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European Reference Network
for rare or low prevalence complex diseases

Network Paediatric Cancer (ERN PaedCan)


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# *The diagnosis, treatment and follow-up of gastrointestinal stromal tumor in an adolescent patient*


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# COI declaration

- Novartis – conference fee, travel, accomodation

# Gastrointestinal stromal tumor

- Mesenchymal tumor of the GI tract
- Usually affects the elderly
- Most commonly found in the bowel
- Proliferation of Cajal's peacemaker cells – spindle cell histology
- *KIT* or *PDGFRA*-mutation associated neoplasm
- Treatment includes surgery and TKI administration

# Question 1

What is the most common site of GIST in the pediatric population?

A. Large intestine
B. Small intestine
C. Stomach
D. Duodenum

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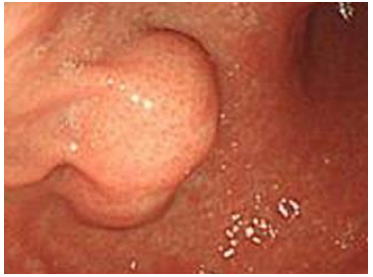
# GIST – differences in the pediatric population

- 0.5-2.0% of diagnosed GISTs is found in children
- Female predominance
- 85% wild-type for *KIT/PDGFRA,* more commonly associated with *SDH* or *IGF1R* abnormalities
- Epithelioid or mixed histology
- Commonly lymph node metastases, but indolent and slow course of the disease

# Case presentation

- Primary NHL suspicion
- Tumor bleeding
- GIST suspicion



Kataoka et al., 2013.

## Presentation

*September 2016*

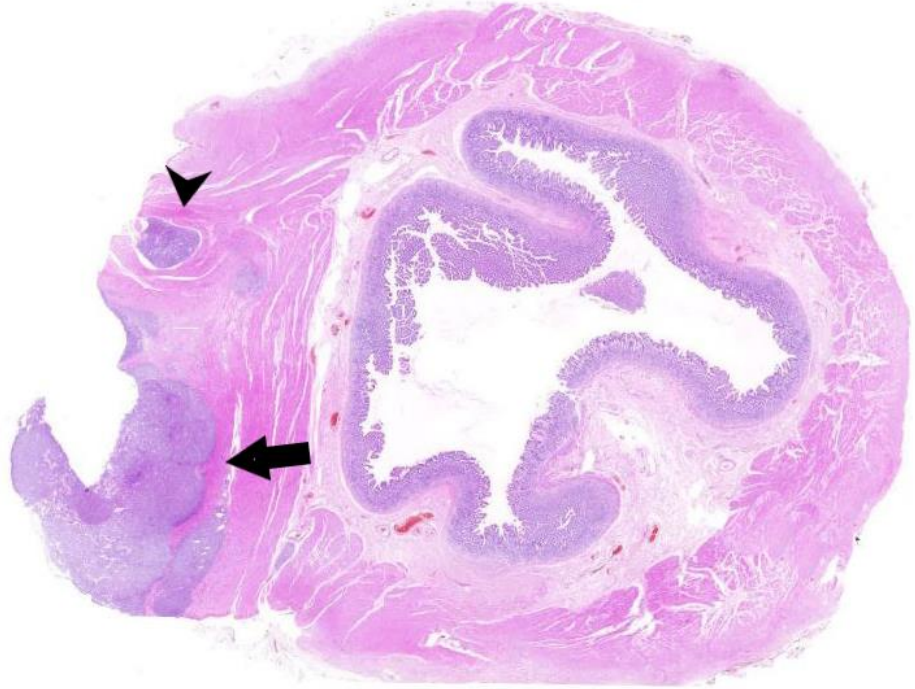
- 10 years old female
- Acute epigastric pain
- Tumor of the stomach verified in USG and CT – fundus and lesser curvature of the stomach

## Biopsy

## Surgery

- Total surgical resection of the lesion
- Smallest margin – 0.1 mm
- No tumor rupture
- Solid, gray mass on gross examination measuring >5 cm in the greatest diameter

