Improving the outcome of GIST treatment - Case reports

10th SPAEN Annual Conference

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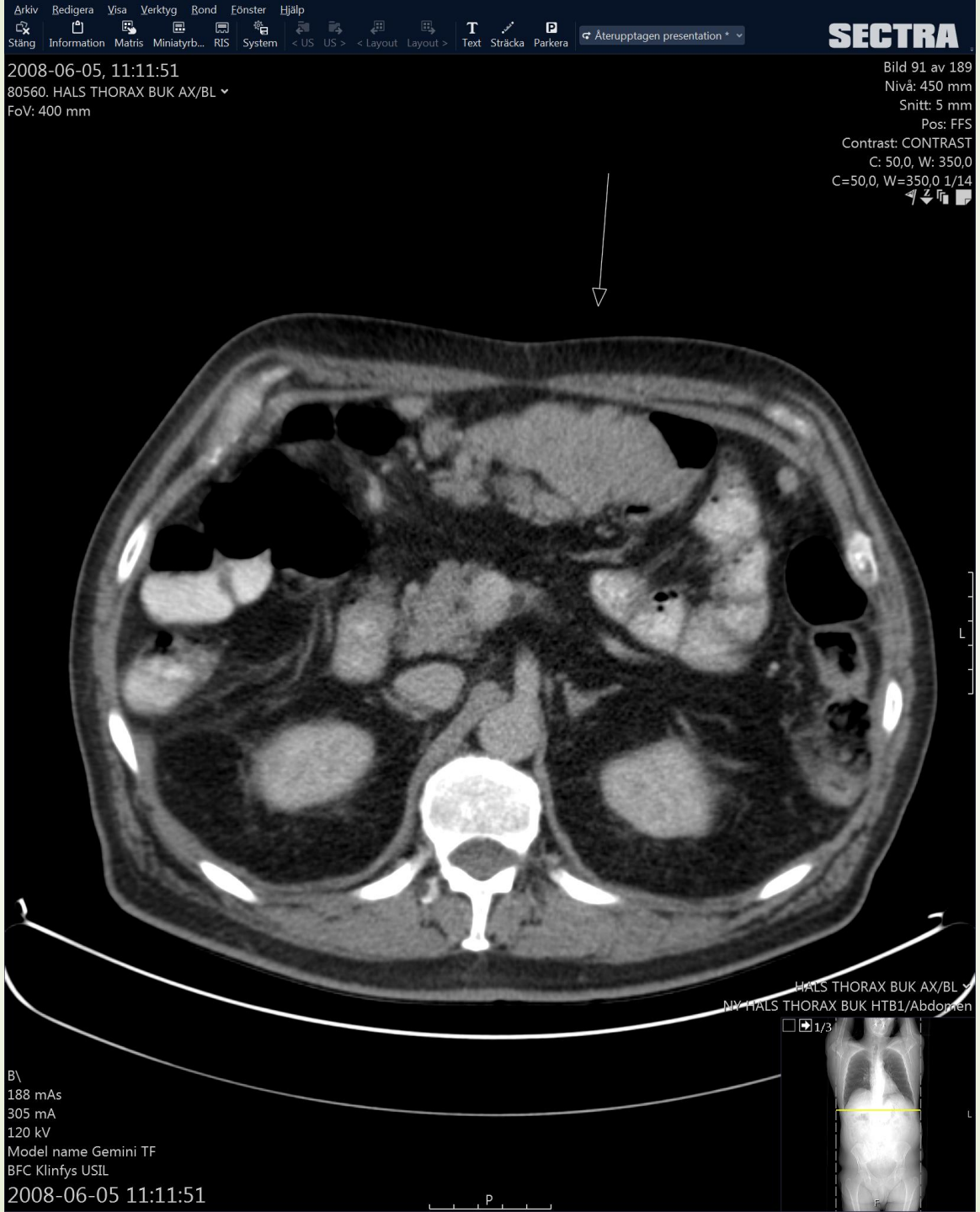
Milan, Italy

Mikael Eriksson

Case 1: Blind but healthy 59-year old man

- In the autumn of 2006 he noticed increased volume of right side of abdomen, but no disturbing symptoms
- At a routine visit at his GP six moths later a distended abdomen was confirmed and a CT scan showed a 14 cm large tumour
- Without diagnostic biopsy, surgery was performed at the local hospital in May 2007, demonstrating a small bowel origin
- Pathology: GIST with very high mitotic count
- Mutation analysis: primary *KIT* exon 17 mutation
- During surgery also disseminated seeding was found with widespread nodules

