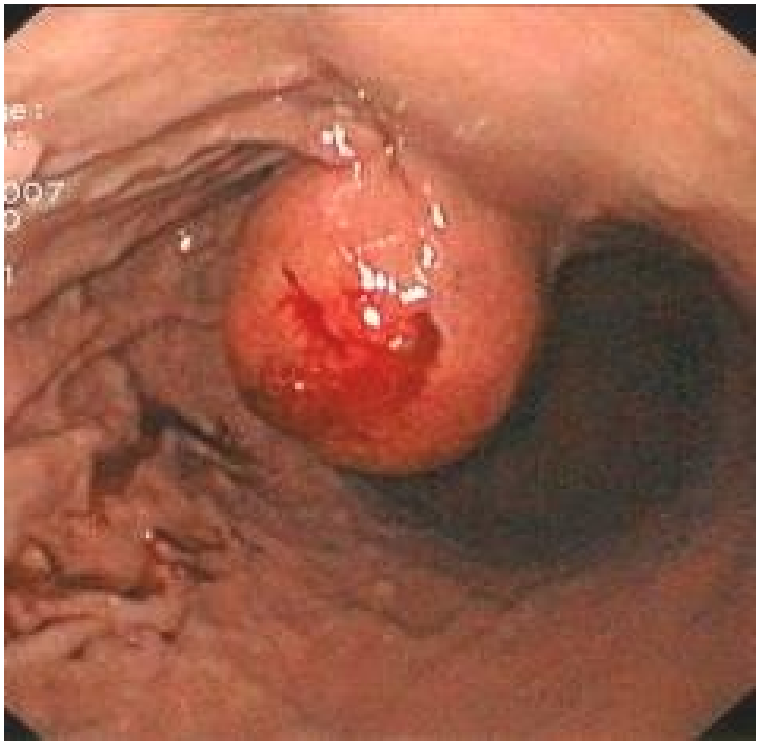
Gastrointestinal Stromal Tumor (GIST)

Bible class 8.9.21 Stefan Christen



Epidemiology

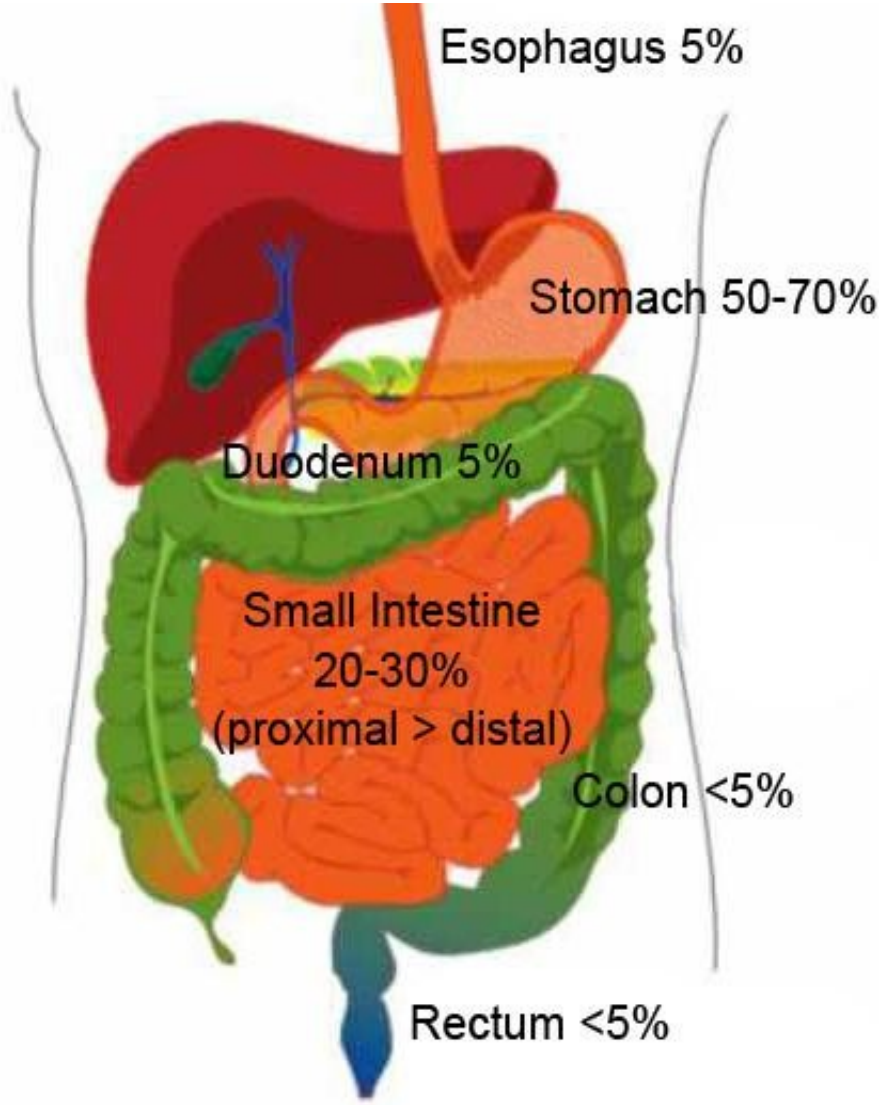
- Incidence approx. 1 / 100'000 /y
- 0.1 – 3% of all GI-tumors
- slight prevalence in males
- mean age 60-65y

- “mini-GISTs” (1–10 mm) are very common (detectable in 22.5% of the autopsies in individuals older than 50 years)

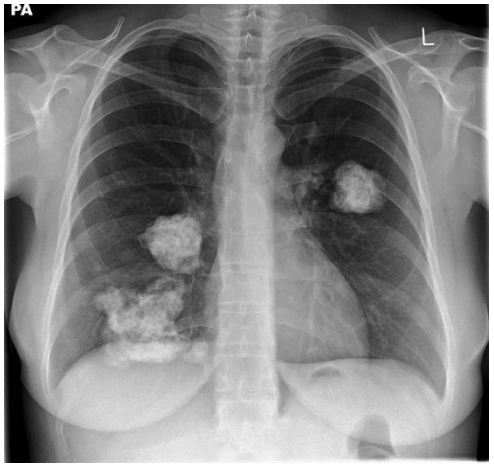
[Kindblom LG et al. Incidence, prevalence, phenotype and biologic spectrum of gastrointestinal stromal cell tumors (GIST) – A population-based study of 600 cases. Ann Oncol 2002;13(Suppl 5):157]
[Nilsson B et al. Gastrointestinal stromal tumors: the incidence, prevalence, clinical course, and prognostication in the preimatinib mesylate era - a population-based study in western Sweden. Cancer 2005;103:821]

Localisation

20% of GIST have metastasis at time of diagnosis
- 65% Liver
- 20% Peritoneum
- very rare Lung, Bone, Lymphnodes



Syndromes linked to GISTs:



- Carney triad syndrome: gastric GISTs, paraganglioma and pulmonary chondromas

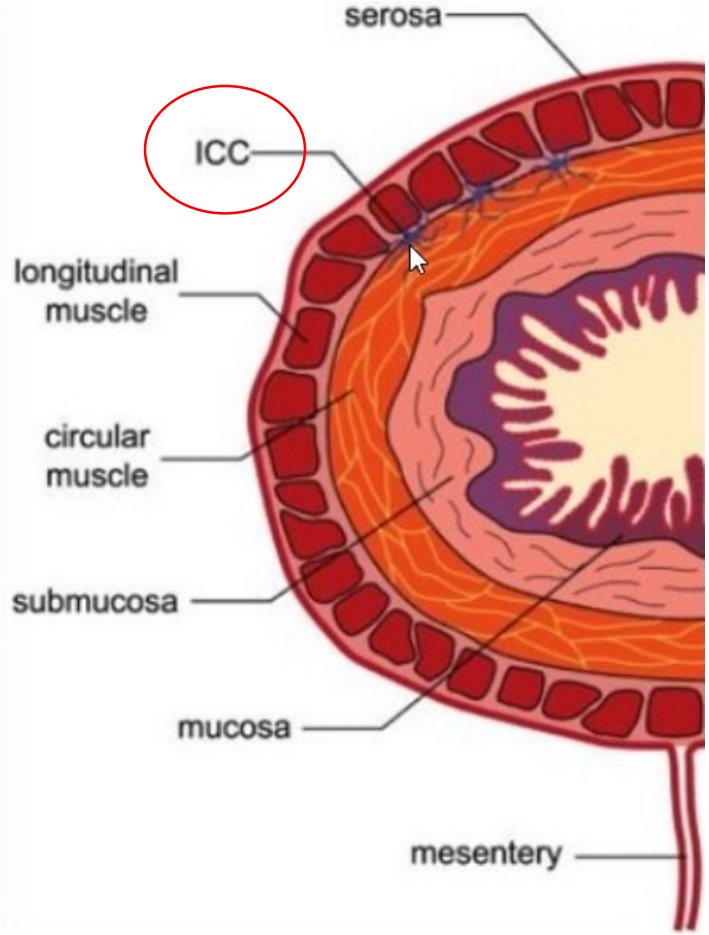
- Carney–Stratakis syndrome: a dyad of GIST and paraganglioma