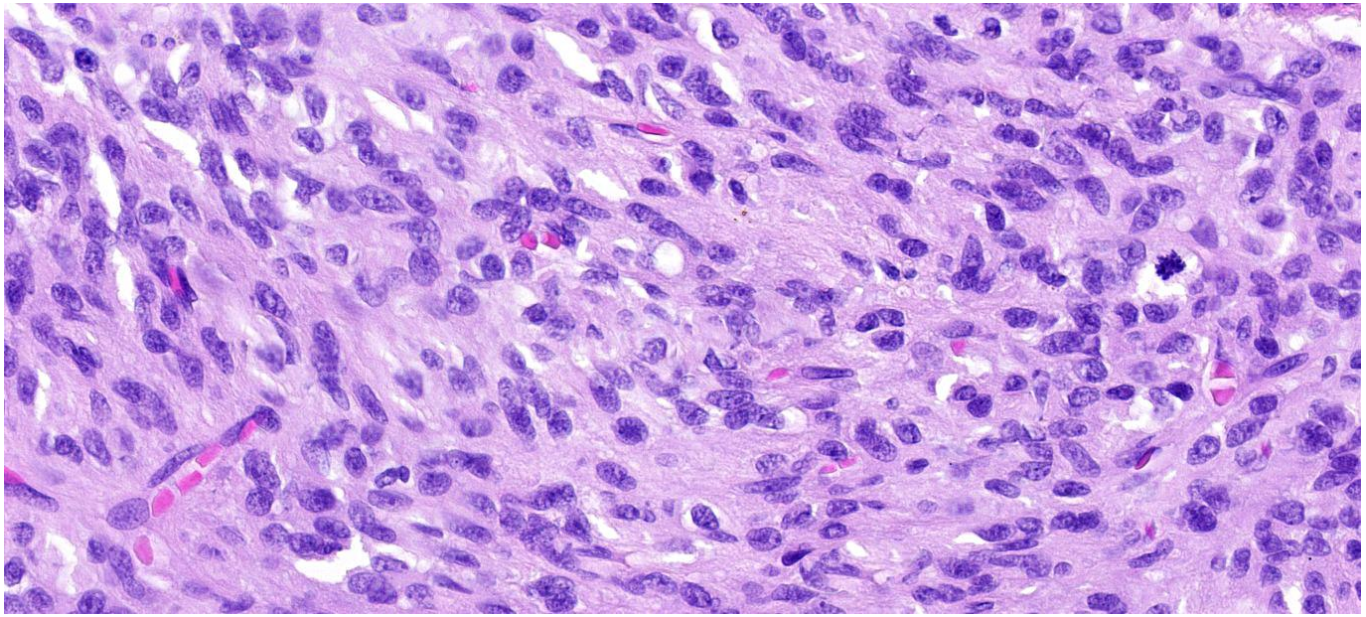
# Histopathological examination



Mixture of epithelioid tumor in nests and elongated cells arranged in fascicles resembling paraganglioma. The mitotic rate 13/50 high-power fields (HPF). Neuro- and vascular invasion positive. The cells stained positive for CD117, chloride channel protein anoctamin 1 (DOG1), CD99, smooth muscle actin (SMA), CD34, neuron specific enolase (NSE), vimentin, Ki67 - 5%, and were negative for desmin, chromogranin A, cytokeratin CK AE1/AE3, synaptophysin and S100.
Smallest margin 0.1 mm.
High-risk GIST, Miettinen's prognostic group: 6a, pT3Nx.

