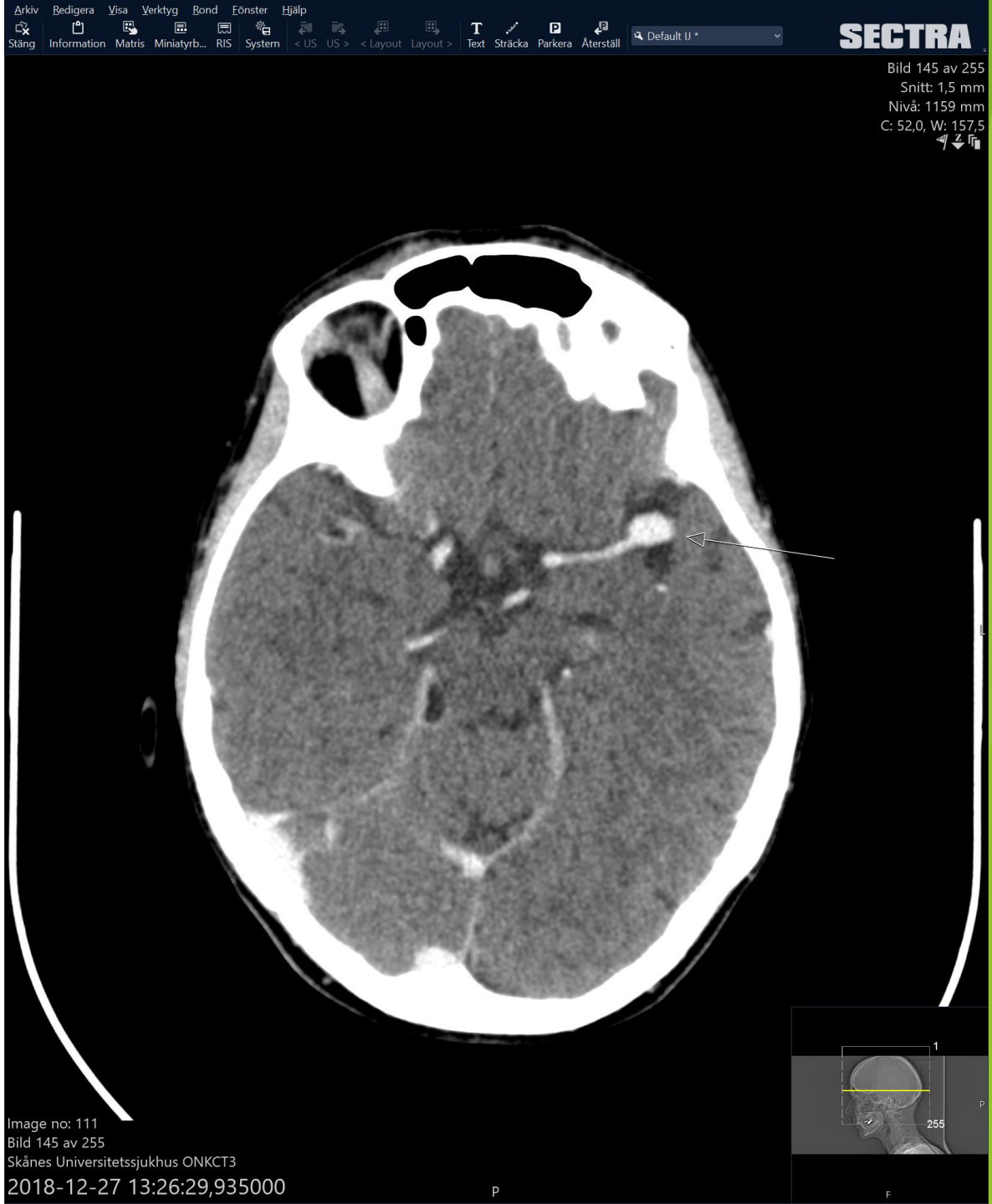
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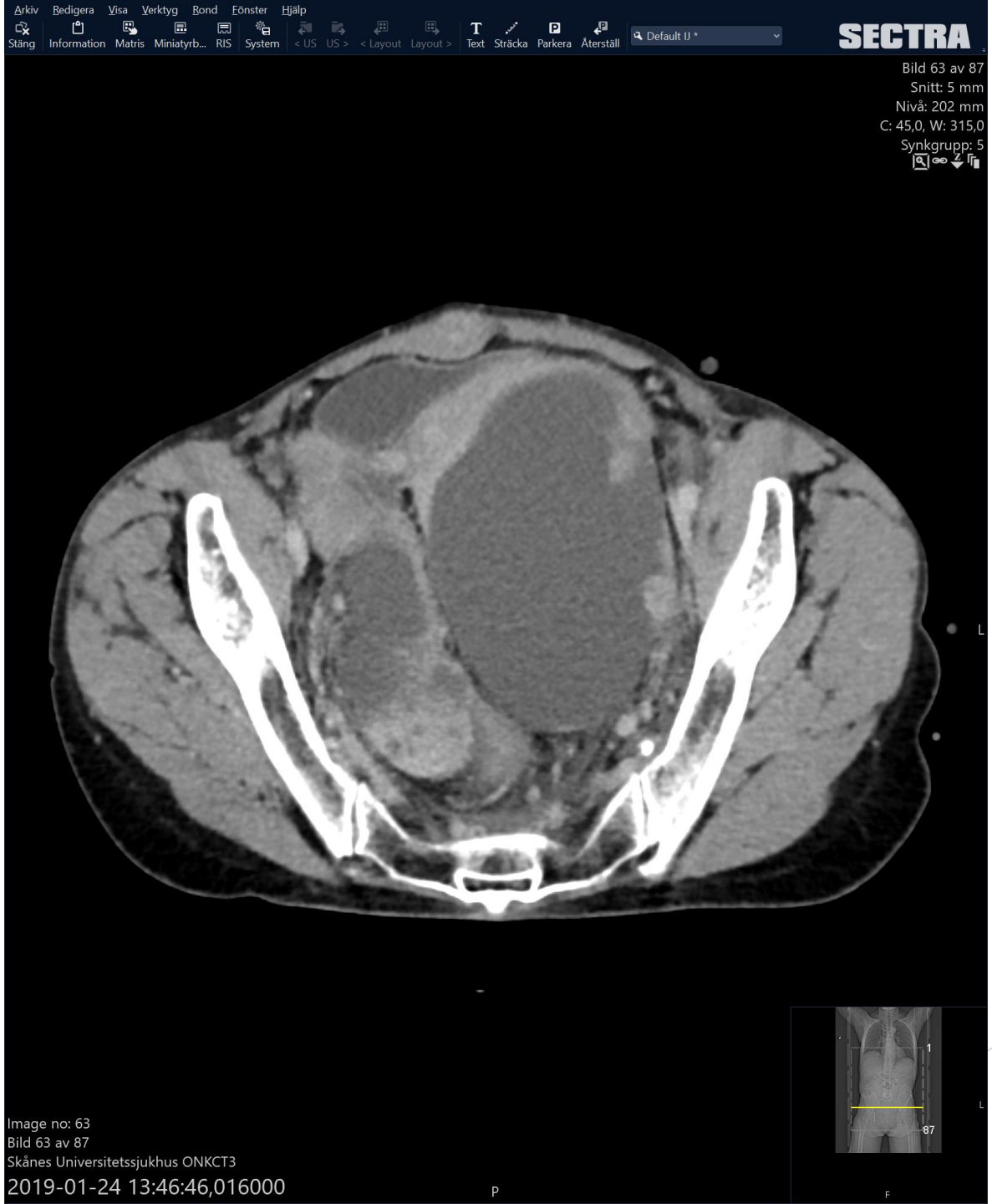
- The aneurysm made it not possible to join the trial
- However, she was successfully operated for her brain aneurysm a week later
- Neurosurgeon: “Very lucky that this aneurysm was found”
- This trial thus probably saved her from a life-threatening bleeding!
