Gastrointestinal Stromatumors - GIST

Bible Class 29. May 2024

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Reiner Wiest

ARE ALL GIST MALIGNANT ?

ARE ALL GIST MESENCHYMAL ?

Do ALL GIST NEED TREATMENT ?

Epidemiology

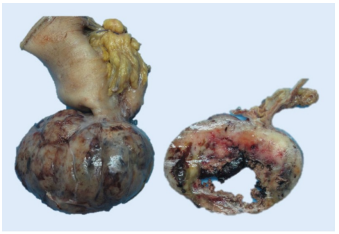
Incidence approx. 6-8 / 100'000 /y

- **0.1 – 3 % of all GI-tumors (rare)**
- **most frequent mesenchymal tumor**
- **slight prevalence in males**
- **mean age 60-65y (but occurence at any age)**

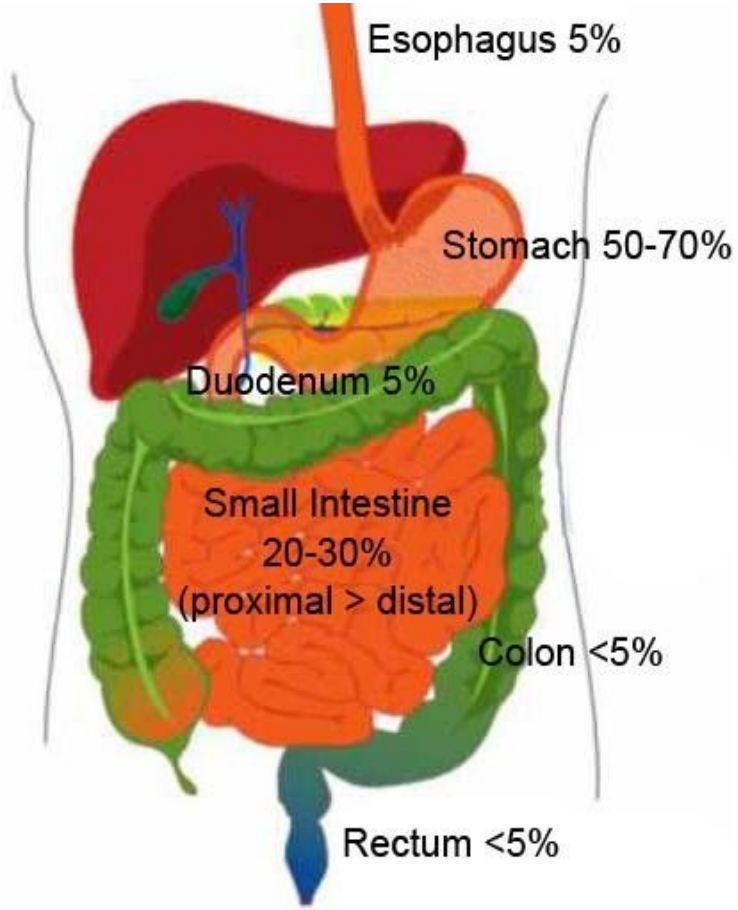
- **“mini-GISTs” (1–10 mm) are very common (detectable in 22.5% of the autopsies in individuals older than 50 years)**

[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: main sites ?



1/3 in small intestine



2/3 in stomach

Pathogenesis - which tissue and cells do GIST stem from ?