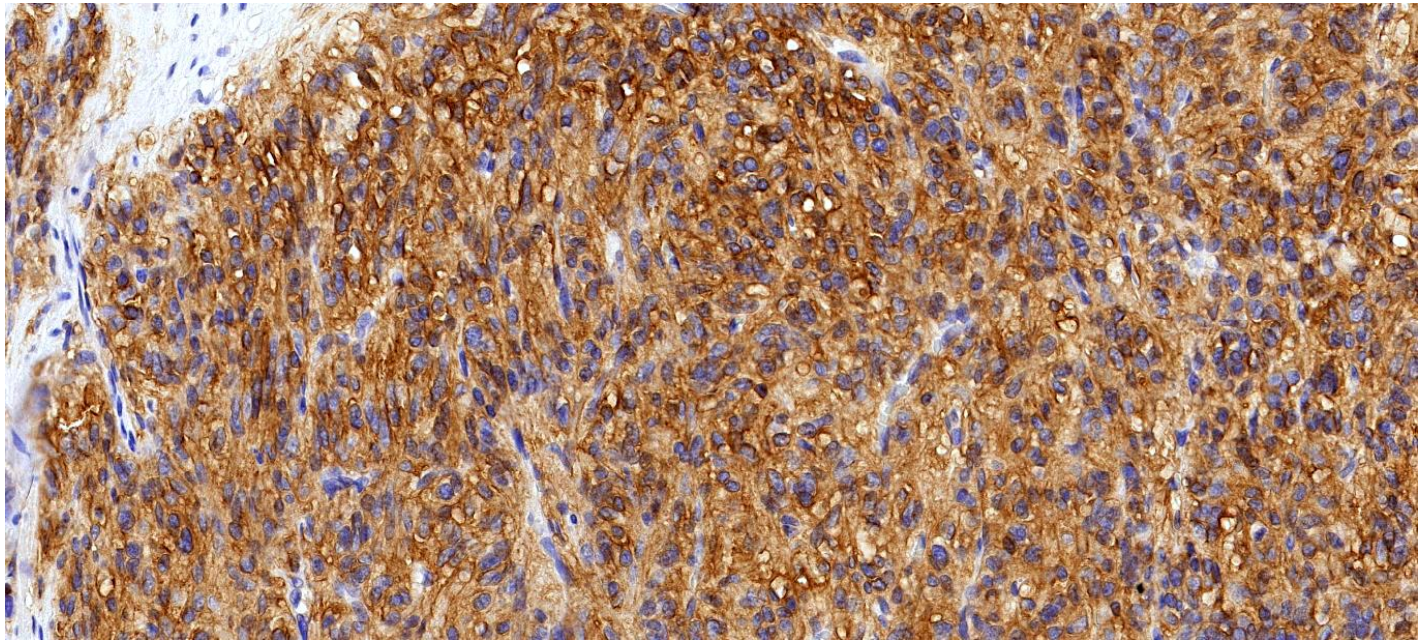
Cross section of the stomach with the tumor (black arrow) anterior vascular invasion (arrowhead), hematoxylin & eosin staining, magn. 12×.

# Histopathological examination



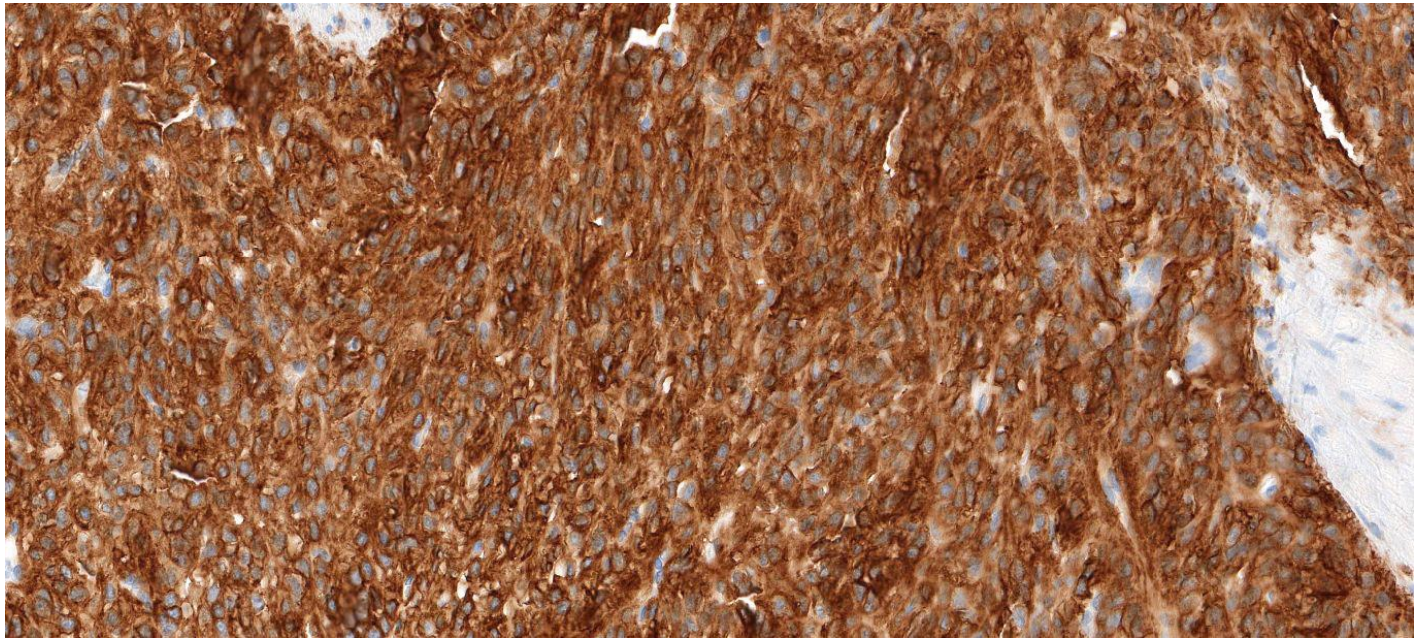
A mixture of epithelioid and elongated tumor cells arranged in fascicles and nests,hematoxylin & eosin staining, magn. 40×.