- He was referred to our Sarcoma/GIST centre, and imatinib (Gleevec) was started in July 2007
- Baseline CT scan did not show any tumours
- Follow-up CT in March 2008 showed several small tumours in the peritoneum → increased imatinib dose: 400 mg x 2
- PET-CT in June 2008 showed further clear progression → sunitinib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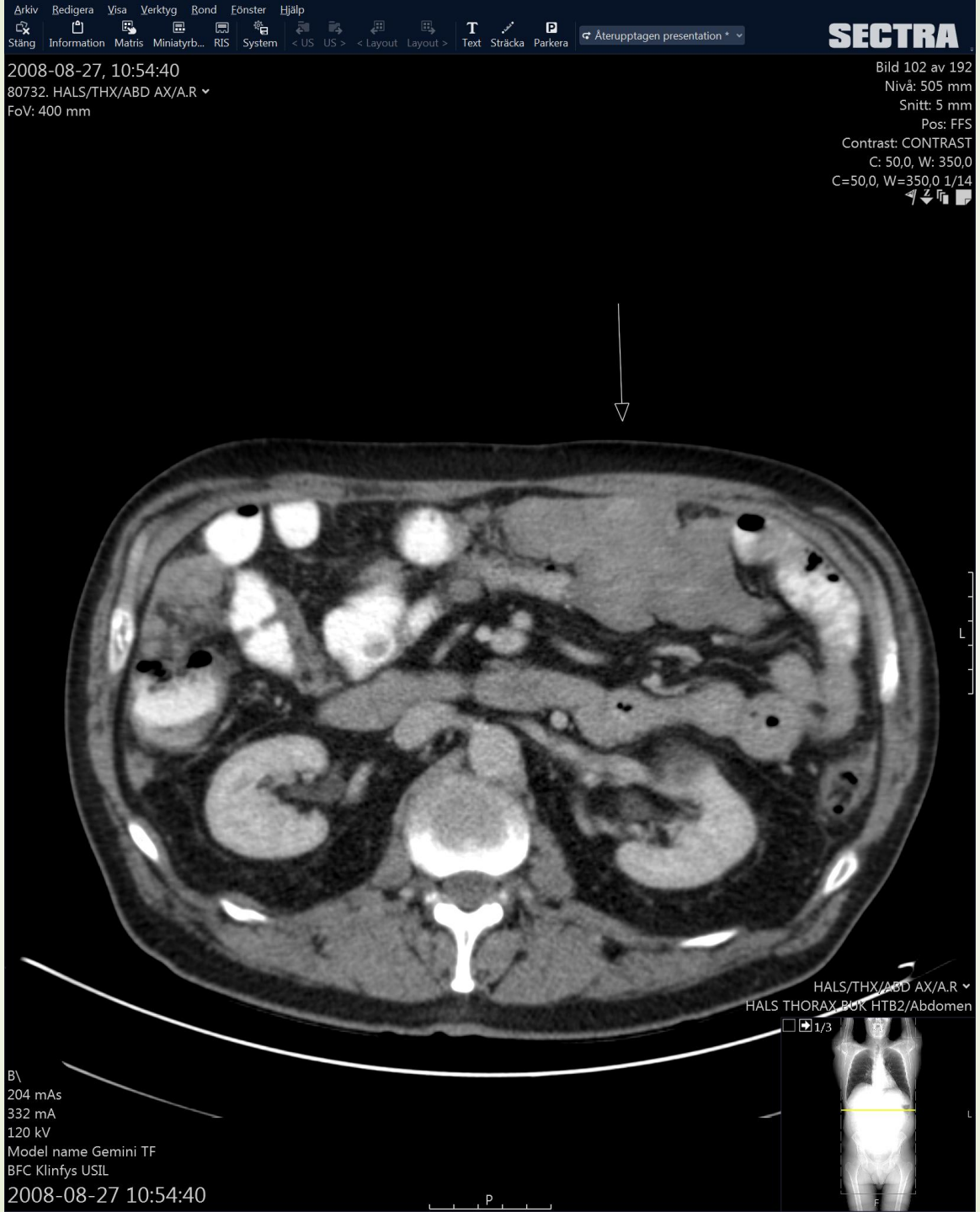
- A new CT scan in August showed further progression
- At that time, regorafenib was not invented, and no other drugs were registered for GIST
- No clinical trial was available at the time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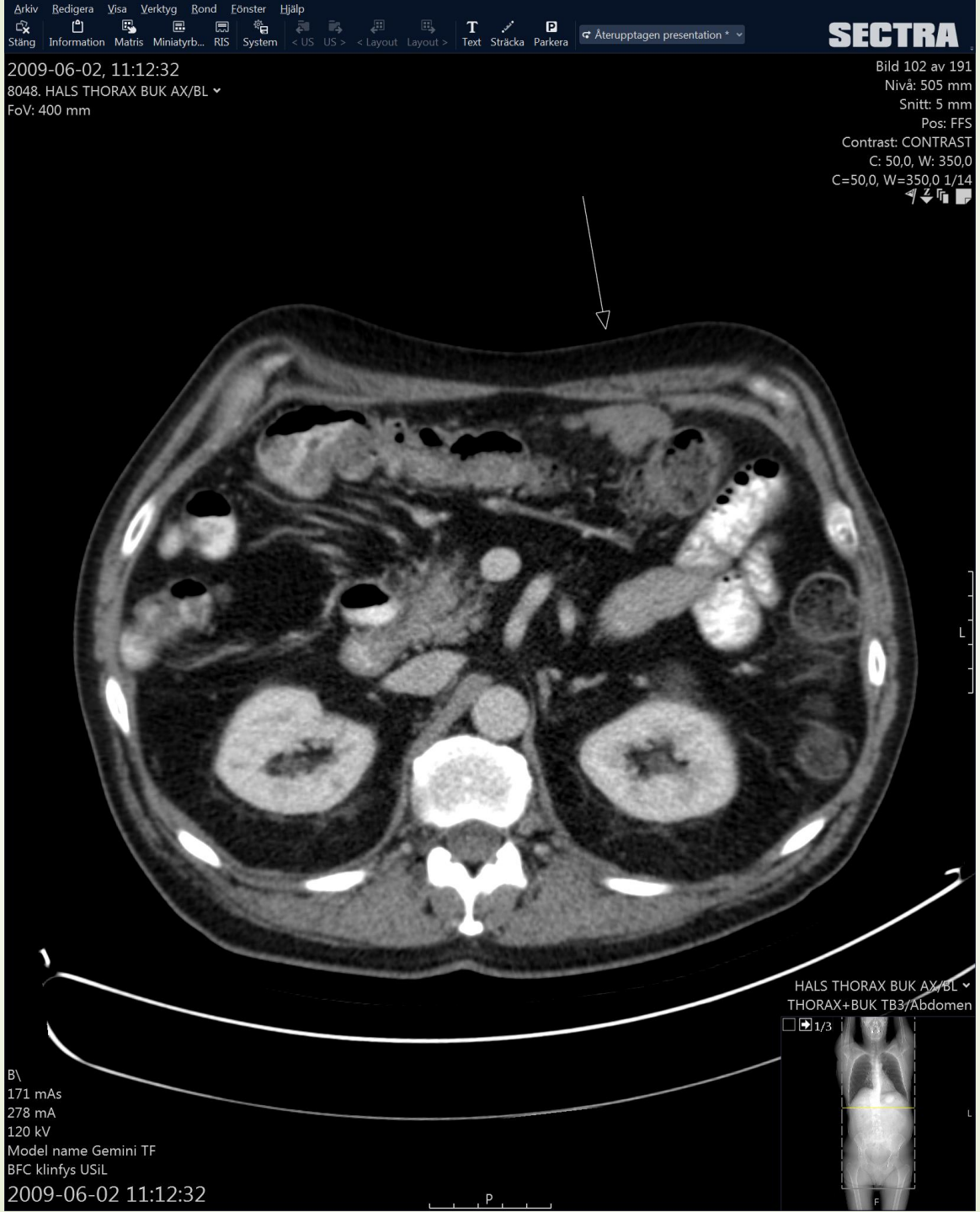
- Sorafenib (Nexavar) was prescribed “off label”
- Some side effects, diarrhoea and hand-foot syndrome, which were much improved by symptomatic treatments