Originate from interstitial cells of Cajal

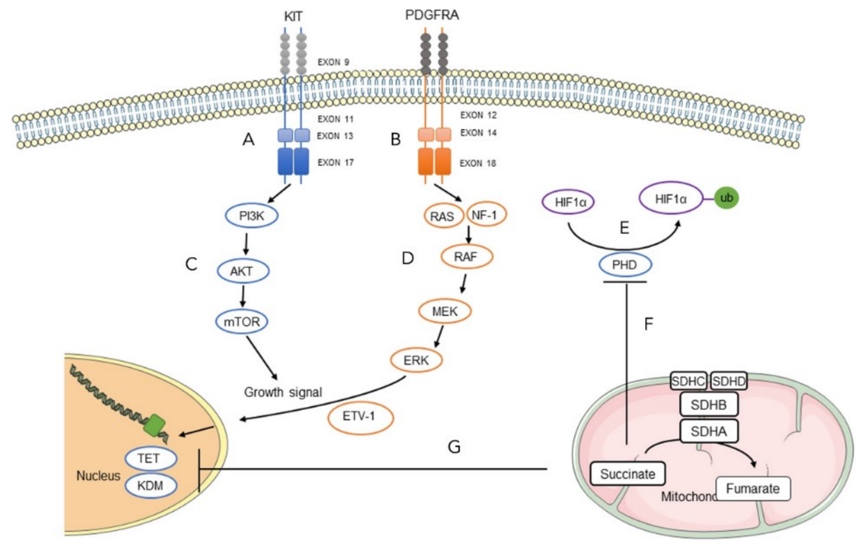
pluripotent mesenchymal stem cells
in normal cells activation of the c-kit tyrosine kinase requires the presence of endogenous ligand (c-kit ligand or stem cell factor)

1998 gain-of-function mutation of c-kit

→ uncontrolled activation TKI

→ uncontrolled growth/ proliferation

- **KIT 80-90% of GIST**
- **PDGFRA 8-15% of GIST**
  (almost all in stomach)



[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**

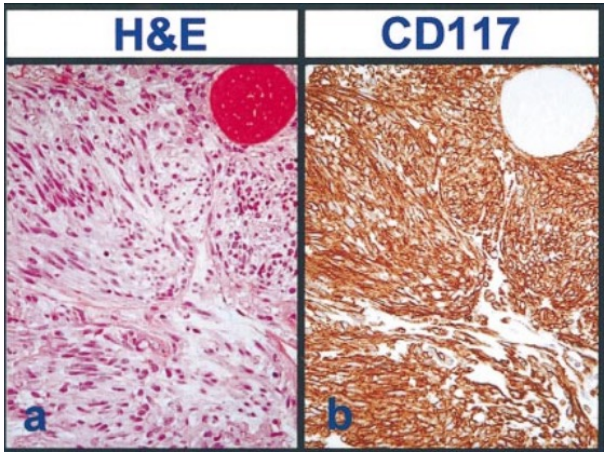
1) **[Heinrich MC et al. Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. J Clin Oncol 2003;21:4342]**

Immuno-histochemistry: for what markers ?

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 % of GISTs are negative for both DOG1 and KIT

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

The diagnosis of GIST does rely on pathology being typically ?

Biomarker	Method	Use	LoE	GoR
Mitotic index	Pathology	Disease classification Prognostic relevance Used for medical treatment decisions	IV	A
KIT mutations	Sanger sequencing or NGS	Disease classification Prognostic relevance Predictive relevance Used for medical treatment decisions Currently actionable/ targetable	I	A
PDGFRA mutations	Sanger sequencing or NGS	Disease classification Prognostic relevance Predictive relevance Used for medical treatment decisions Currently actionable/ targetable	I/III	A
NTRK mutations	Sanger sequencing or NGS	Disease classification Predictive relevance Used for medical treatment decisions Currently actionable/ targetable	III	A
BRAF mutations	Sanger sequencing or NGS	Disease classification Predictive relevance Used for medical treatment decisions Currently actionable/ targetable	V	B
SDH mutations/ epimutations	IHC	Disease classification Prognostic relevance Predictive relevance Used for medical treatment decisions	I	A

GoR, grade of recommendation; IHC, immunohistochemistry; LoE, level of evidence; NGS, next-generation sequencing; PDGFRA, platelet-derived growth factor receptor alpha; SDH, succinate dehydrogenase.

Positivity for CD117 (KIT) and/or DOG1

KIT/ PDGFRA negative

↓

Test BRAF, NTRK, SDH

All negative ↓

exclude NF1 and/or SDH-mutations

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%**

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%)