# Histopathological examination



Tumor cells stained positive for CD117, magn. 200×.

# Histopathological examination



Tumor cells showed positive staining for DOG1, magn. 200×.

# Question 2

What is the preferred imaging diagnostics modality when diagnosing/following-up pediatric GIST?

A. Ultrasonography

B. CT

C. PET-CT

D. MRI

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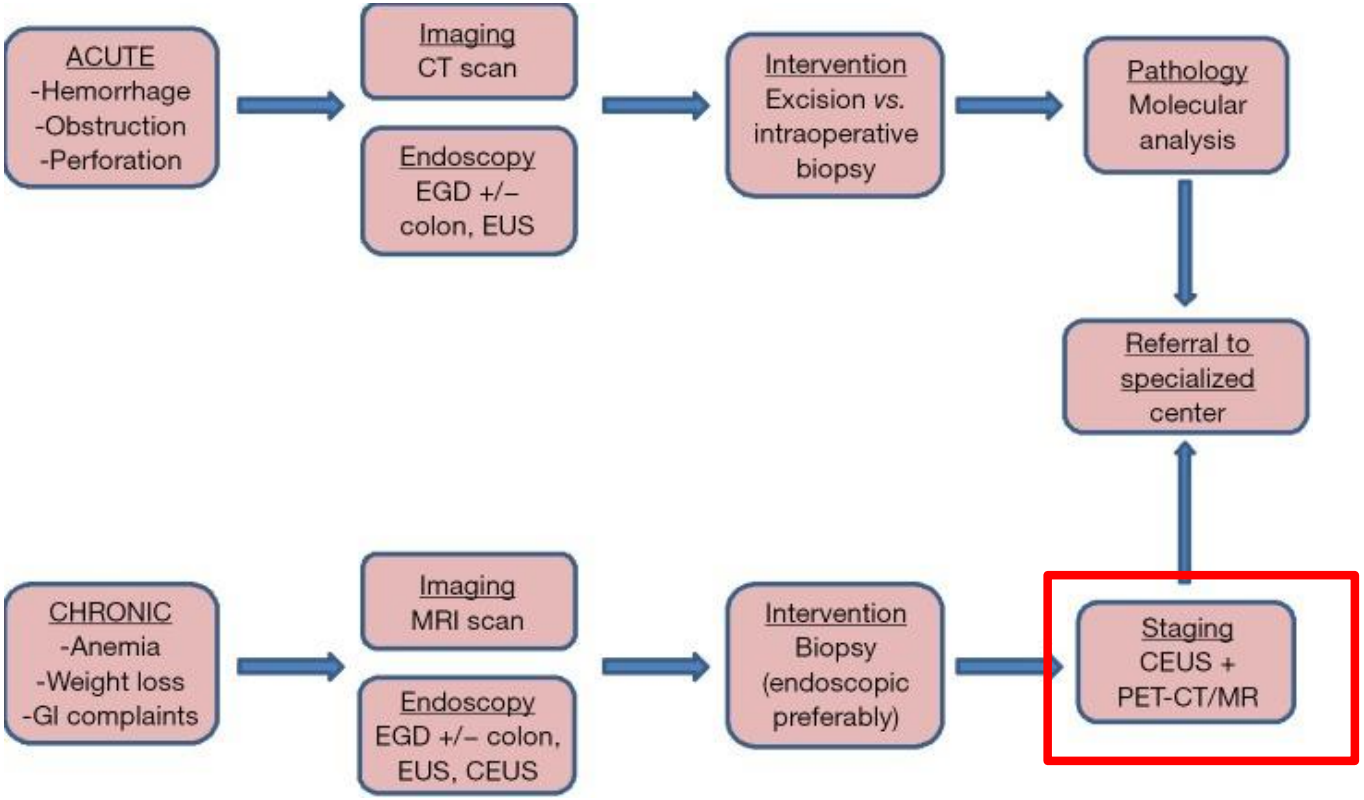