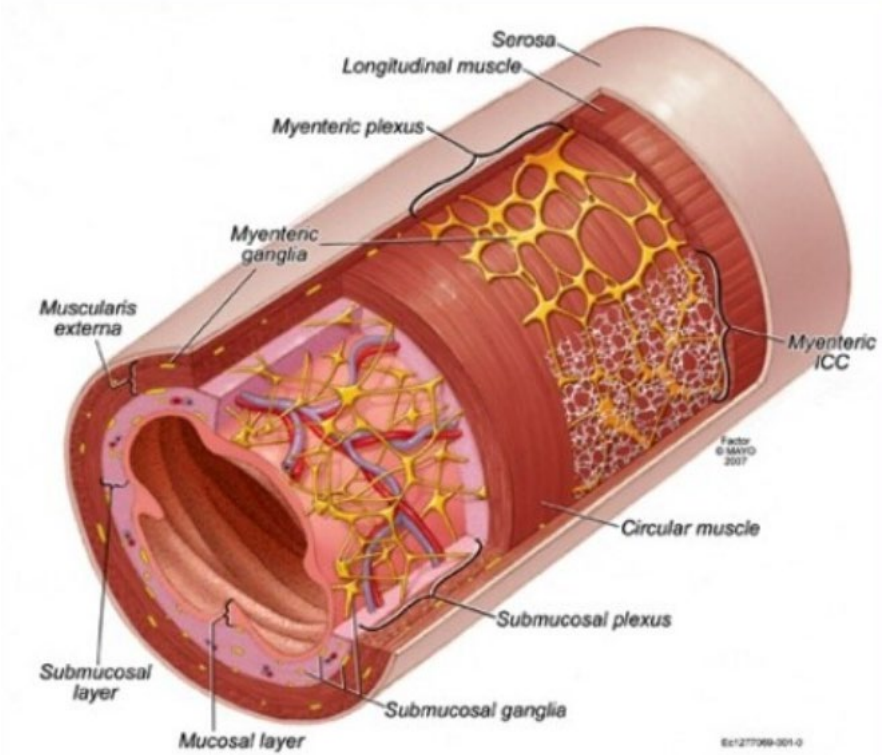
- Neurofibromatosis type 1: leading to wild-type, often multicentric GIST, predominantly located in the small bowel

- Families with germline autosomal dominant mutations of KIT are extremely rare
  - → presenting with multiple GISTs at an early age

Etiology - Pathogenesis

- Originate from interstitial cells of Cajal





[Hirota S et al. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. Science 1998;279:577]

Etiology - Pathogenesis

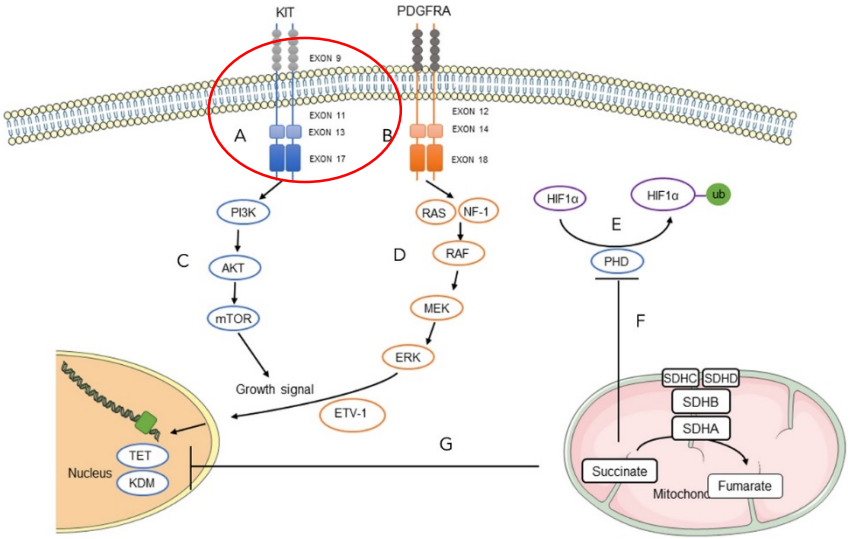
- Originate from interstitial cells of Cajal
  - pluripotent mesenchymal stem cells
  - In normal cells activation of the of the c-kit tyrosine kinase requires the presence of an endogenous ligand (c-kit ligand or stem cell factor)

1998 gain-of-function Mutation of c-kit

→ uncontrolled activation of tyrosine kinase

→ uncontrolled growth / proliferation

- KIT 90-95% of GIST
- PDGFRA 5-8% of GIST



[Hirota S et al. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. Science 1998;279:577]

Molecular genetics – c-Kit-mutation analysis

- c-Kit-Mutation[1)]
  - Exon 9: poorer response to Imatinib, poorer prognosis
  - Exon 11: better response to Imatinib, better prognosis

Mutation type	Approximate frequency	Histological type	Anatomical site	*In vitro* susceptibility to imatinib	Response to Imatinib *in vivo*
KIT mutation	80–85%	Predominately spindle cell			
Exon 9	10%		Small bowel	Yes	Intermediate
Exon 11	60–70%			Yes	Excellent
Exon 13	1%			Yes	Some responses*
Exon 17	1%			Yes	Some responses*

- No known mutation: 'wild type' GIST, poor prognosis

1) [Heinrich MC et al. Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. J Clin Oncol 2003;21:4342]

Recommendations for Mutational Analysis

- **Primary disease**
- not routinely recommended due to insufficient data to support its use for improved risk stratification and prognostication of risk for relapse in individual patients.

- **Metastatic or advanced disease**

- *KIT* exon 11 mutations are associated with higher response rates and longer progression-free survival than *KIT* exon 9 mutations.

- Mutational analysis → impact on the dose of imatinib for small bowel GISTs because *KIT* exon 9 mutations are shown to respond better to higher-dose imatinib.

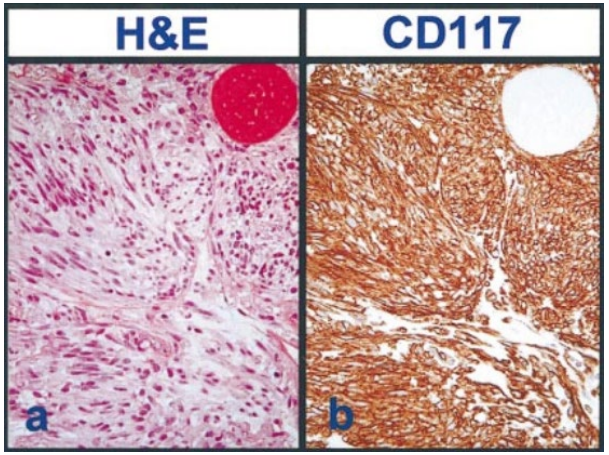
Histologic patterns

- spindle cell type 70%
    - DD includes: leiomyoma, leiomyosarcoma, schwannoma, intra-abdominal desmoid-type fibromatosis, inflammatory myofibroblastic tumor, solitary fibrous tumor, sarcomatoid carcinoma.
- predominantly epithelioid cell type 20%
    - DD includes: metastatic melanoma, clear cell sarcoma, epithelioid variants of leiomyosarcoma, and epithelioid hemangioendothelioma.
- mixture of both spindle and epithelioid cells 10%

Immunehistochemistry

- **95% are positive for KIT (CD117) or DOG1**

- Other markers:

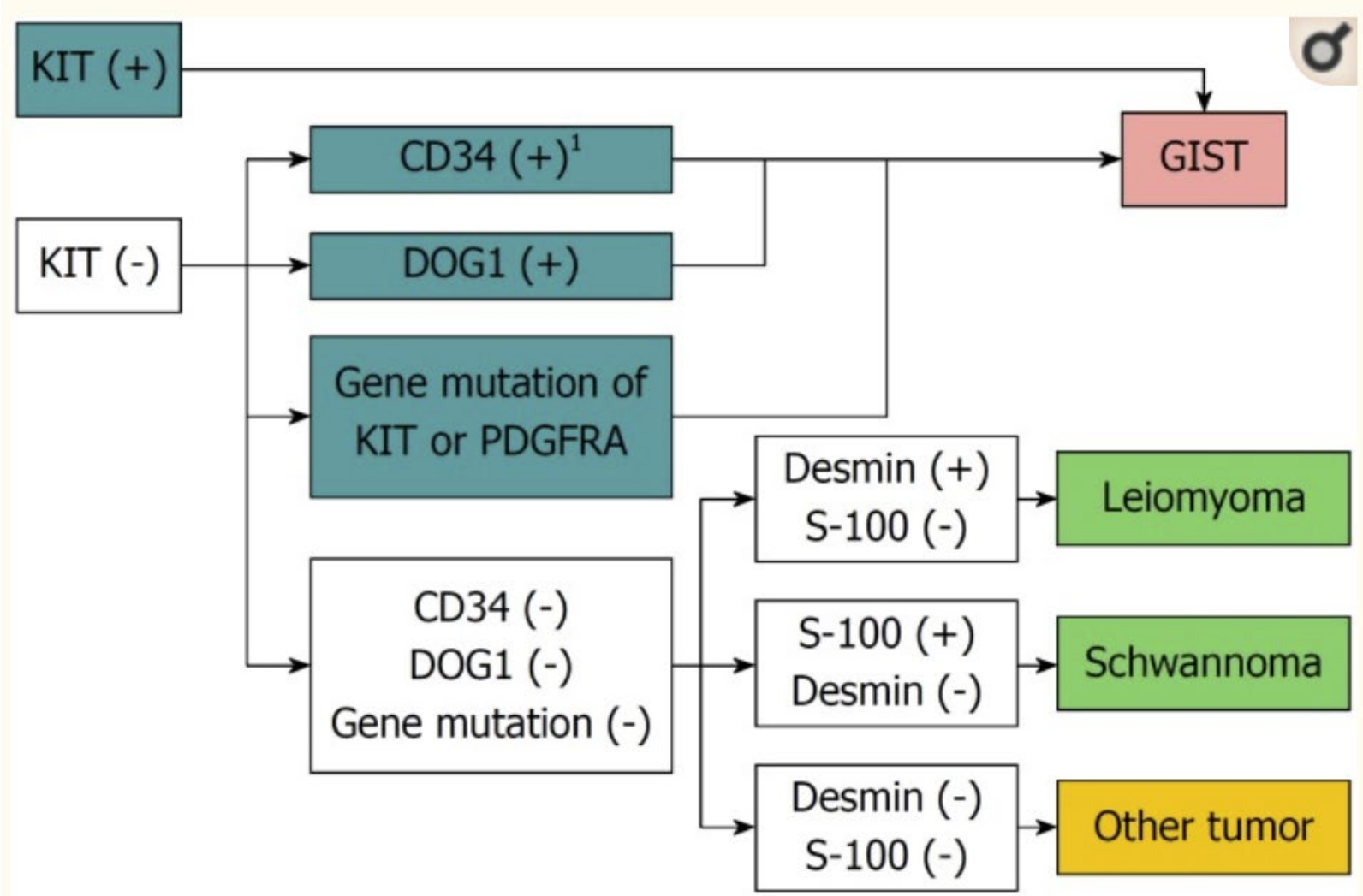


- CD34 antigen (70%)
- smooth muscle actin (SMA; 30%–40%)
- desmin (< 5%)
- S100 protein (~5%)

- 5% of GISTs are “KIT-negative”
- 2.6% of GISTs are negative for both DOG1 and KIT

- → challenging diagnosis- mutations in the *PDGFRA* gene.

Immunehistochemistry

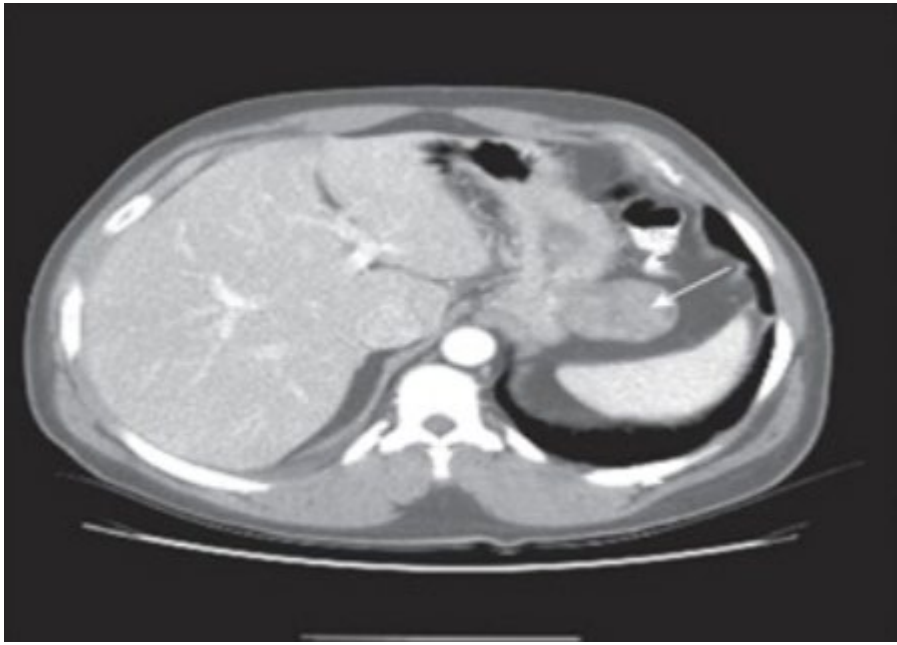


Clinical presentation

- **No symptoms** 15 – 30%
  - Incidental findings e.g. on endoscopy, radiology, resections for other reasons
- **Symptomatic GIST** ~75%
  - GI bleeding 25 – 53% (overt bleeding 34%)
  - Abdominal pain 20 – 50%
  - Passage 10 – 30%: N/V, early satiety, ileus, pain
  - Palpable mass 8 – 13%

[Mucciarini C et al. Incidence and clinicopathologic features of gastrointestinal stromal tumors. A population-based study. BMC Cancer 2007;7:230]

Diagnostic workup



- **Diagnostic modalities**:
  - Endoscopy
  - Endosonography
  - Radiology (**CT**, PET-CT, MRI)
  - Histology / immunohistochemistry

- **Diagnostic modality of choice**:
  - EUS-guided biopsy / FNA (if feasible)

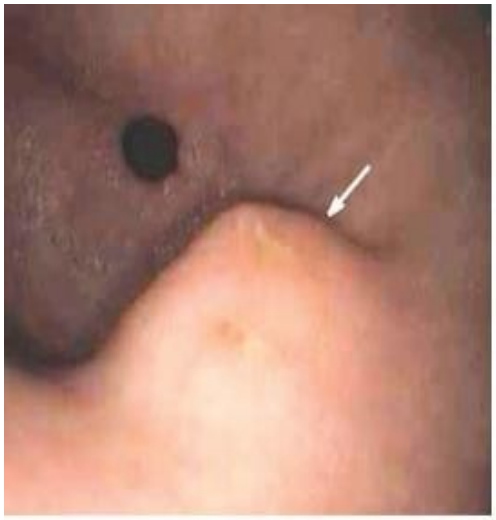
Is biopsy mandatory?

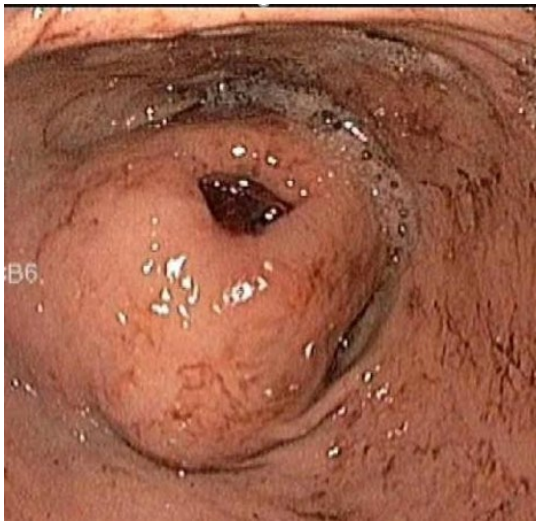
- In some situations biopsy may not be necessary (ie classic EUS findings, tumor easily resectable, preoperative therapy not required)

Diagnostic workup

Endoscopy

- Endoscopic features of GIST:





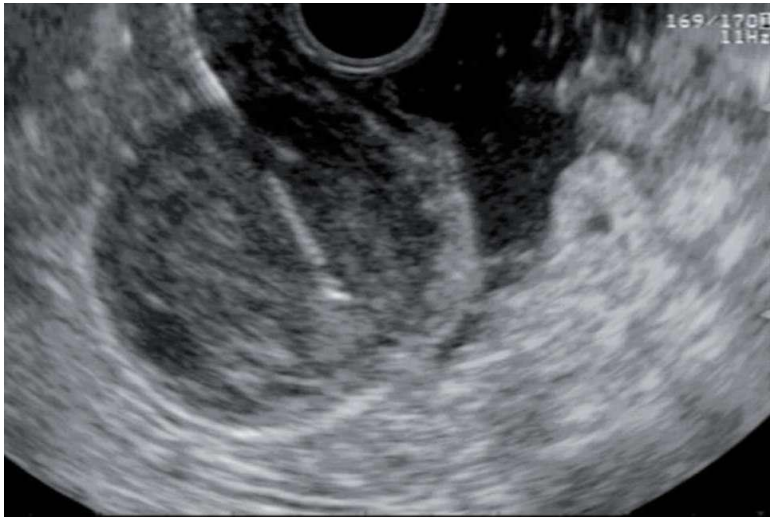
- Drawback of Endoscopy w/ biopsy (stacked / bite-on-bite):
  - Risk of bleeding / tumor perforation
  - Poor diagnostic yield (17-42%)

[Hunt GC et al. Yield of tissue sampling for submucosal lesions evaluated by EUS. Gastrointest Endosc 2003;57:68]
[Cantor MJ et al. Yield of tissue sampling for subepithelial lesions evaluated by EUS: a comparison between forceps biopsies and endoscopic submucosal resection. Gastrointest Endosc 2006;64:29]