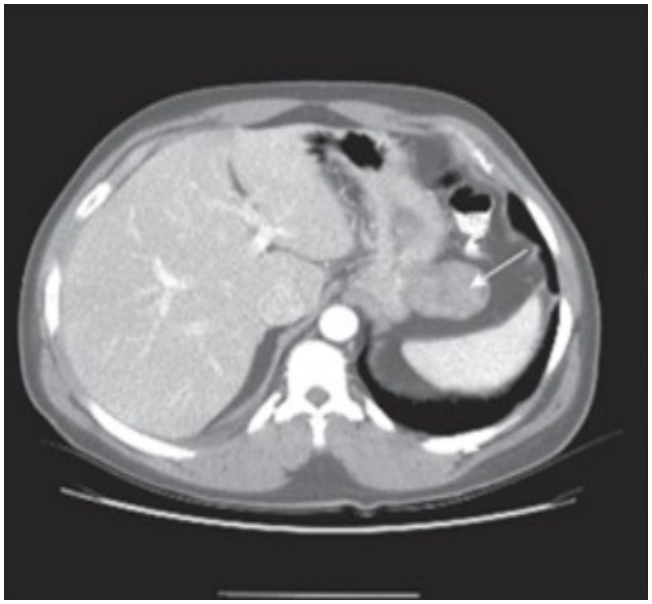
  Abdominal pain 20 – 50%

  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)
  - Triple-phase CT 1st choice
  - Histology / immunohistochemistry

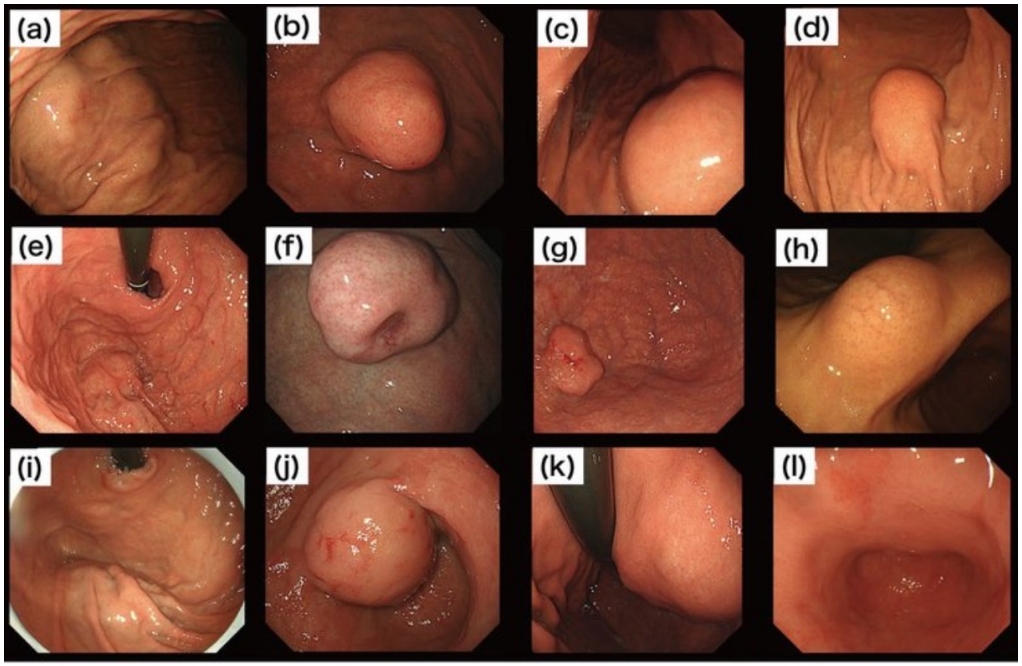
- **Diagnostic modality of choice:**
  - EUS-guided biopsy / FNB (if feasible)

Is biopsy mandatory?