- Now, it was also possible to enter in VOYAGER after a treatment pause
- She was randomised to avapritinib
- A baseline CT was done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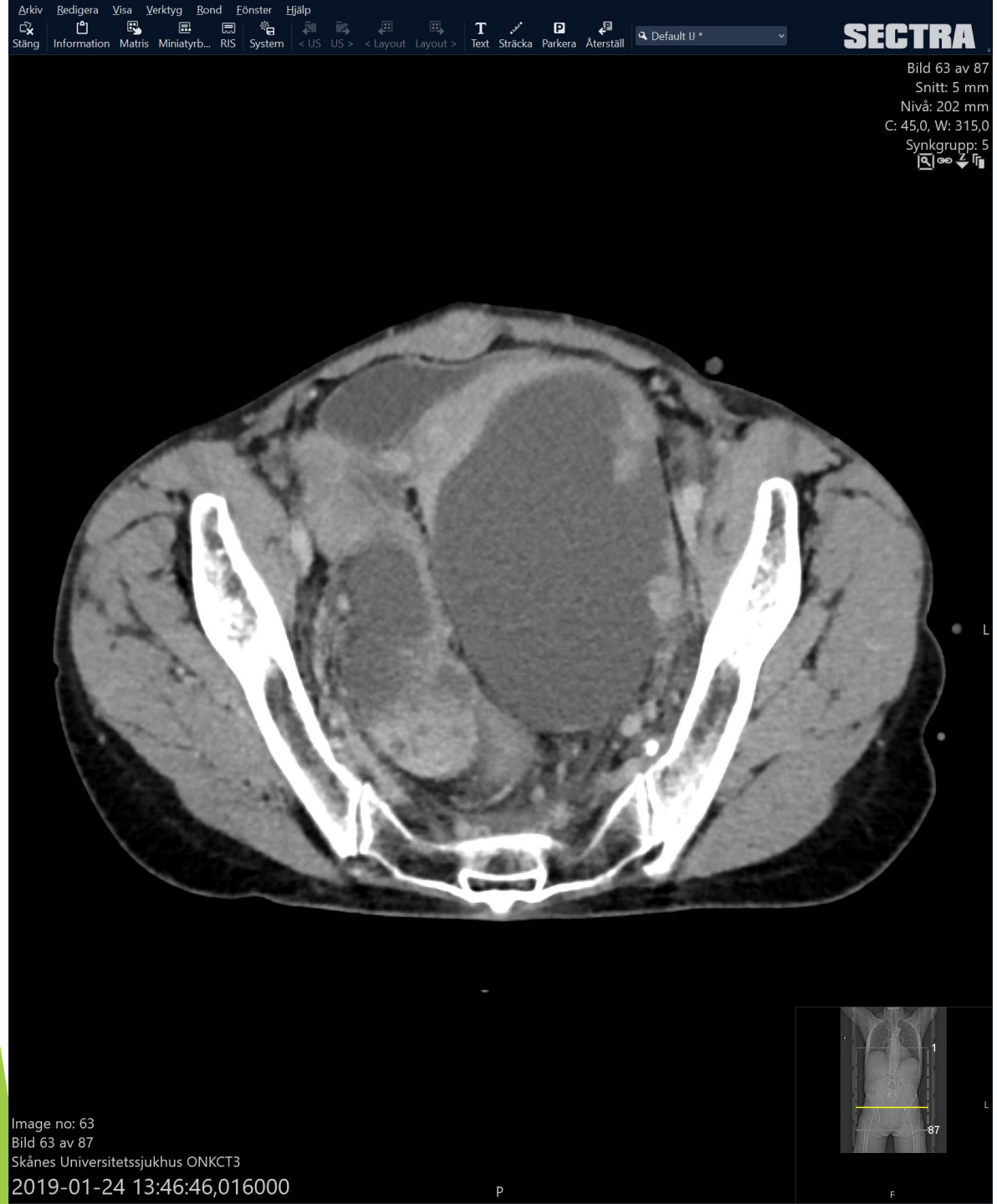
- Avapritinib was started January 30, 2019
- Treatment was tolerated well beside of facial oedema and severe eye irritation (which later lead to a dose reduction)