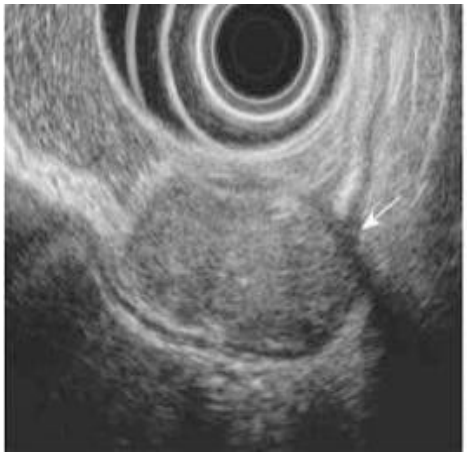
Diagnostic workup

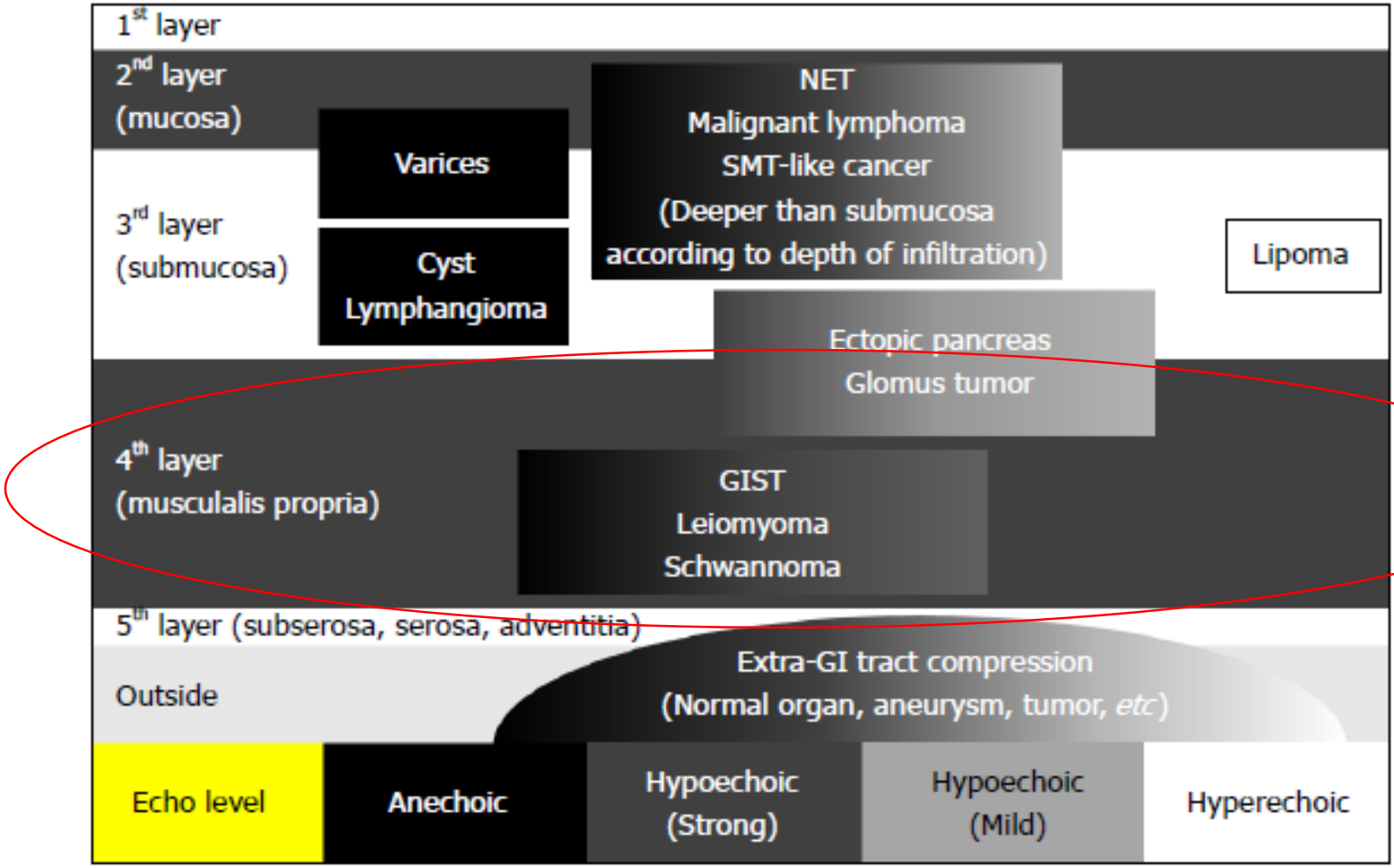
EUS

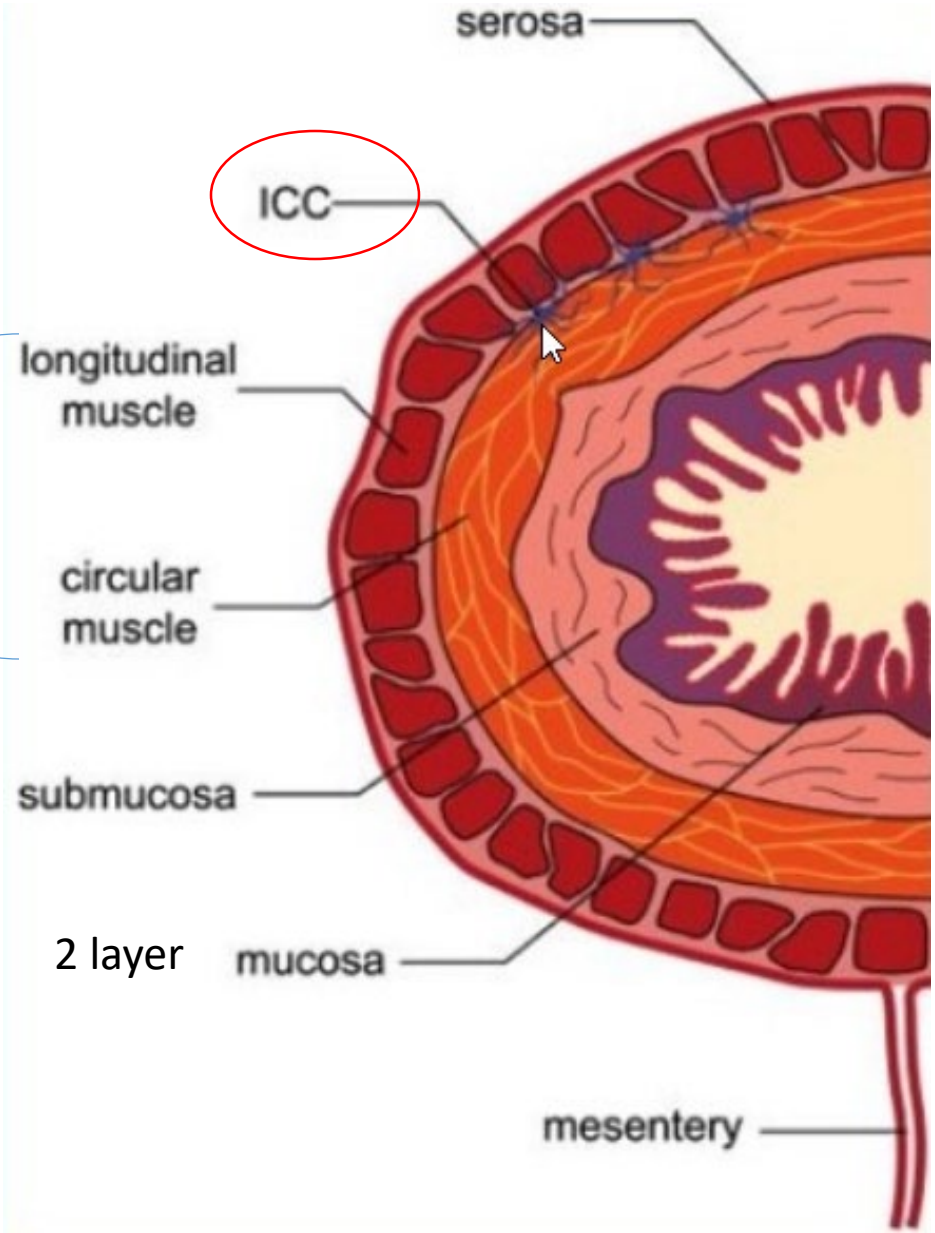
- Classic EUS features of GIST:

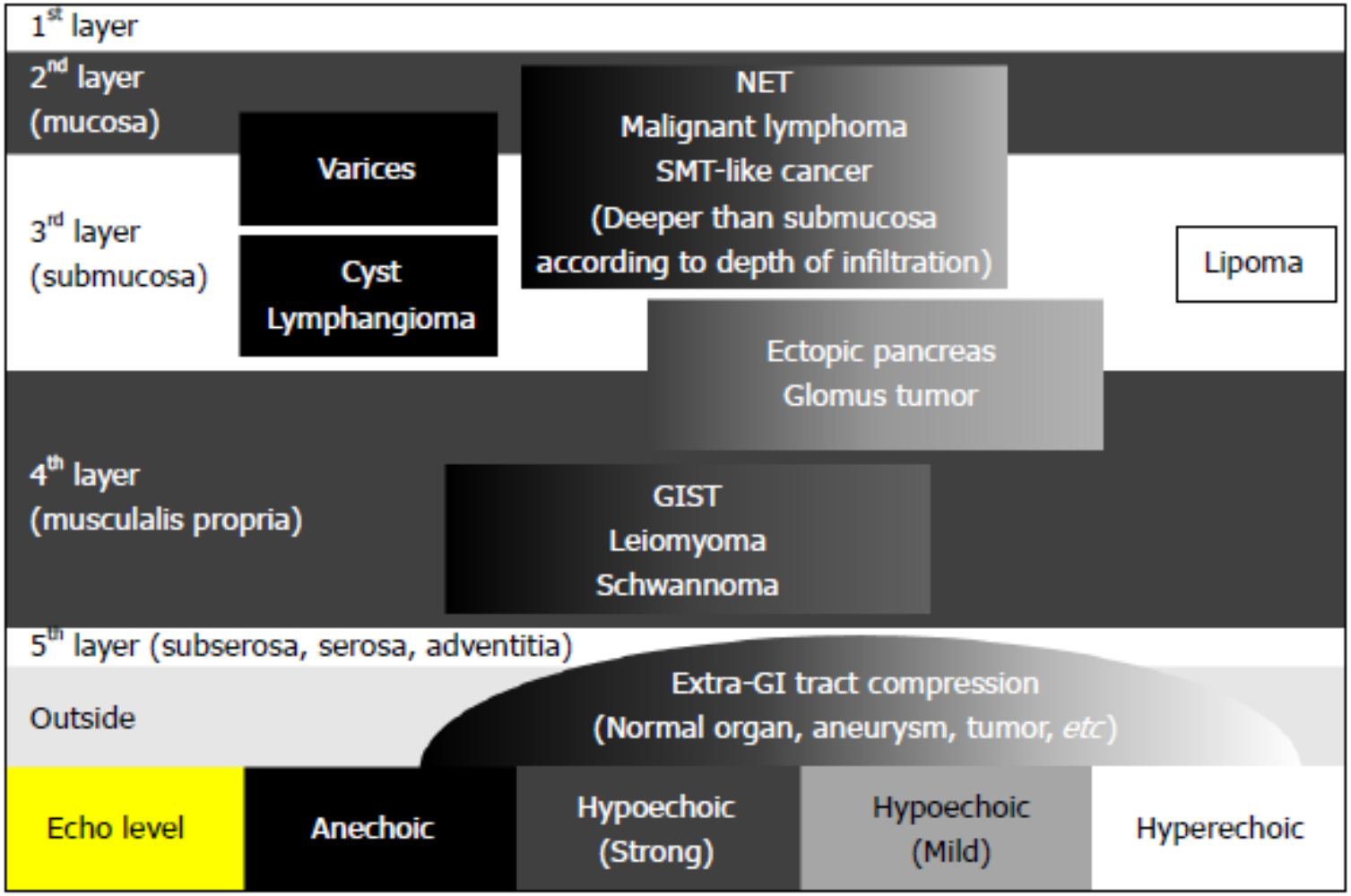


- fourth wall layer (muscularis propria)
- round to oval shape
- hypoechoic




1st layer
2nd layer
(mucosa)
Varices
NET
Malignant lymphoma
SMT-like cancer
(Deeper than submucosa
according to depth of infiltration)
3rd layer
(submucosa)
Cyst
Lymphangioma
Lipoma
Ectopic pancreas
Glomus tumor
4th layer
(musculalis propria)
GIST
Leiomyoma
Schwannoma
5th layer (subserosa, serosa, adventitia)
Outside
Extra-GI tract compression
(Normal organ, aneurysm, tumor, etc)
Echo level
Anechoic
Hypoechoic
(Strong)
Hypoechoic
(Mild)
Hyperechoic

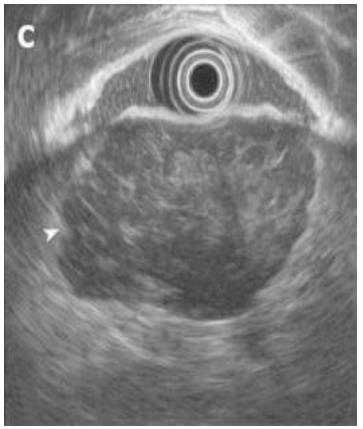

serosa
ICC
longitudinal muscle
4 layer
circular muscle
3 layer
submucosa
2 layer
mucosa
mesentery


1st layer
2nd layer
(mucosa)
Varices
NET
Malignant lymphoma
SMT-like cancer
(Deeper than submucosa
according to depth of infiltration)
3rd layer
(submucosa)
Cyst
Lymphangioma
Lipoma
Ectopic pancreas
Glomus tumor
4th layer
(musculalis propria)
GIST
Leiomyoma
Schwannoma
5th layer (subserosa, serosa, adventitia)
Outside
Extra-GI tract compression
(Normal organ, aneurysm, tumor, etc)
Echo level
Anechoic
Hypoechoic
(Strong)
Hypoechoic
(Mild)
Hyperechoic

EUS +/- biopsy/FNA – Advantages:

Most accurate and reliable method to secure a diagnosis of GIST

- Tissue sampling
  - Diagnostic rate using EUS-FNA 62-93%
    - 71% for 1-2cm→ 86% for 2-cm to 4-cm tumors, and 100% for > 4-cm tumors
  - solid mass of < 1 cm is technically difficult →EUS-FNA is recommended for masses of > 1 cm



- Helps assessing malignant potential
  - *Diameter* (ie >3-4cm)
  - Echogenic foci
  - *Irregular borders*
  - Cystic spaces
  - Lymph nodes

≥ 2 criteria met: sensitivity 80-95%

≥ 1 criteria met: sensitivity 91%, specifity 88%, PPV 83%

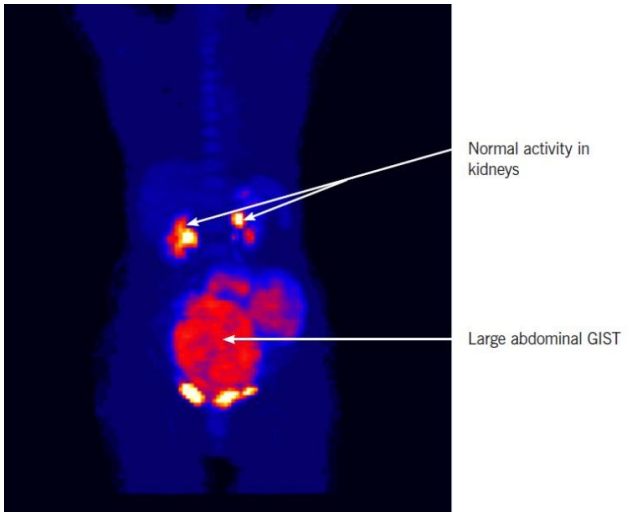
[Ando N et al. The diagnosis of Gi stromal tumors with EUS-guided fine needle aspiration with immunohistochemical analysis. Gastrointest Endosc 2002;55:37]

[Chak A et al. Endosonographic differentiation of benign and malignant stromal cell tumors. Gastrointest Endosc 1997;45:468]

[Palazzo L et al. Endosonographic features predictive of benign and malignant gastrointestinal stromal cell tumours. Gut 2000;46:88]

Diagnostic workup

^{18}FDG-PET



- GIST highly metabolically active
- May not detect GIST <2cm

- Assess complex metastatic disease in patients who are being considered for surgery

- Correlation between ^{18}FDG-Uptake & mitotic index

- Monitoring tumor response to therapy

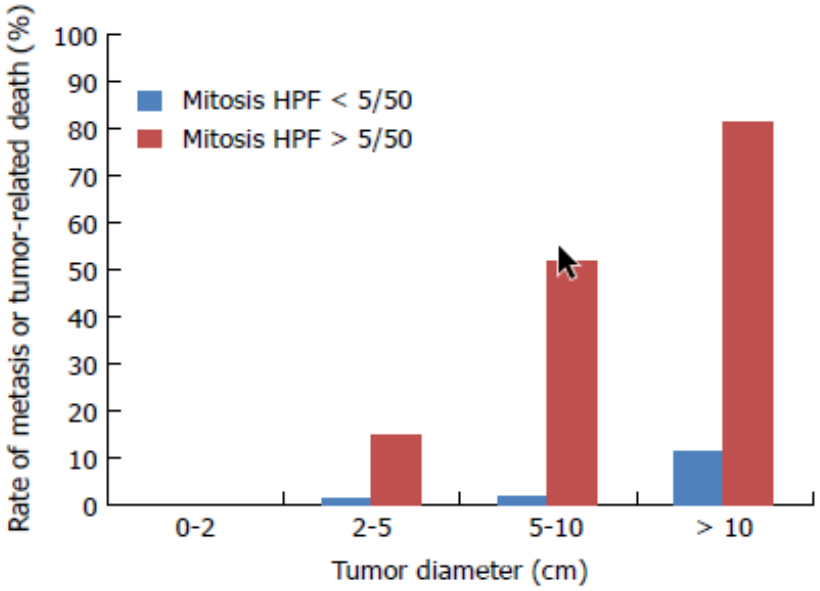
[Kamiyama Y et al. 18F-fluorodeoxyglucose positron emission tomography: useful technique for predicting malignant potential of gastrointestinal stromal tumors. World J Surg 2005;29:1429]

[Stroobants S et al. 18FDG-Positron emission tomography for the early prediction of response in advanced soft tissue sarcoma treated with imatinib mesylate (Glivec). Eur J Cancer 2003;39:2012]
[Antoch G et al. Comparison of PET, CT, and dual-modality PET/CT imaging for monitoring of imatinib (STI571) therapy in patients with gastrointestinal stromal tumors. J Nucl Med 2004;45:357]

Prognosis

- Not only large GISTs with a high mitotic index have a risk to build metastasis, also small GISTs with a low mitotic index rarely show a malignant course with metastasis.
- GIST is considered to be a **potentially malignant tumor**
- They are not classified as benign or malignant but stratified by their clinical risk of malignancy:
- Very low, Low, intermediate and high