- CT scan in November 2008 showed good regression of all tumours
- New CT scans in June and December 2009 showed somewhat further regression
- In December also a PET scan was performed showing no positivity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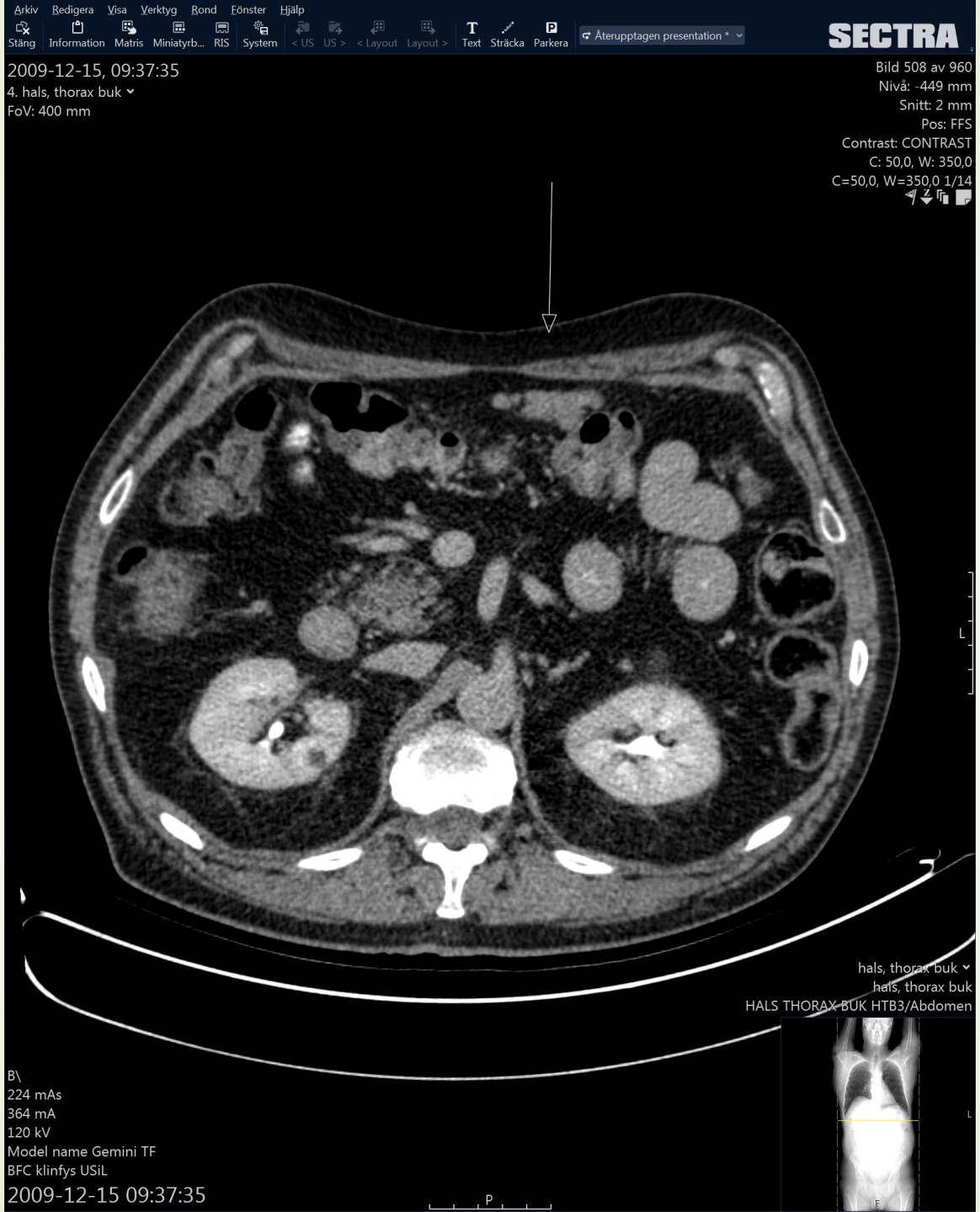
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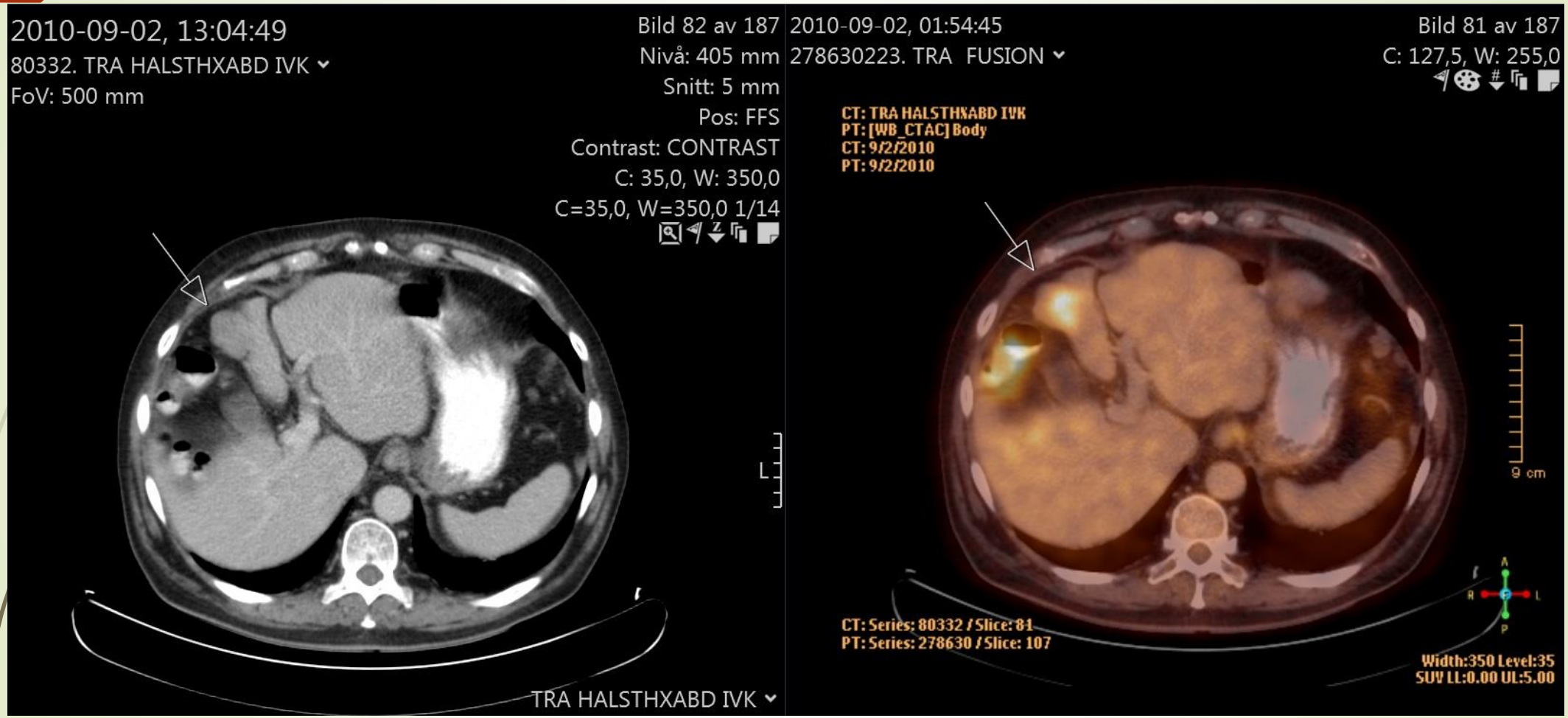
- However, in June 2010 a slight progression could be seen, but the patient had no abdominal symptoms and tolerated the treatment well, so we continued
- A PET-CT in September 2010, two years after start of sorafenib, showed a further progression and also metabolic activity in the largest tumours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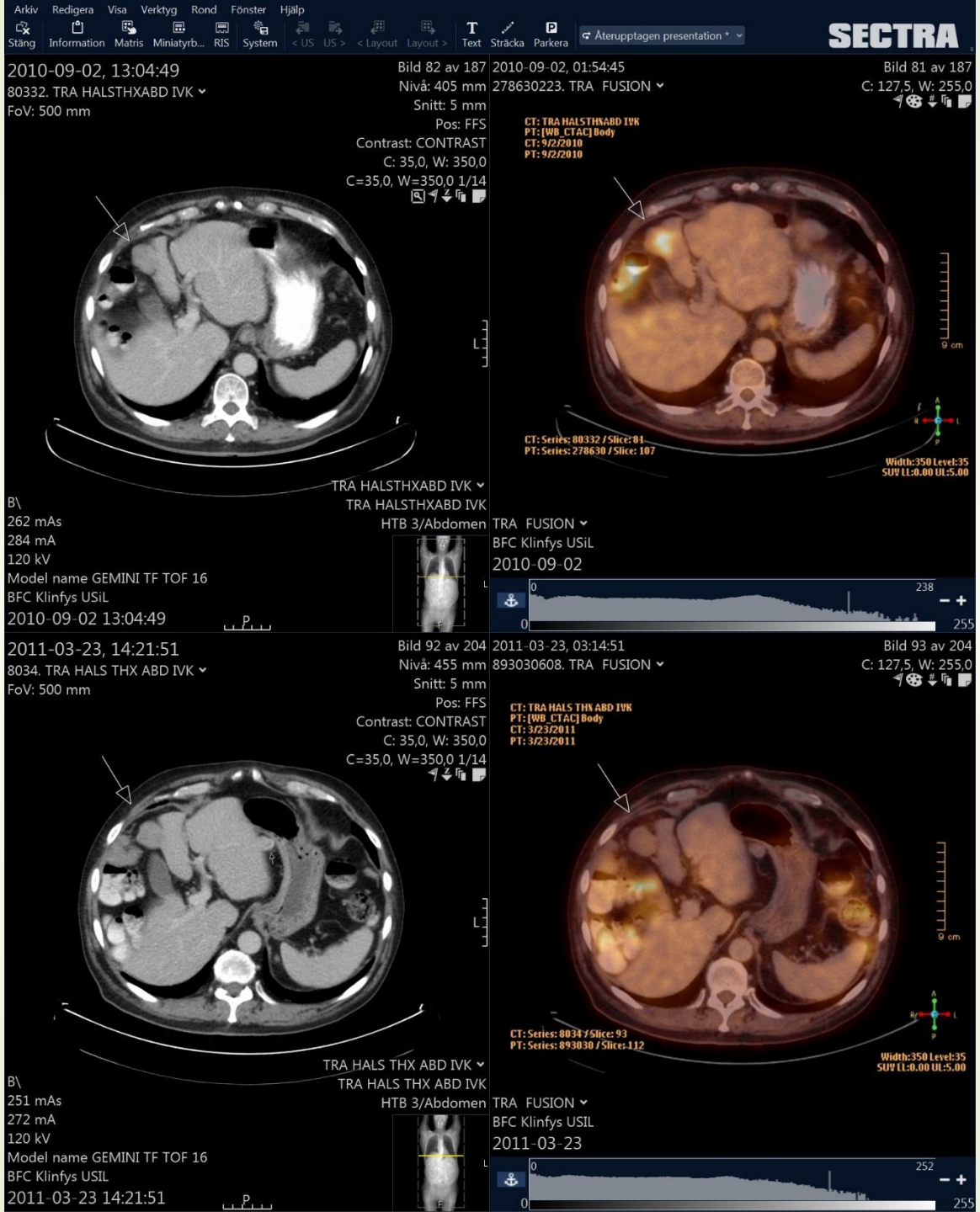
What to do now?