PET-CT is not validated in children

Pediatric gastrointestinal stromal tumors—a review of diagnostic modalities. Quiroz et al., 2018.

# Case follow-up

*May – September 2019*
- PET-CT – metabolic progression of previously found lesion; SUV = 6.9
- MRI – corresponding
- CT – submucosal tumor in the posterior-lower wall of the pyloric sphincter, best seen in the arterial phase, max. 7 mm

New soft tissue lesions → Metabolic progression in PET-CT → Genetic diagnostics

*November 2017 – October 2018*
- USG, CT – nodular mass (max. 15 mm) near duodenum
- PET-CT uptake near lesser curvature of the stomach (max. 9 mm); SUV = 3.4
- Biopsy - gastritis

*August 2019*
- *KIT* and *PDGFRA* mutation testing
- *KIT* mutation in exons 13 and 17

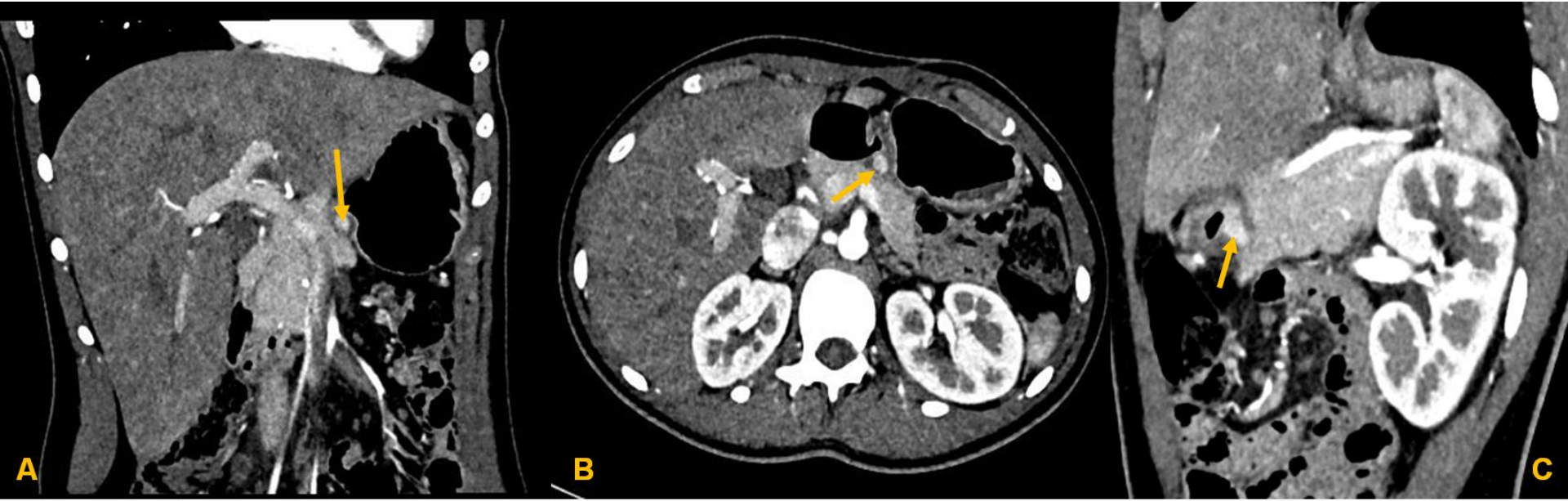
# Progression management

*December 2020*
- 2 new nodular masses near pyloric sphincter seen in CT and PET-CT (SUV = 11.1)
- Imatinib dose escalation – 800 mg