- The metastatic risk of GIST increases according to the tumor size and the mitotic count



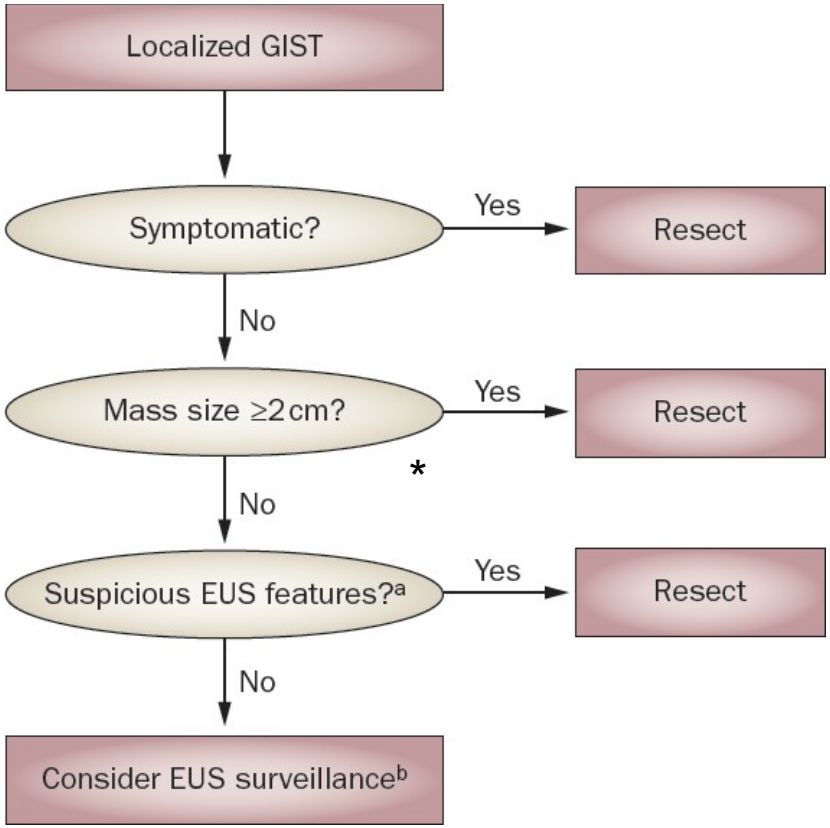
Risk stratification

Table 1 Risk Stratification of Primary GIST by Mitotic Index, Size, and Site

Tumor Parameters		Risk for Progressive Disease*(%), Based on Site of Origin			
Mitotic Rate	Size	Stomach	Jejunum/Ileum	Duodenum	Rectum
≤ 5 per 50 HPF	≤ 2 cm	None (0%)	None (0%)	None (0%)	None (0%)
	> 2, ≤ 5 cm	Very low (1.9%)	Low (4.3%)	Low (8.3%)	Low (8.5%)
	> 5, ≤ 10 cm	Low (3.6%)	Moderate (24%)	Insufficient data	Insufficient data
	> 10 cm	Moderate (10%)	High (52%)	High (34%)	High (57%)
> 5 per 50 HPF	≤ 2 cm	None†	High†	Insufficient data	High (54%)
	> 2, ≤ 5 cm	Moderate (16%)	High (73%)	High (50%)	High (52%)
	> 5, ≤ 10 cm	High (55%)	High (85%)	Insufficient data	Insufficient data
	> 10 cm	High (86%)	High (90%)	High (86%)	High (71%)

- **small intestinal GISTs are more aggressive than gastric GISTs of equal size**

Management localized GIST



a) Possible high-risk EUS features:

- irregular border
- Cystic spaces
- Ulceration
- echogenic foci
- heterogenity

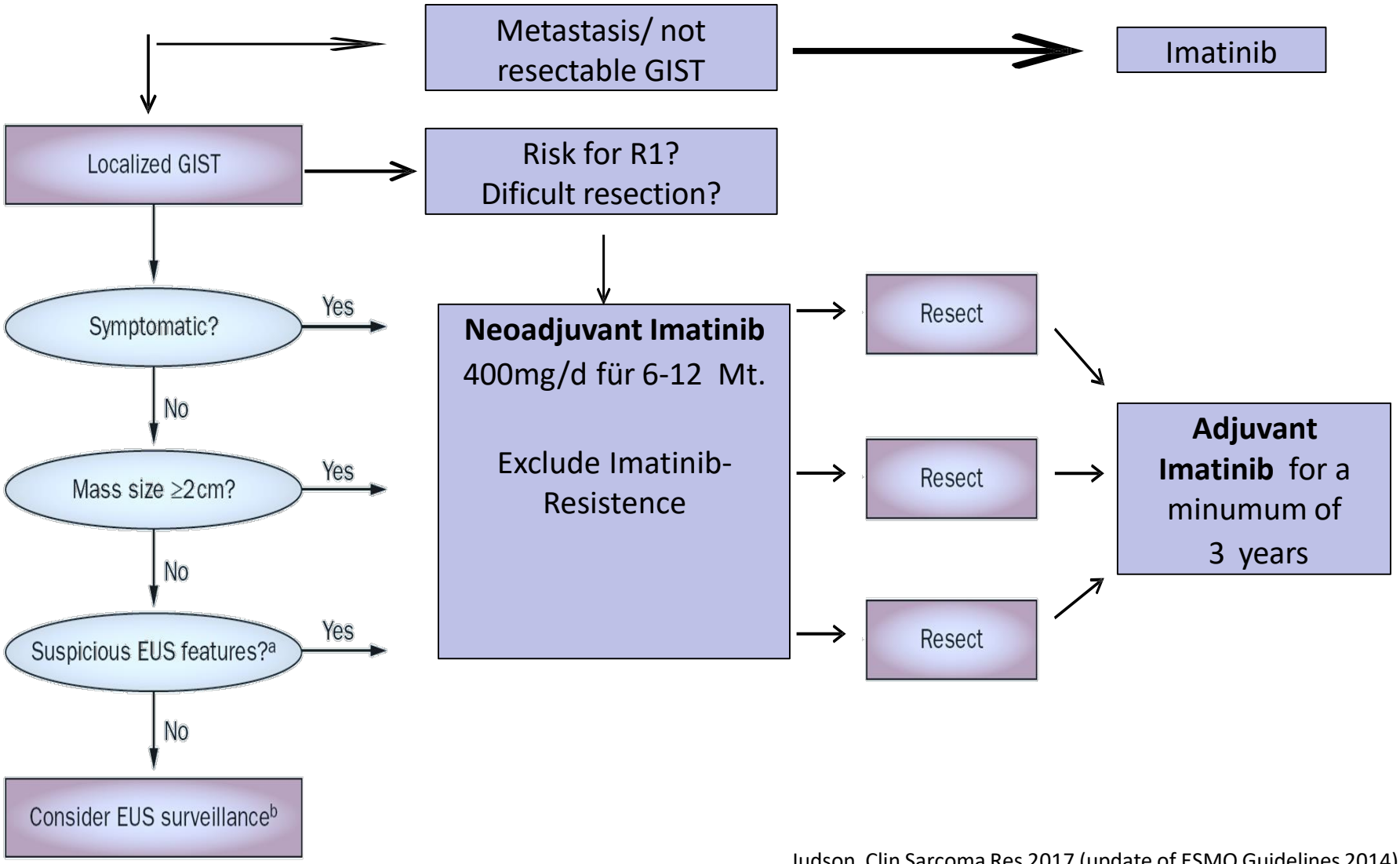
Principles of surgery in localized GIST

- Complete tumor removal with clear resection margins
- Avoidance of tumor rupture
- Gastric GIST: lap. wedge resection when feasible
- Routine lymphadenectomy not necessary [1)]

- GISTs with very low, low, and moderate risks are followed up by CT every 6 mo to 1 year
- high-risk and clinically malignant GISTs (metastasis, injury to the pseudocapsule, peritoneal dissemination, or infiltration of other organs) are followed up by CT every 4 to 6 mo

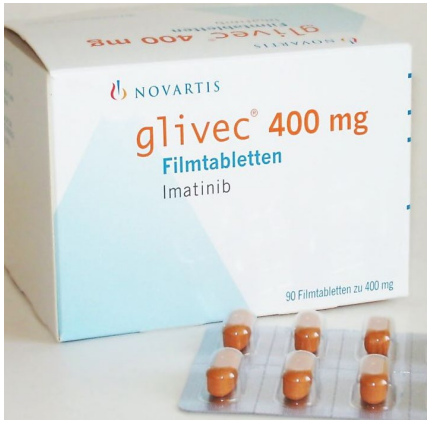
1) [DeMatteo RP et al. Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. Ann Surg 2000;231:51]