- First evaluating CT scan was done in late March 2019
- A dramatic tumour regression was seen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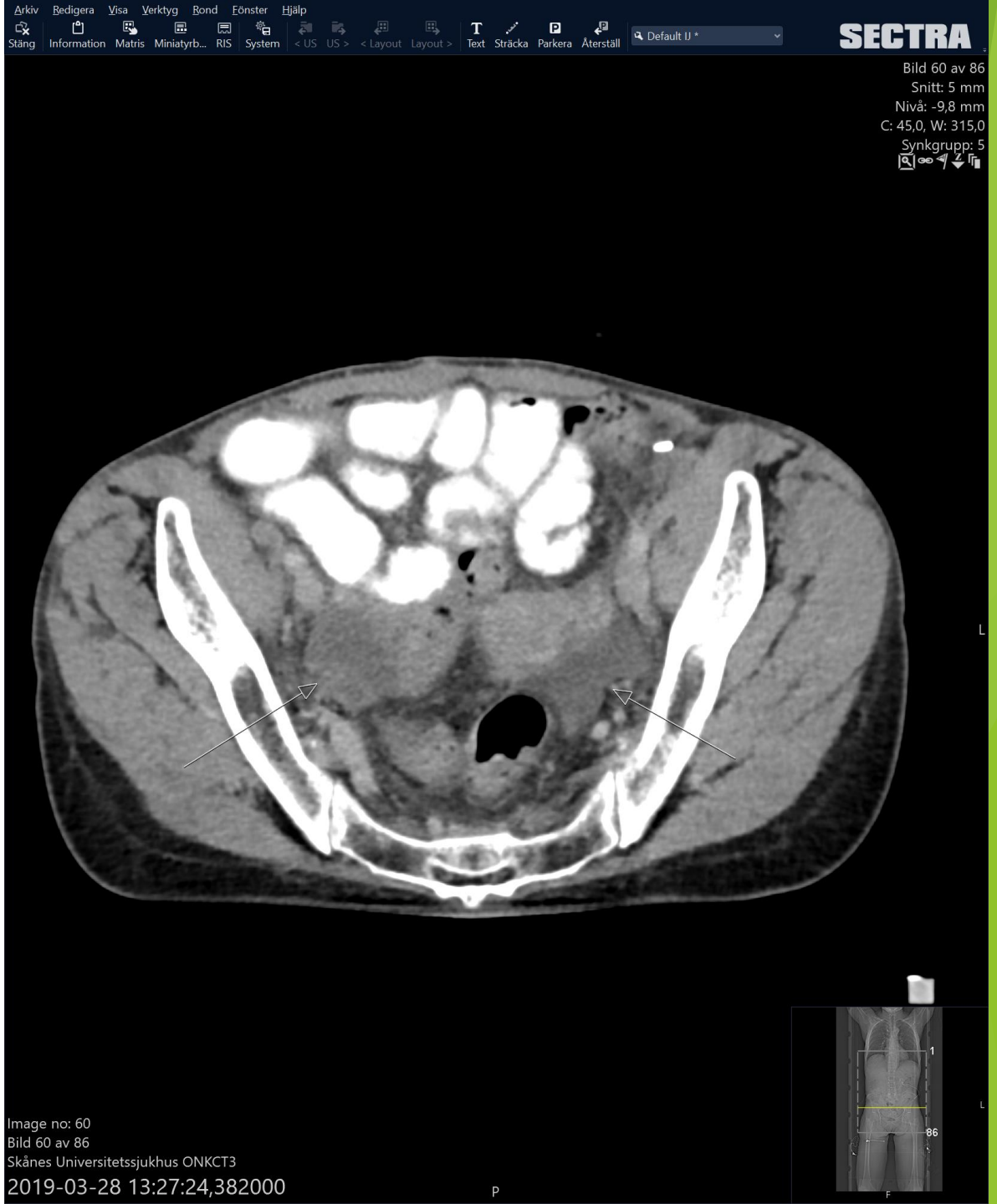
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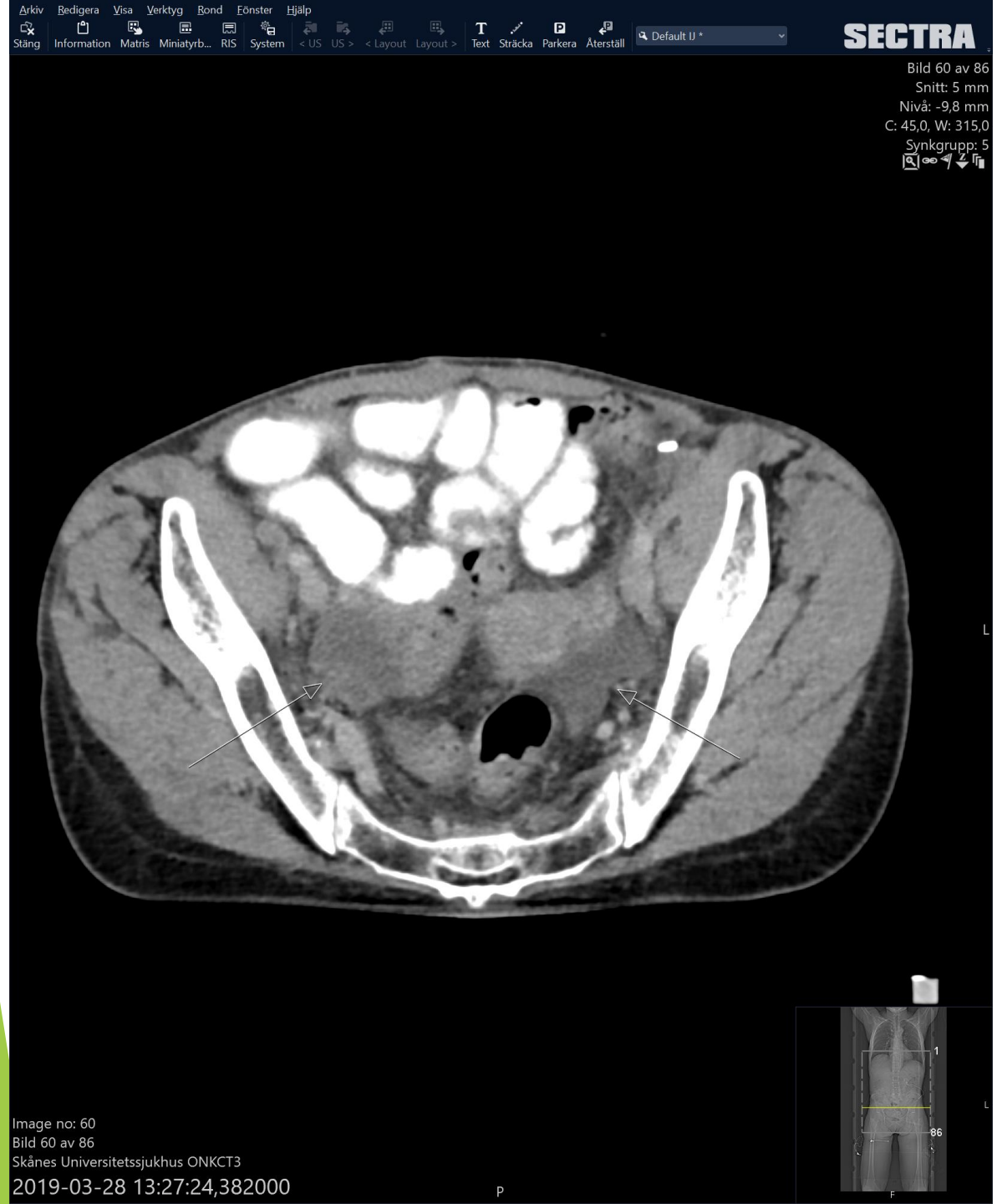
- Treatment continued throughout 2019 and every new CT scan demonstrated further regression