- Re-challenge with imatinib may help some patients in this situation but usually only for a short time, and there was no clear response on imatinib initially for this patient
- Since sorafenib had been very effective during two years, we kept this drug and added a mTOR-inhibitor, everolimus
- PET-CT in November 2010 showed status quo with no further progression
- PET-CT in March 2011 showed a metabolic regression and no tumour growth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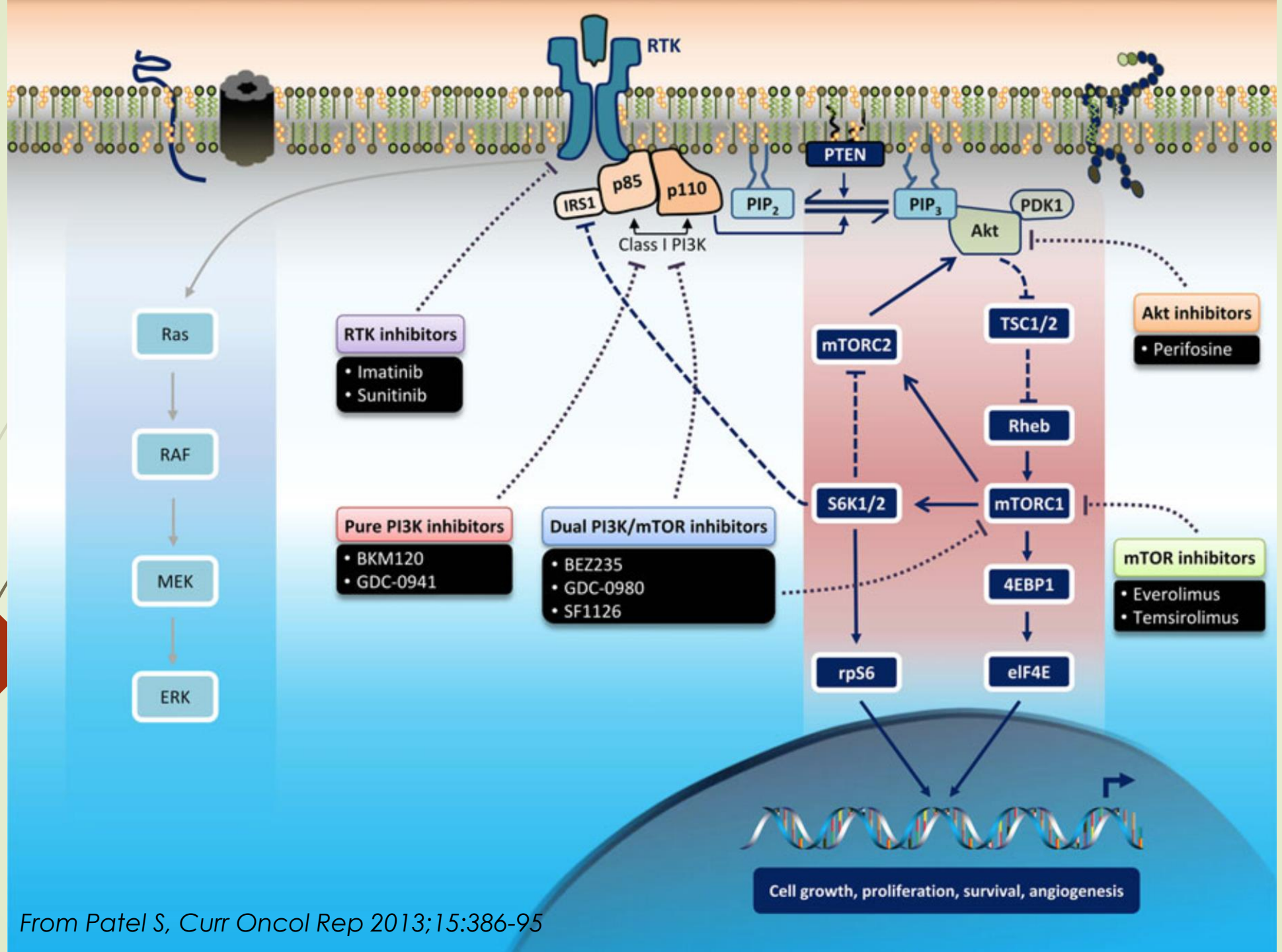
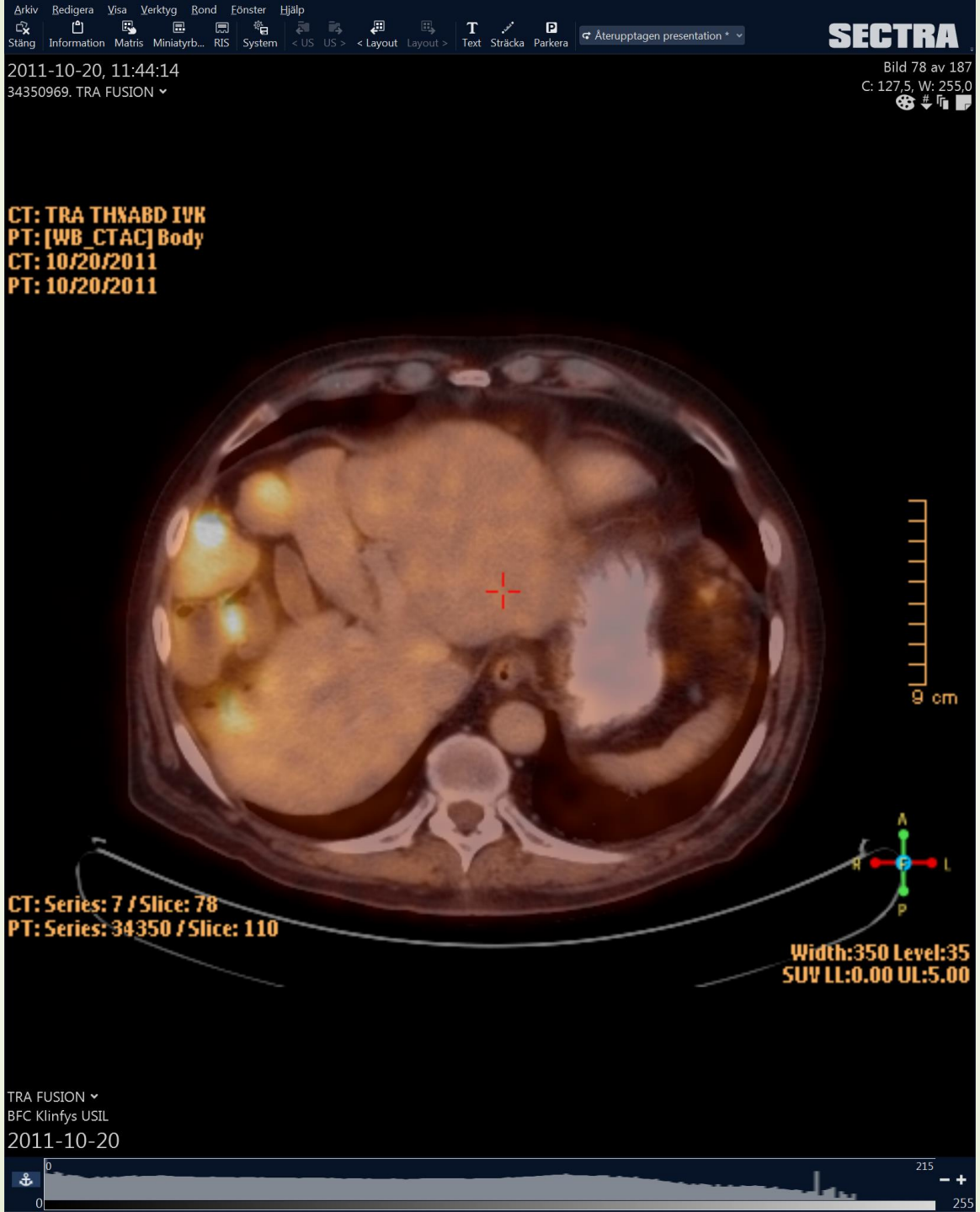