Management of GIST

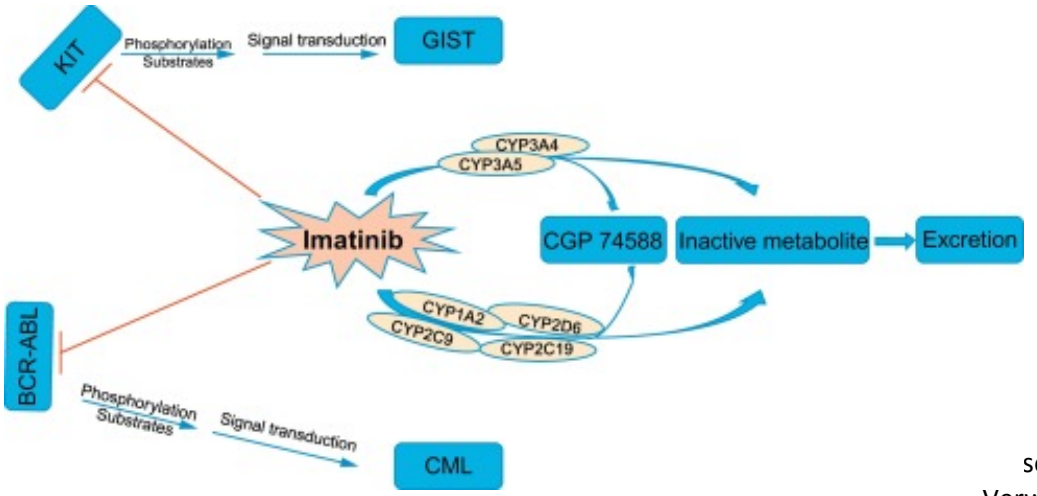


Judson, Clin Sarcoma Res 2017 (update of ESMO Guidelines 2014)
Chak A , Gastrointest Endosc 1997
Sepe, Nat Rev Gastroenterol Hepatol 2009

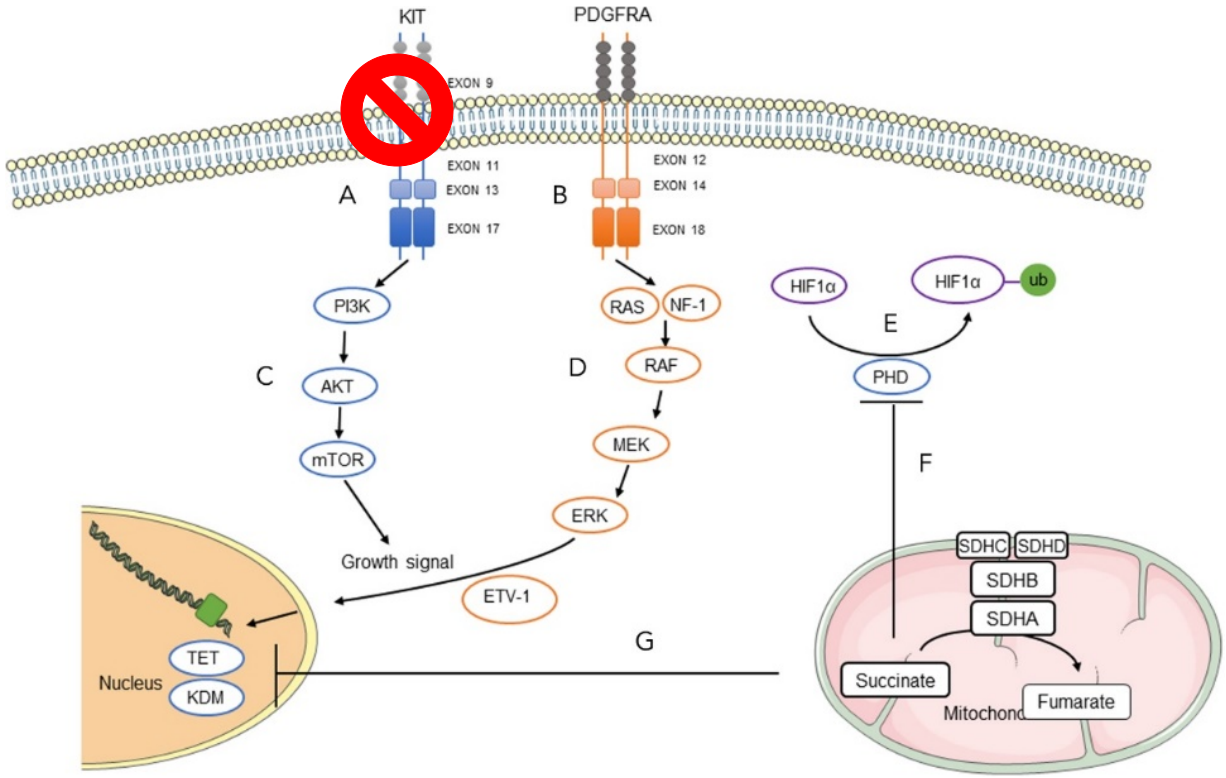
Imatinib (Glivec)

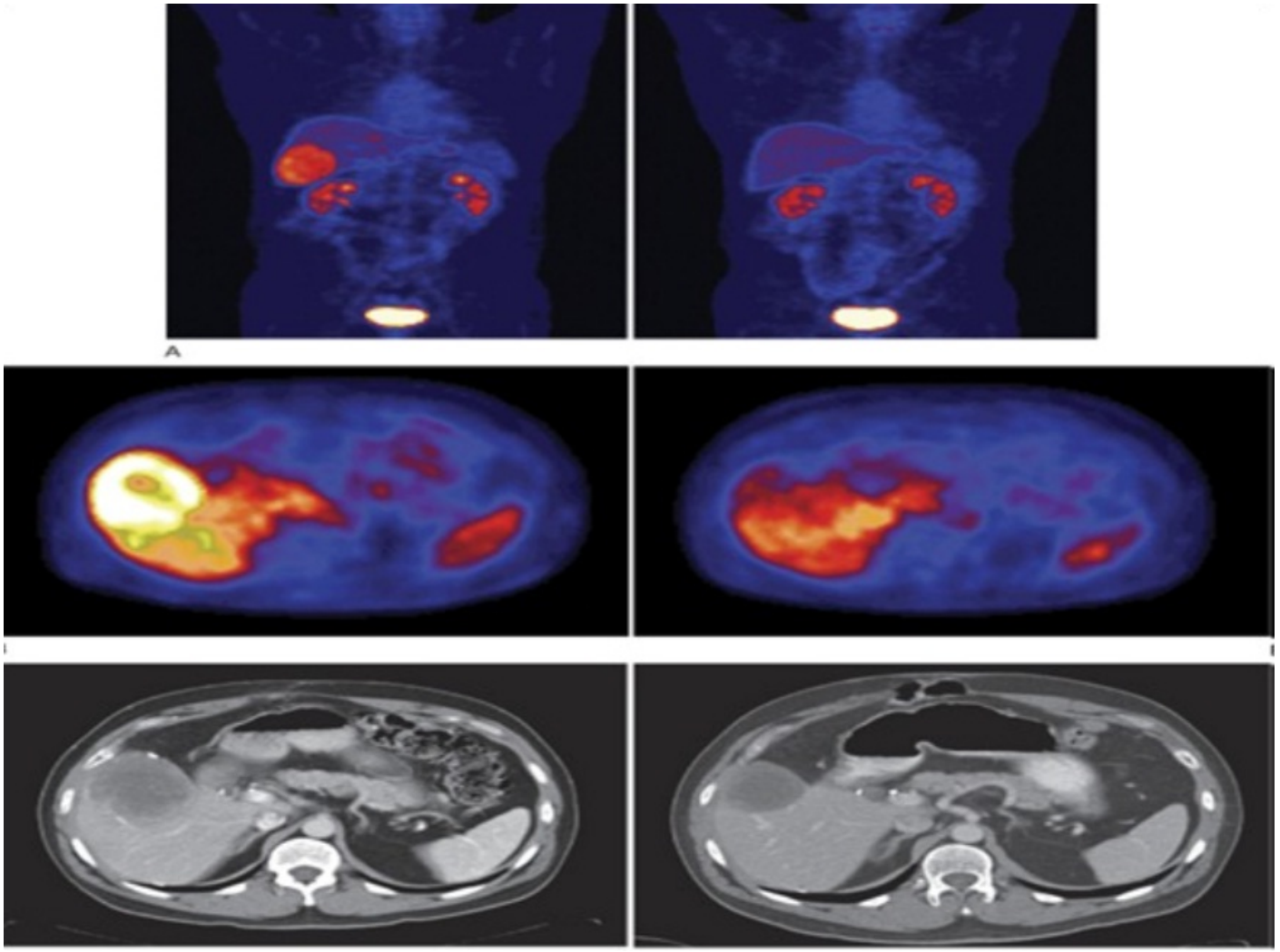


- Tyrosinkinase-Inhibitor: KIT, abl, Bcr-abl, PDGF-R
- Responsrate 83 – 89 % of Patient
- Effect depends on mutation
  - Beste effect in exon 11 mutation
  - In exon 9 mutation use higer dose
  - Almost no effegt in PDGFRA exon 18 mutation D842 V and NF-1 in advanced GIST



son, Clin Sarcoma Res 2017 (update of ESMO Guidelines 2014)
Verweij J, Lancet 2004 Blake CD, J Clin Oncol 2008


KIT
PDGFRA
EXON 9
EXON 11
EXON 13
EXON 17
EXON 12
EXON 14
EXON 18
A
B
PI3K
AKT
mTOR
C
RAS
NF-1
RAF
MEK
ERK
D
Growth signal
ETV-1
HIF1α
HIF1α
ub
E
PHD
F
SDHC
SDHD
SDHB
SDHA
Succinate
Fumarate
Mitochond
G
TET
KDM
Nucleus