- In late December -19, CT showed almost a complete remission, but there was a small cystic lesion close to the left ovary which was not suspected to be GIST!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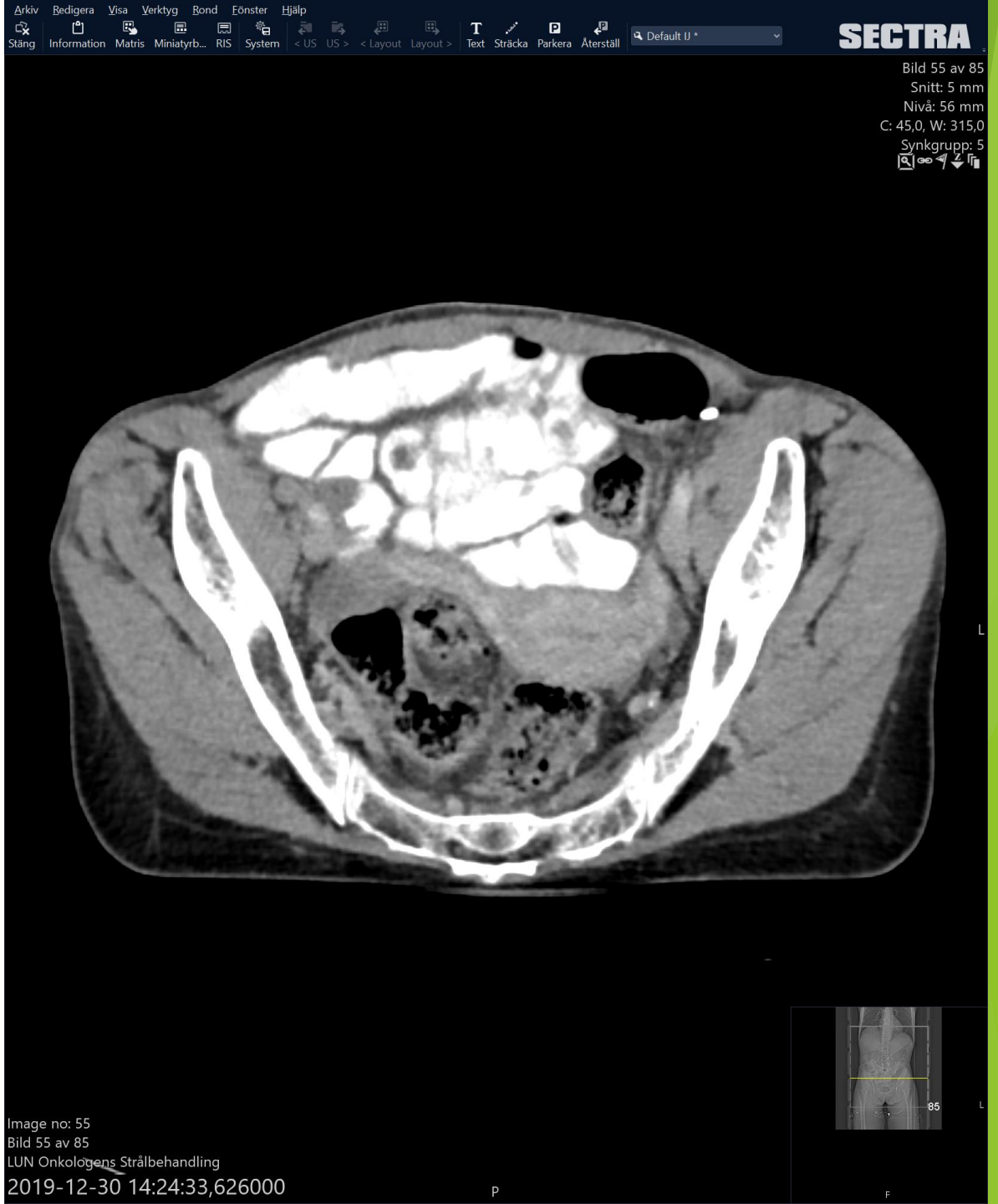
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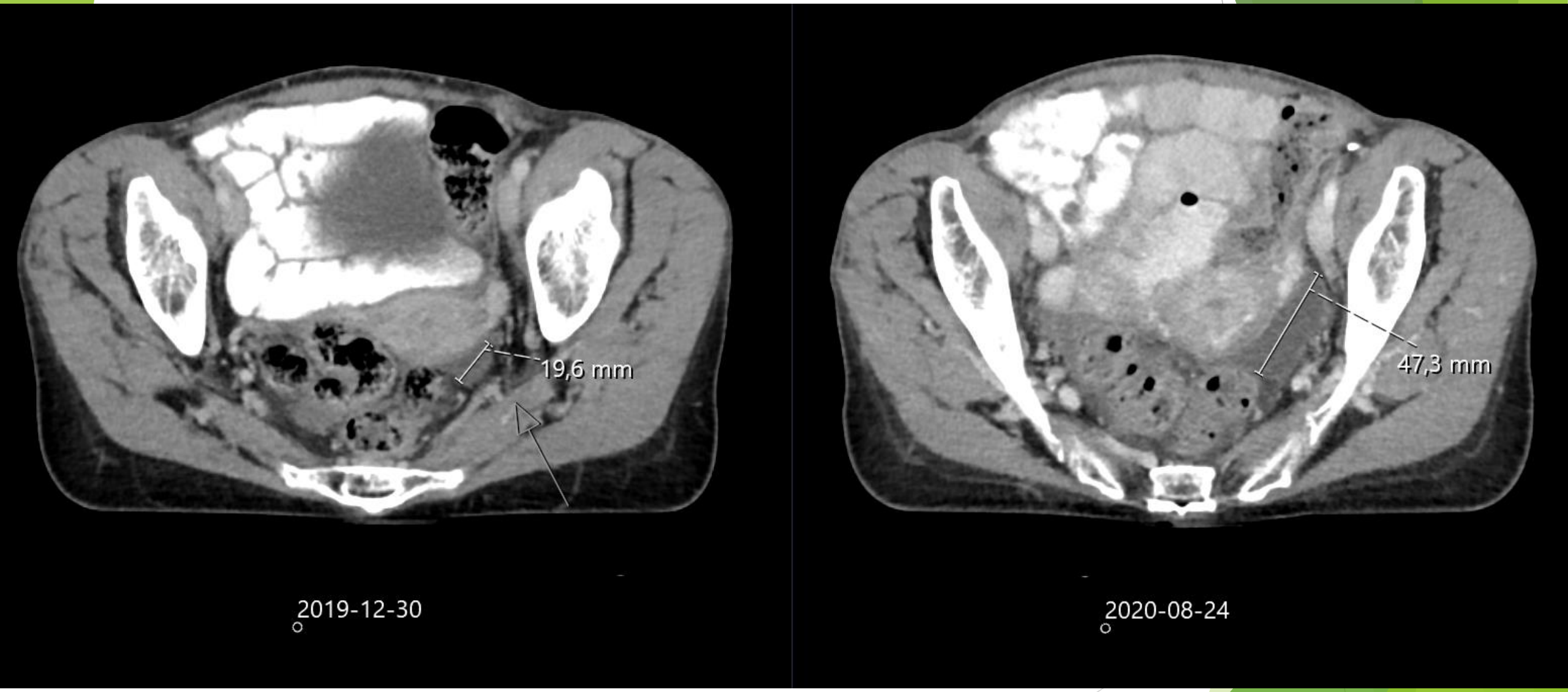