*December 2019*
- Imatinib dose 400 mg
- Stabilization of the disease

*April 2021*
- Reoperation – only 20% of the stomach near cardia/fundus left, Billroth II method, free margins (R0)
- Stomach-jejunium anastomosis
- Repeated *KIT* and *PDGFRA* mutation testing – no mutations

# Imaging diagnostics - progression




Coronal (A), axial (B), and sagittal (C) view of the contrast-enhanced CT abdominal scans, showing intensely enhanced solid mass (marked with yellow arrow). December 2020.

# Further follow-up

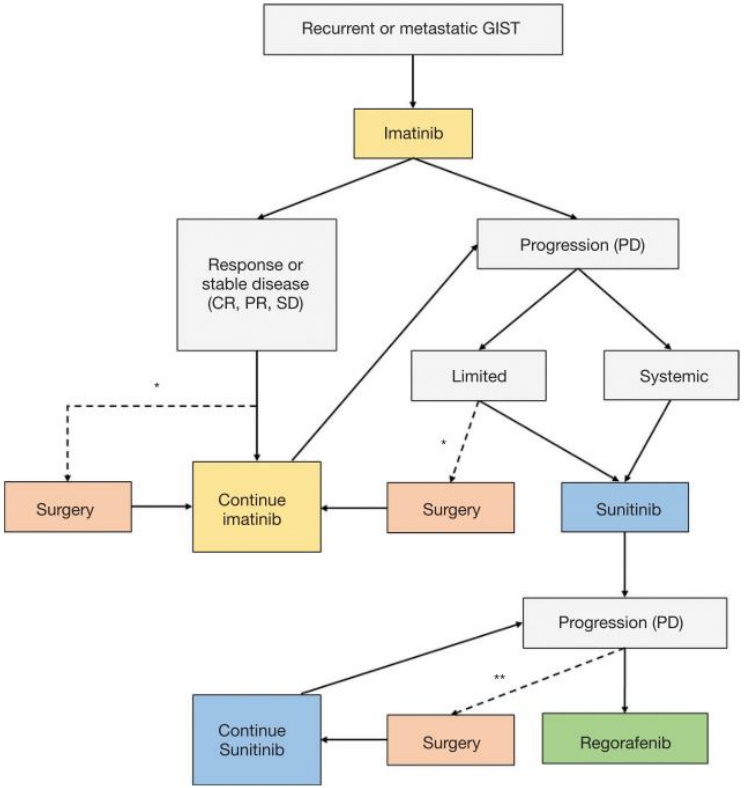
*January 2023 – May 2023*
- 1 new cystic mass near duodenum in CT
- Removal of the cyst - 6x4x2 cm - probably originating from the mesentery of the small intestine
- Relapse excluded


*May 2021 – December 2021*
- Regular visits in the outpatient clinic
- CT performed every 3 months, PET every 6 months, USG every 3 months