From Patel S, Curr Oncol Rep 2013;15:386-95

- October 2011, 13 months after addition of everolimus, a PET-CT showed metabolic progression and slight tumour growth
- No symptoms, tolerated the combined treatment well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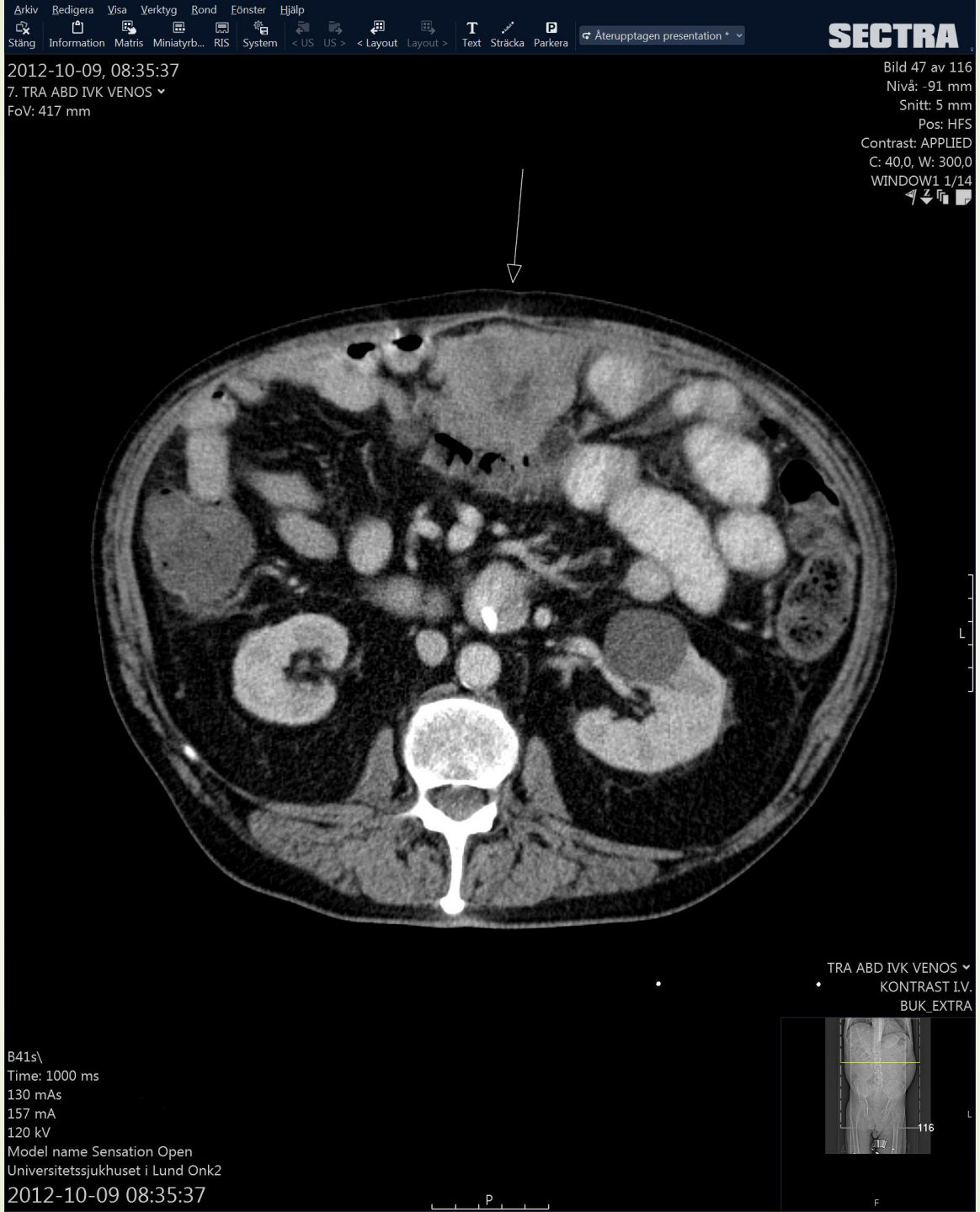
- February 2012 status quo
- April and July 2012 further slow progression without tumour-related symptoms
- August 2012 epigastric pain
- CT scan found a new lesion in upper abdomen, 8 x 6 cm
- No change in other lesions since July
- A new CT in October showed further increase of this lesion, the rest of the disease under control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What to do with *just one* growing lesion?

- Local treatment should be considered:

  - surgery
  - radiotherapy
  - radiofrequency ablation
  - vascular embolisation

- After discussion at our multidisciplinary tumour board, we decided to suggest radiotherapy, which at that time was investigated within a clinical trial
- The patient accepted the suggestion and joined the trial
- A radiotherapy dose of 40 Gy in 20 days was given in October 2012 and was very well tolerated
- A CT scan in December showed slight regression of the tumour

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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.

Gastrointestinal stromal tumors (GIST) frequently give rise to liver and intra-abdominal metastases. Imatinib, an inhibitor of KIT, PDGFRA, and a few other kinases, is the standard first-line agent for metastatic GIST [1,2] with responses lasting for a few years, but acquired drug resistance is frequent. Sunitinib is approved for patients whose GIST is refractory to imatinib or who do not tolerate imatinib [3], and regorafenib for those whose disease does not respond to imatinib and sunitinib [4]. The median time to GIST progression on sunitinib and regorafenib is 6 and 5 months, respectively [3,4]. Most patients with advanced GIST will eventually receive palliative care.

Some retrospective data suggest that radiotherapy is not beneficial in the treatment of GIST [5], and GIST has been considered radiotherapy-resistant or minimally responsive [6–9]. Current treatment guidelines do not discuss radiotherapy as a therapeutic option [1], or consider it only for palliation of rare bone metastases [2]. However, results from a few case reports (reviewed in [10]) and a retrospective series with 15 patients [11] suggest that advanced GIST is not uniformly radioresistant and that selected patients may benefit from radiotherapy.

To our knowledge, no prospective study has investigated palliative radiotherapy as the treatment of GIST. We report here the first prospective trial addressing this patient population.

Patients and methods

Study design

The study was a non-randomized, prospective multicenter trial. Patients were registered centrally and reviewed for eligibility prior to radiotherapy initiation. The primary endpoint was target lesion response to radiotherapy. Secondary objectives included time to progression (TTP) of the irradiated lesions, TTP of GIST at any site, survival, and adverse effects associated with radiotherapy.

Patients

Eligible patients had histologically verified inoperable GIST, either locally advanced or metastatic disease. Tumor immunostaining for KIT was done in all cases as part of the diagnostic