- In August -20 the cystic lesion began to grow dramatically, and it was situated at a site for a former GIST metastasis.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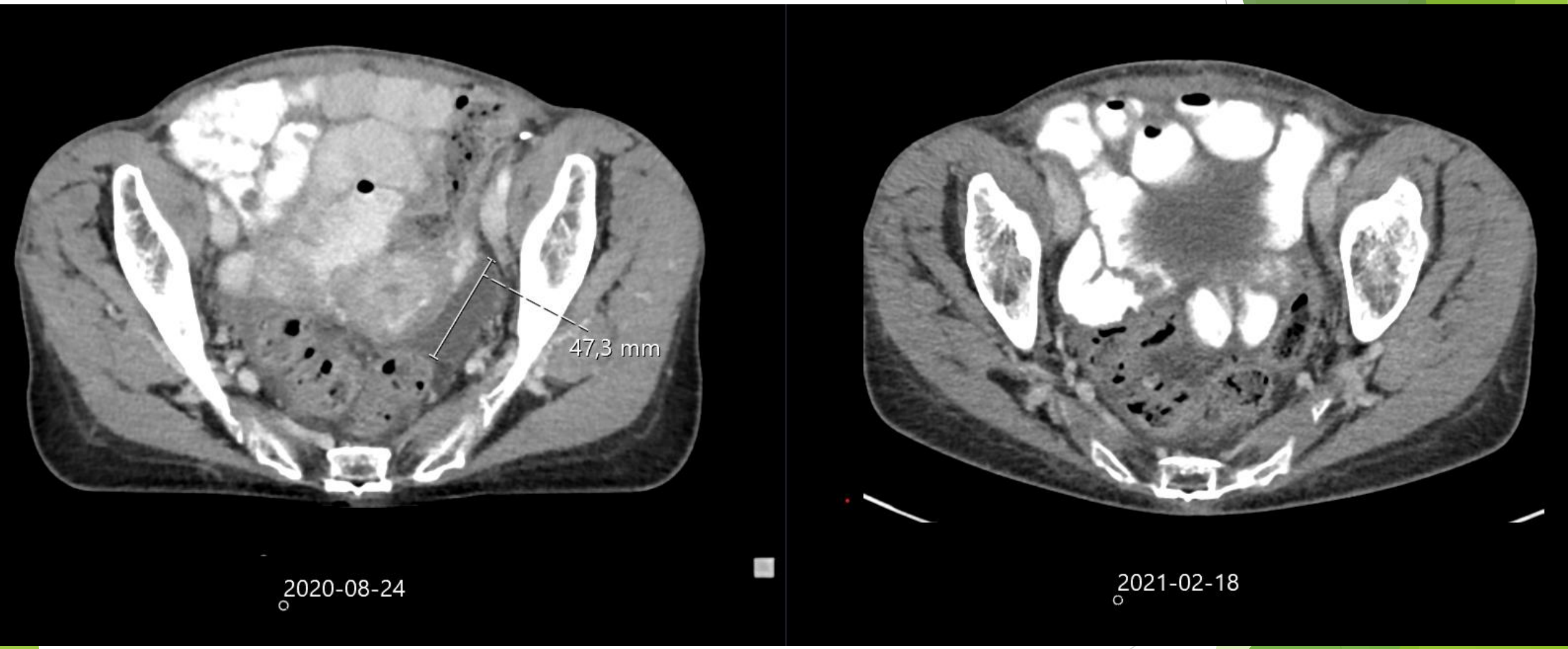
- A radical surgery was performed in October 2020, and the pathology report confirmed that the lesion was a GIST recurrence
- No other signs of progression has been detected up to the latest CT scan in February -21, and she is now in complete remission and without any symptoms 12 years after GIST diagnosis and 9 years after first metastatic lesion
- Tolerates avapritinib in reduced dose (200 mg daily) well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*Comments:*

- *Avapritinib seems to be effective in all PDGFRA exon 18 mutations, not only D842V.*
- *Avapritinib approved for all exon 18 mutations in USA, but only for D842V in Europe!*
- *Orphan indication → very expensive!*
- *This case shows the possible very long disease history of GIST, starting back in 2009, and today, after several surgeries and different drugs, the patient is in a very good shape and without visible disease.*

# The era of targeted treatment