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

Diagnostic workup

- **Endoscopic features of GIST:**



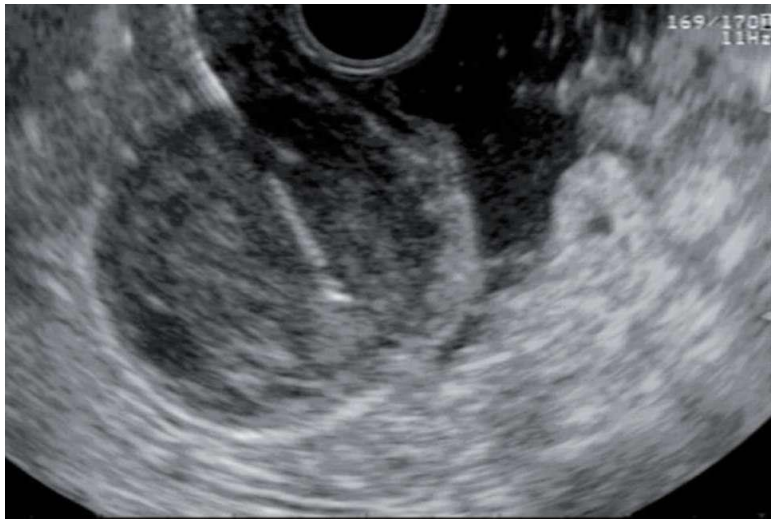
- **Drawback of Endoscopy w/ biopsy (stacked / bite-on-bite):**
  - **Risk of bleeding / tumor perforation**
  - **Poor diagnostic yield (17-42%)**

[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: method of choice

EUS

Classic features of GIST:



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

EUS +/- biopsy – advantages:

Most accurate method: secure diagnosis of GIST

- **solid mass of < 1 cm is technically difficult**
  →Tissue acquisition is recommended only for masses of > 1 cm

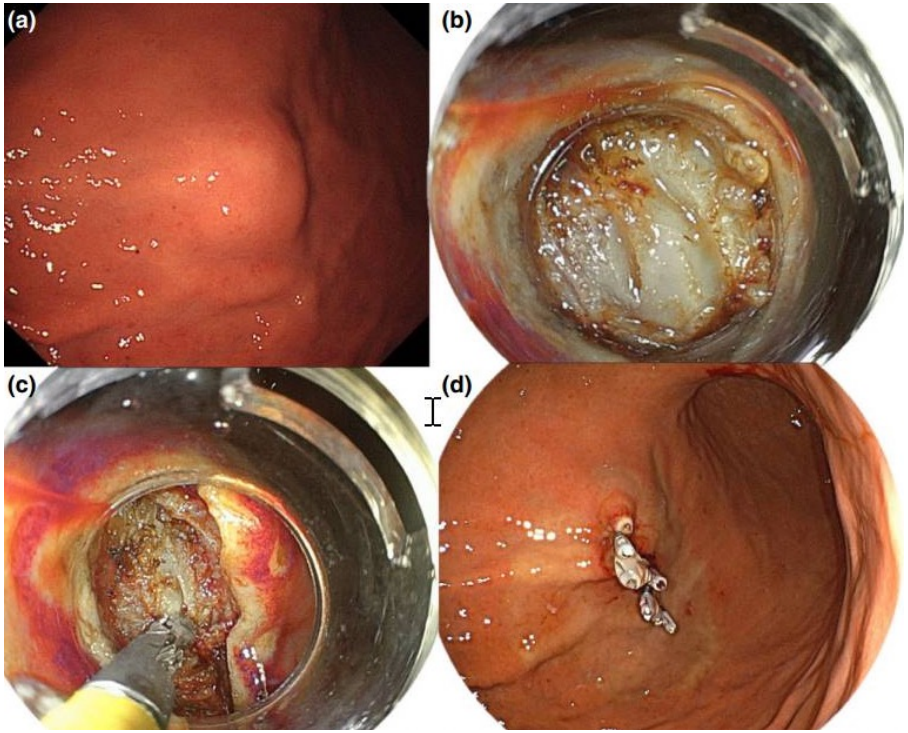
- **EUS-FNB outperforms FNA**
  71% for 1-2cm → 86% for 2-cm to 4-cm tumors
  close to 100% for > 4-cm tumors

- **Mucosal incision associated biopsy (MIAB) = e.g. De-Roofing**
  → 3 RCT vs. FNB: equally effective, diagnostic accuracy (GIST > 2cm)
  → subgroup analysis: lesion < 20 mm MIAB superior (91% vs. 71%)

[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]