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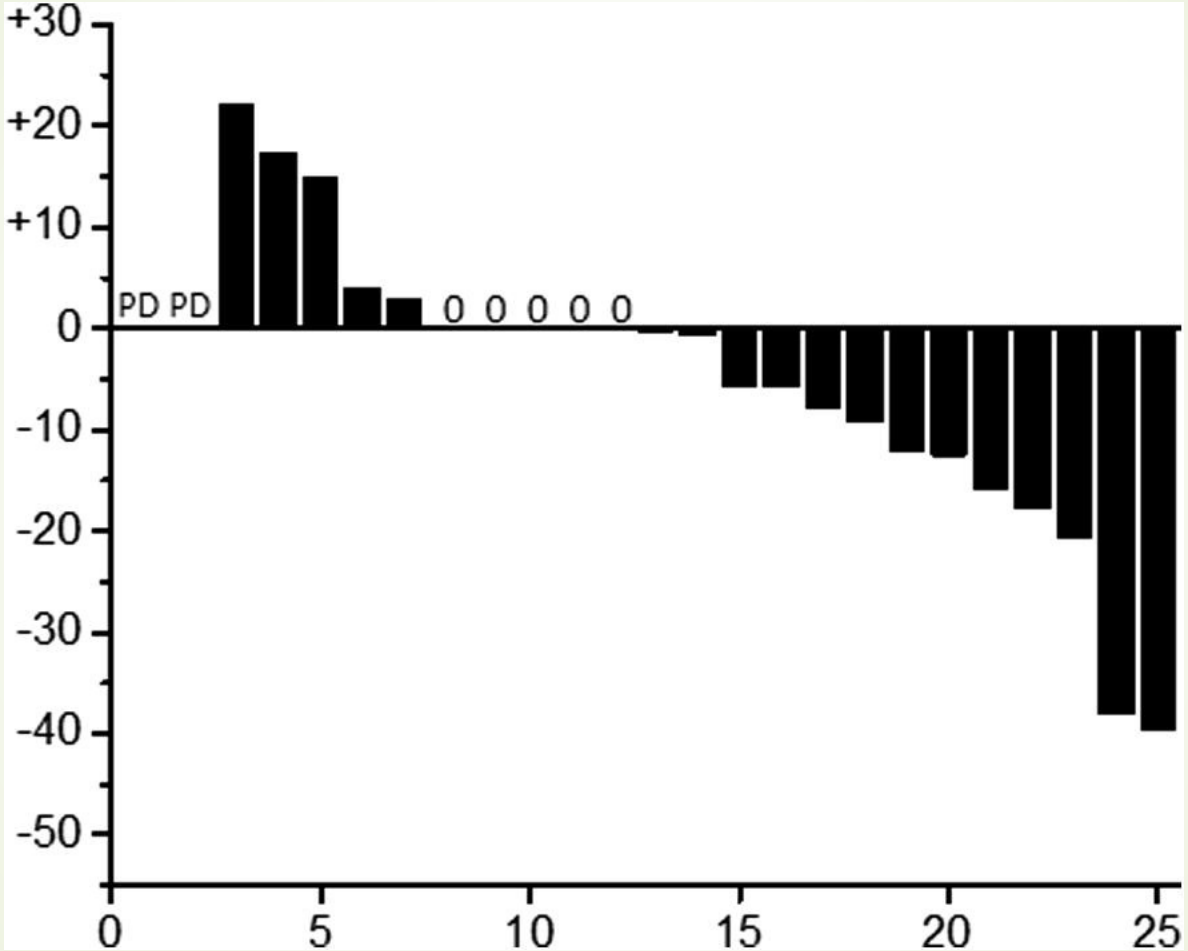
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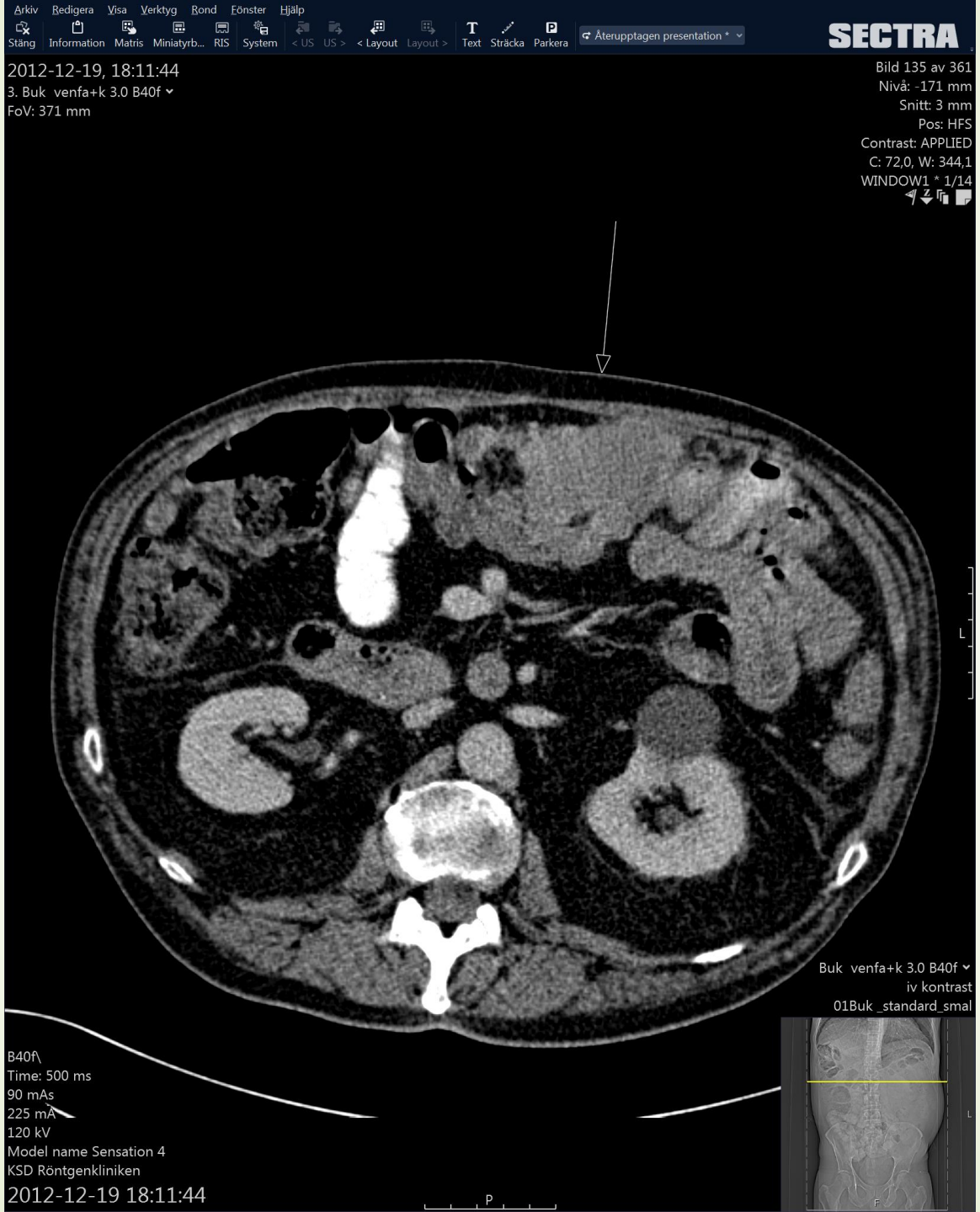
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- January 2013 status quo
- May 2013 general progression but still without much symptoms and very active
- Abdominal discomfort started in June, and with further progression we tried to switch sorafenib to pazopanib
- No further effect was seen, however
- The patient died in December 2013, more than three years after start of combination therapy with mTOR inhibition, and 14 months after radiotherapy

Conclusions

- Even GIST patients refractory to imatinib and sunitinib may have a long survival with other tyrosine kinase inhibitors (and not only regorafenib)
- mTOR-inhibition may add effect to TKIs
- Local treatment alternatives as surgery or radiotherapy may not be forgotten in a GIST generally controlled by TKI but with one or a couple of lesions growing

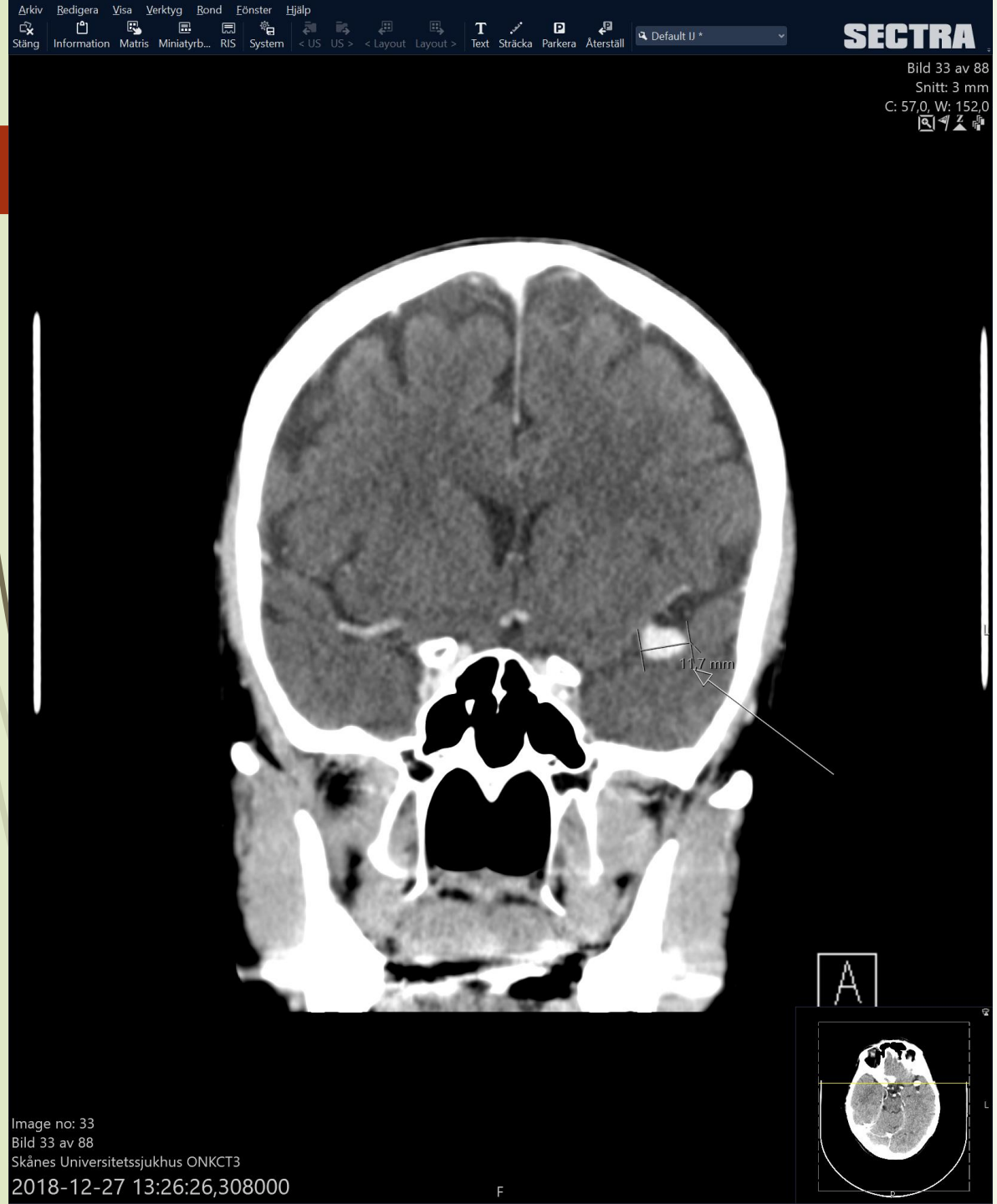
Case 2: 54-year old healthy woman

- Autumn 2009 increasing distension of abdomen and a growing tumour on the left side
- CT scan: 14 x 10 x 14 cm; 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