- PET scan and CT scans in a patient with a GIST metastatic to the liver, before (left) and after treatment with imatinib mesylate

Imatinib

- **Settings / Indications?**
  - **Adjuvant setting**:
  - prolongs relapse-free survival (RFS), overall survival not affected[1)]

    At 1y RFS 98% vs. 83%, HR 0.35; best response for GIST >10cm with HR 0.28

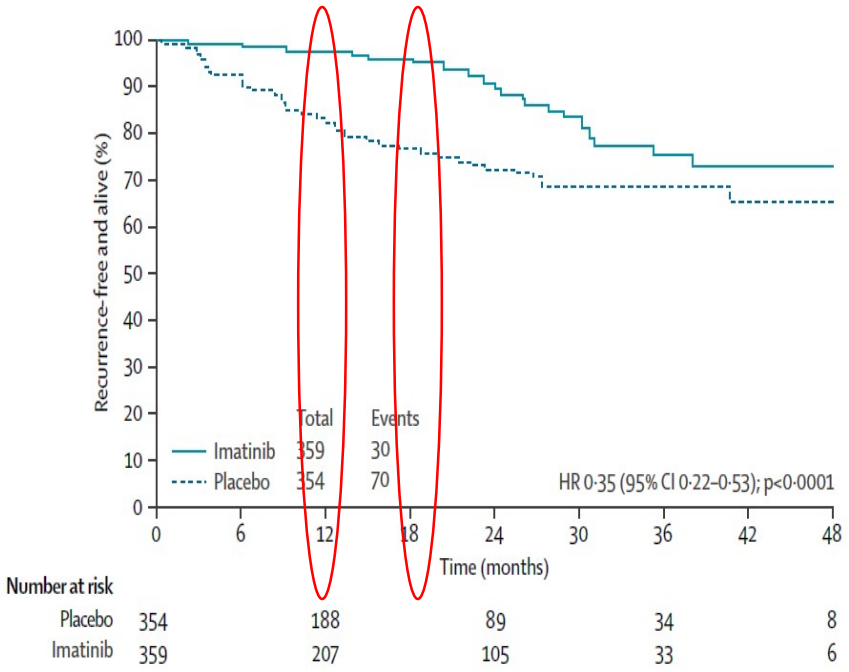
    - dose / duration? 400mg/d at least 1y

      High risk GIST: better RFS / OS with therapy 3y[2)]
  - **Additive setting**: incomplete resection (R1/2), intraoperative tumor perforation
  - **Neoadjuvant setting**: Primarily unresectable / marginally resectable GIST (e.g. large tumor and/or poorly positioned, high operative risk, organ-preserving surgery)

1) [DeMatteo RP et al. Lancet 2009;373:1097], [Kang B et al. J Clin Oncol 2009;27(Suppl):abstract#e21515]
2) [Joensuu H et al. Twelve versus 36 months of adjuvant imatinib (IM) as treatment of operable GIST with a high risk of recurrence: Final results of a randomized trial (SSGXVIII/AIO). J Clin Oncol 2011;29(Suppl): ASCO 2011, #LBA1]

Adjuvant setting

- Randomised, double-blinde, placebo-controlled study
- GIST ≥ 3 cm, KIT-positiv, completely resected
- 400mg/d Imatinib (n=359) vs. placebo (n=354) over 1 year



Results:

1 year without reccourence
Imatinib (98%) vs. Placebo (80%)

Imatinib-group: higher reccourence rate 6 month after therapy

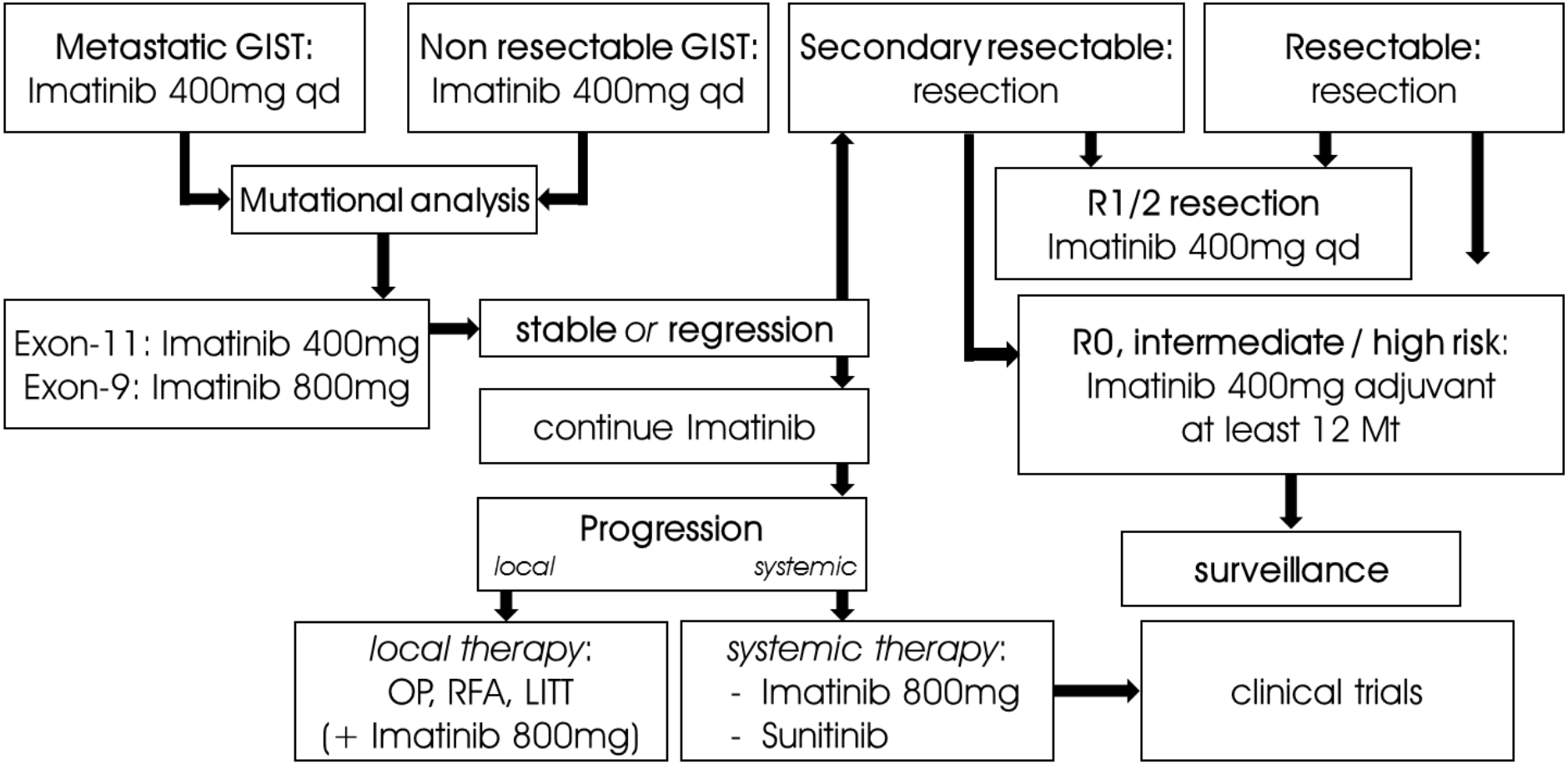
De Matteo, Lancet 2009

Metastatic or inresectable GIST

- Continous Imatinib (400mg/d), often relaps after stopping
  - If tumorprogression mesurement of serumlevel (interactions, malcompliance)
  - Real failure of therapy:
    - Rise dose (better survival than change to Sunitinib)
    - Second line therapy Sunitinib (Sutent®, Multikinase-Inhibitor)
    - Third line therapy Regorafenib (Stivarga®, Multikinase-Inhibitor)

Judson, Clin Sarcoma Res 2017 (update of ESMO Guidelines 2014)
Hsu JT et al, Oncotarget. 2017 Apr

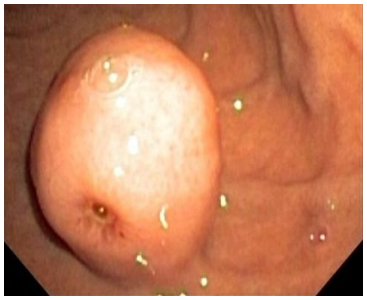
Therapeutic algorithm



Pediatric GISTs

- fundamentally different clinicopathologic entities (1-2% of all GISTs).
- typically lack *KIT/PDGFRA* mutations
- predominantly in girls, multiple nodules in the stomach
- distinct genomic profile→ overexpression of *IGF1R*
- Most pediatric wild-type GISTs progress to malignancy without acquiring large-scale chromosomal aberrations
- indolent clinical course despite a high rate of recurrence, are associated with longer survival even in patients with metastatic disease
- predominant clinical symptom is anemia

Summary GIST



- GIST **most common** mesenchymal GI-neoplasie
- Ca. **70% benigne**, but all sizes can develope maligne
- **EUS with FNP to confirm the diagnosis**
- **Complete Resektion** as only currative Treatment
- Risk of reccourence depends on size, localisation and mitotic rate→ **Imatinib** (as adjuvant and neoadjuvant therapy)
- In advanced GIST Imatinib first choice
- Sunitinib (Sutent®) as 2. and Regorafenib (Stivarga®) 3. line therapy

Thank you!