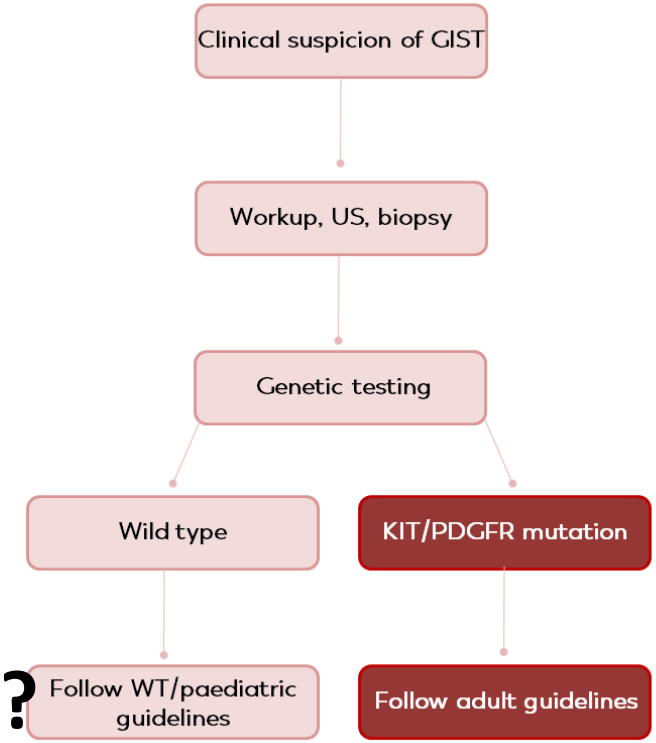
*Since May 2023*
- The patient is regularly seen in the outpatient clinic
- Follow-up protocol
- No additional treatment needed, patient is asymptomatic

# Quality of life

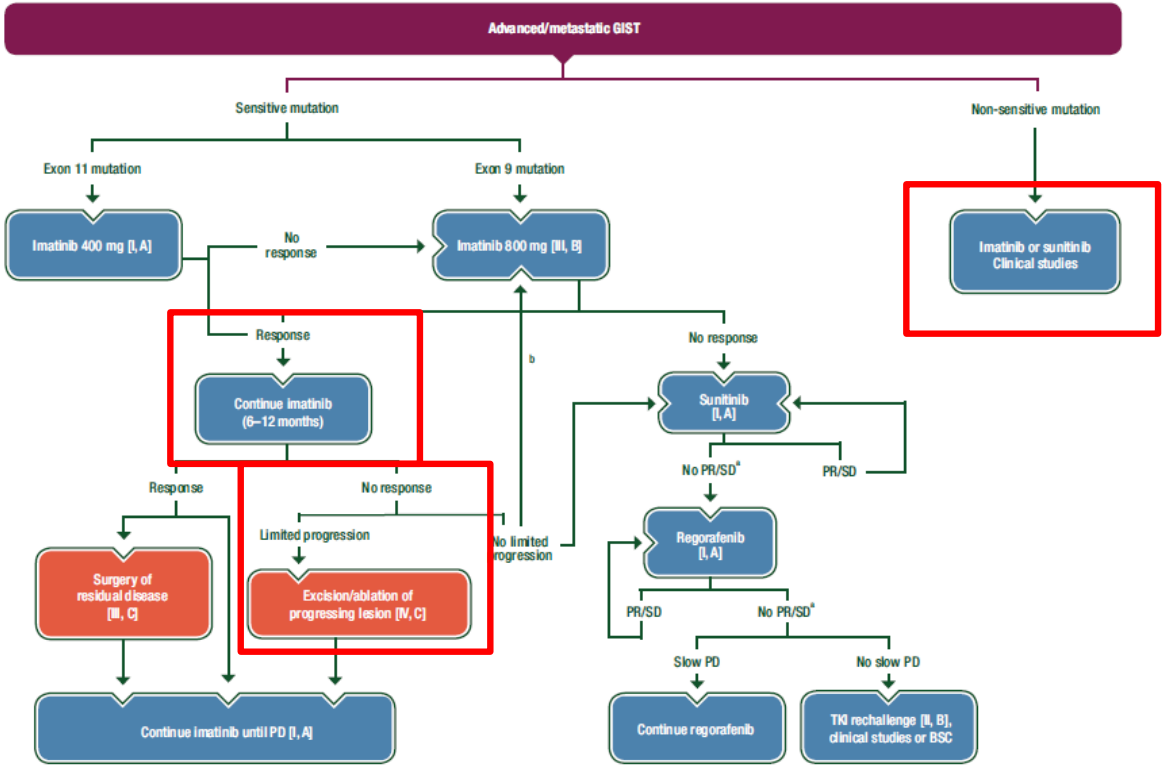
- Sugery: only 20% of the stomach left – only small portions of food might be ingested.
- Imatinib treatment: facial edema, transient nausea, lower limb numbness for 3 weeks, hypomagnesemia and mild anemia, mild hair loss and recurrent nasal hemorrhages.
- Frequent visits in the outpatient clinic – travels, school absences, less contact with friends.