- April 2012 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

- Continued with imatinib 200 mg daily, could not tolerate a dose increase
- CT scan in October 2017 showed two small suspected lesions in the pelvic region, 10 and 7 mm in size
- Next CT 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 2018 showed only one remaining lesion of 8 mm
- CT scan in December 2018, however, showed a dramatic GIST increase

- Information was given about the on-going international trial VOYAGER randomising between regorafenib and the new TKI avapritinib
- Avapritinib has shown very promising results in early trials, but with some problematic side effects as cognitive disturbances and 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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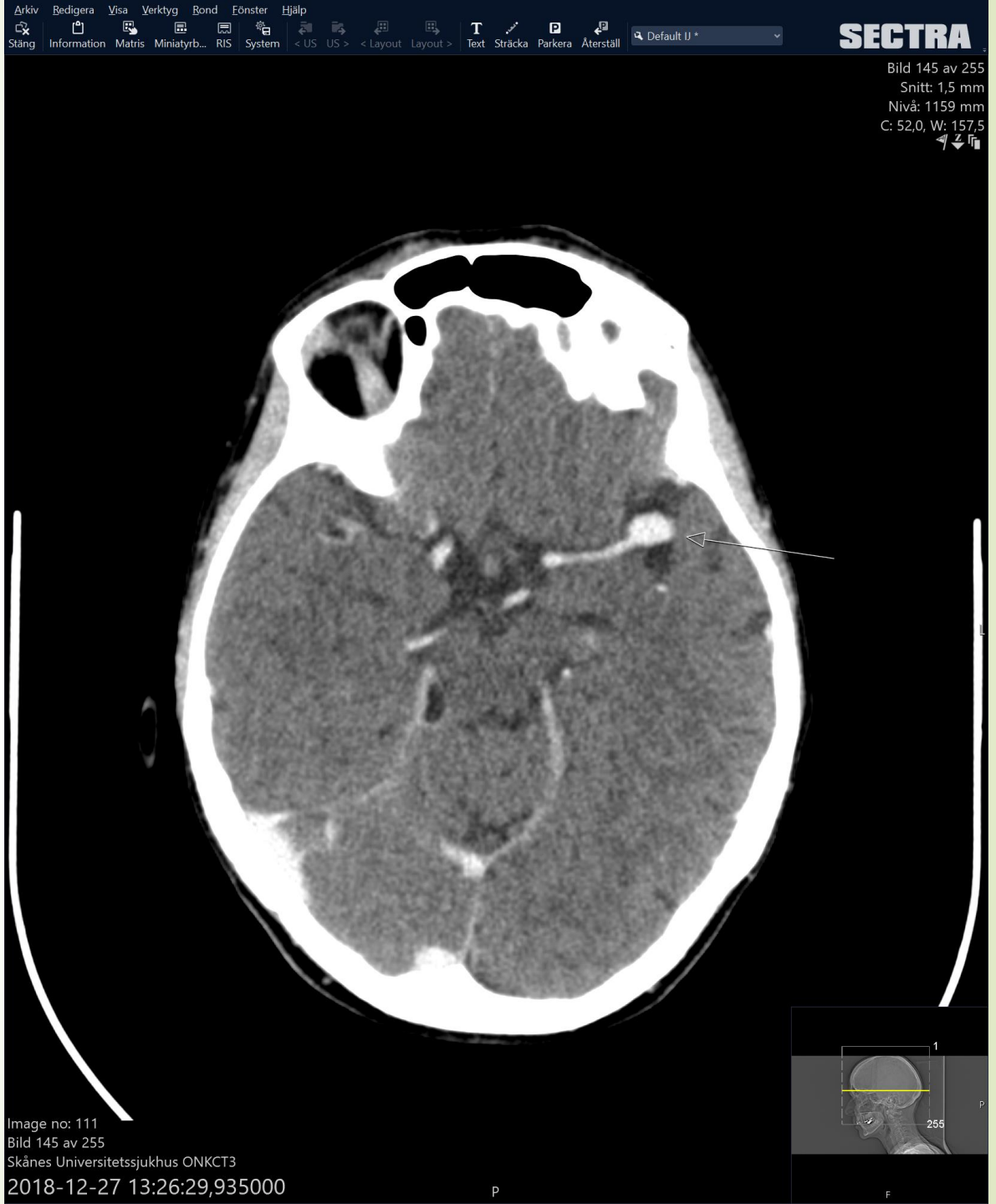
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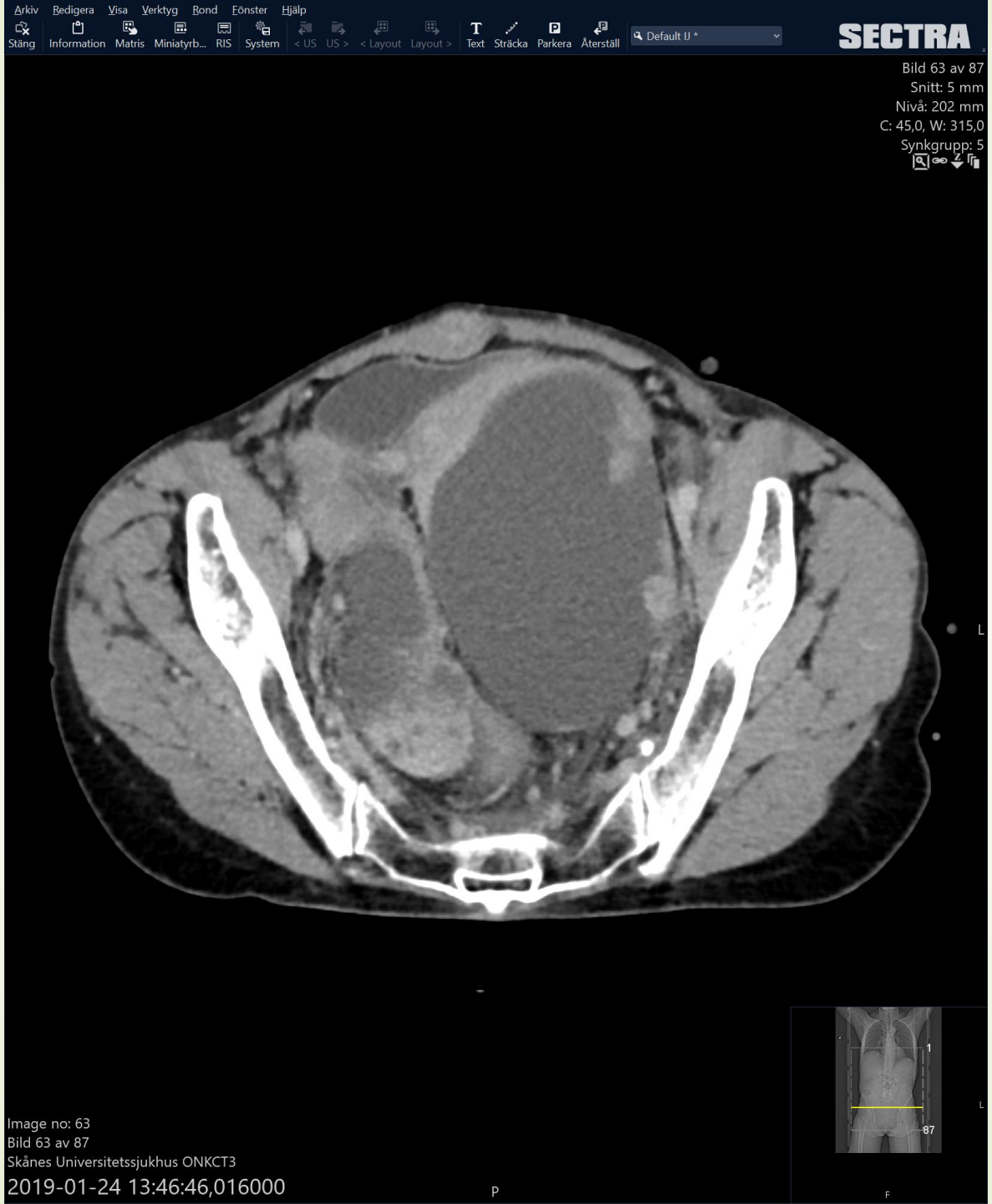
- The aneurysm made it not possible to join the trial
- However, she was successfully operated for her brain aneurysm a week later
- Neurosurgeon: “Very lucky that this aneurysm was found”
- This trial thus probably saved her from a life-threatening bleeding!
- Now, it was also possible to enter in VOYAGER 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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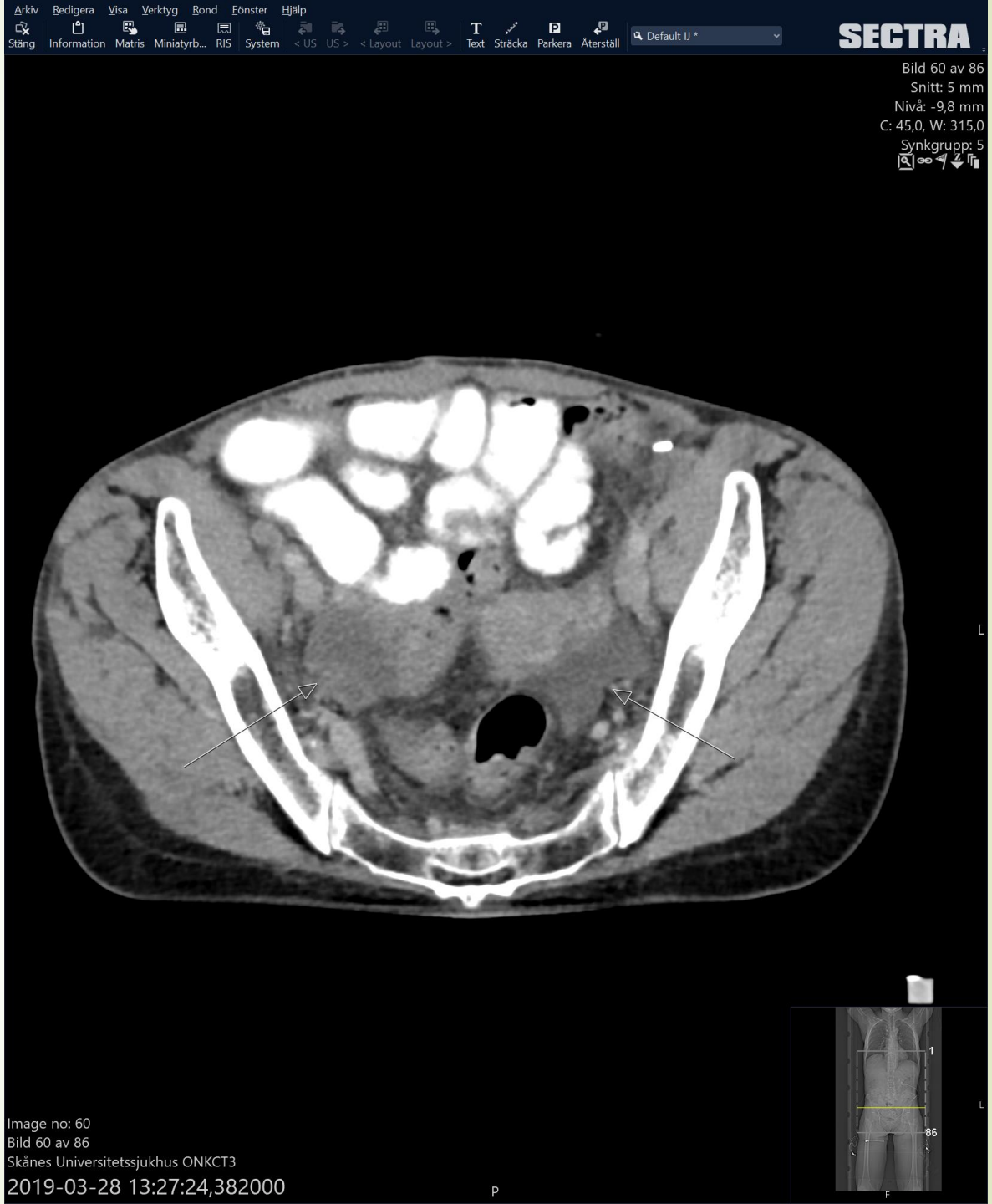
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86
Image no: 60
Bild 60 av 86
Skånes Universitetssjukhus ONKCT3
2019-03-28 13:27:24,382000
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- Treatment continued throughout 2019 and every new CT scan demonstrated further regression
- Last CT was performed December 30, and showed almost a complete remission!