Proposed algorithm for clinical management of patients with recurrent or metastatic GIST. Kikuchi *et al.,* 2018.




Suggested management guidelines for pediatric GIST. Modified from Pappo *et al.,* 2011.




Management of advanced/metastatic GIST. ESMO Clinical Practice Guidelines. Casali *et al.,* 2018.
Guidelines endorsed by ERN GENTURIS (European Reference Network – Genetic Tumour Risk Syndromes).

# *KIT* mutations & imatinib sensitivity

| Genetic Type | Frequency | Anatomic Location | Treatment |
|---|---|---|---|
| ***KIT* mutations** | | | |
| Exon 8 | <0.1% | | |
| Exon 9 | 6% | small & large bowel | Imatinib sensitiv (800 mg/d) |
| Exon 11 | 66% | all locations | Imatinib sensitive |
| Exon 13 | 1% | all locations | usually secondary mutation resistant to imatinib, responds to sunitinib |
| Exon 17 | <1% | all locations | secondary mutation resistant to imatinib and sunitinib; have been shown to respond to other TKI like regorafenib |

Update on Molecular Genetics of Gastrointestinal Stromal Tumors. Brčić *et al.*, 2021.

# Question 3

Why should pediatric/AYA patients with GIST be closely checked and followed-up with imaging diagnostics, even after the disease is treated?

A. GIST might be associated with other neoplasms

B. GIST treatment with TKI might have cardiopulmonary side-effects

C. GIST's progression may occur as pulmonary metastases

D. There are no such indications

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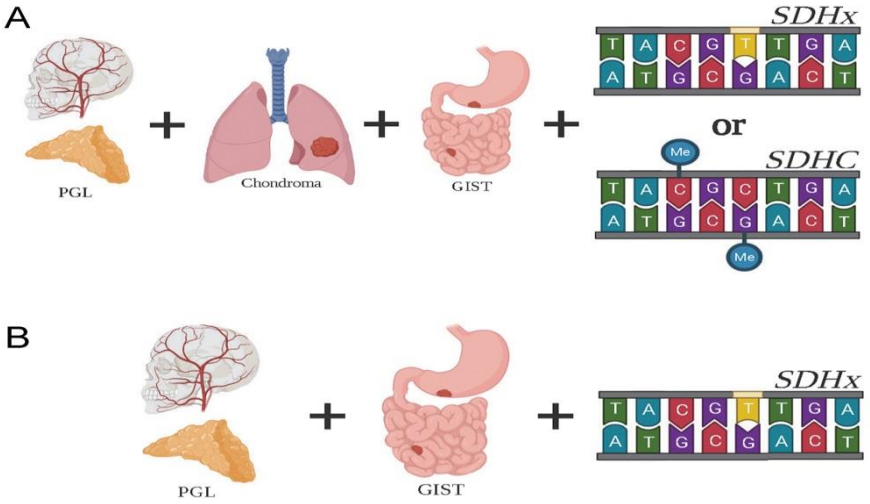
# Carney-Stratakis triad / Carney dyad

| | Carney Triad | Carney-Stratakis Syndrome |
|---|---|---|
| GISTs possible? | yes | yes |
| Paragangliomas possible? | yes | yes |
| Pulmonary chondromas possible? | yes | no |
| Familial (heritable)? | no | yes |
| Gender-related? | mostly female | equal gender occurrence |
| Mutations in *KIT* or *PDGFRA*? | no | no |
| Mutations in SDH subunits? | no | yes in 9 of 11 families |
| Chromosomal loss of SDH? | yes in some | yes in some |

= Carney-Stratakis syndrome (CSS)




A case of Carney triad complicated by renal cell carcinoma and a germline *SDHA* pathogenic variant
Wurth *et al.,* 2021

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# DISCUSSION

Funded by the European Union's Health Programme

# Take home messages

GIST is very rare in pediatric population – spreading information about its management seems essential

Different imaging modalities allow for progression/relapse monitoring

There are no unanimous pediatric GIST guidelines, yet full genetic testing is crucial to choose the best treatment

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