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Skånes Universitetssjukhus ONKCT3
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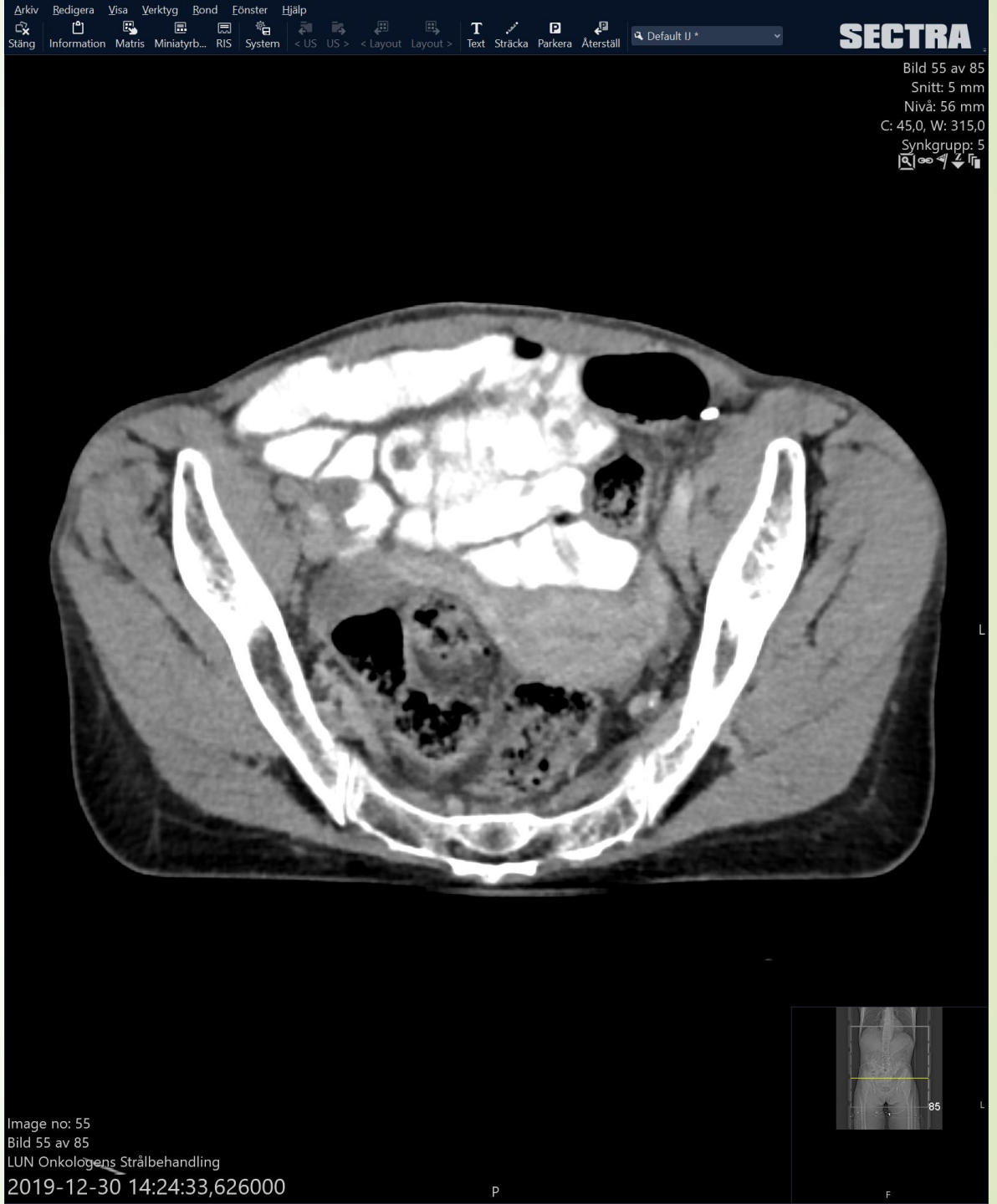
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Bild 55 av 85
LUN Onkologens Strålbehandling
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Conclusions

- 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 almost without visible disease
- Imatinib may be very effective also in other mutations than *KIT* exon 9 and 11
- Avapritinib (which will be called AYVAKIT) is one of two new very promising TKIs showing that we improve treatment possibilities effectively over time (the other is ripretinib)