Trindale AJ. Endoscopy International Open 2019; Osoegawa T et al. Dig Endo 2019

Mucosa-incision-associated biopsy for SMT/GIST



1. Submucosal injection
at site of incision
+ 0.0001 % epinephrine

2. Incision at apex of submucosal tumor + needle-knife or ESD-knife

3. Tissue biopsy from SMT
e.g. jumbo-jaw-biopsy
+ see tissue deformation at site of biopsy within tumor

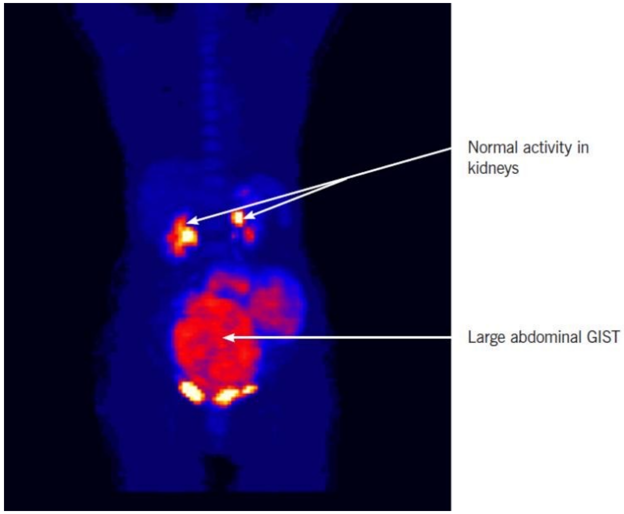
4. Closure of incision by endoClip

PS: however bleeding risk up to 5%

Osoegawa T et al. Dig Endo 2019

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

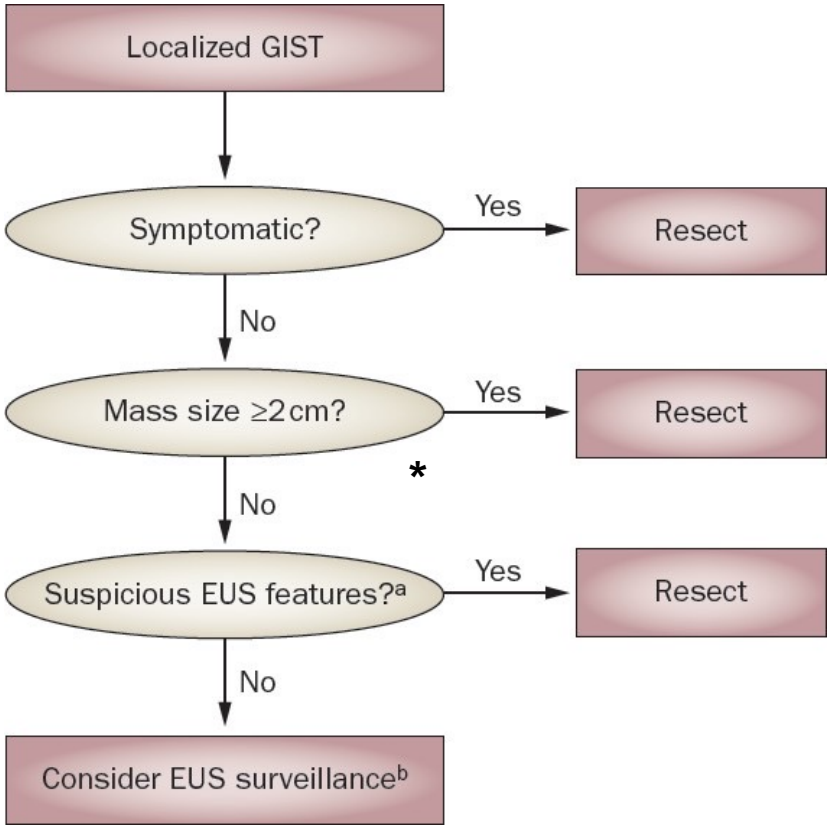
- Correlation between ^{18}FDG-Uptake & mitotic index

- Monitoring tumor response to therapy (early on)

[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]

How to manage/treat localized GIST ?



A) Possible high-risk features on EUS:

irregular border
cystic spaces
ulceration
echogenic foci
heterogeneity

B) When Surveillance is sufficient:

Only when age, comorbidities, site of tumor hinder /limit resection: then surveillance „after a thorough discussion with the patient regarding the risks and benefits“

No large, prospective studies!
Optimal frequency not defined!

6- to 12-mo intervals

Low compliance for follow-up!

Endoscopic resection SMT/GIST < 20 mm ?

ESGE:

Consider removal gastric GIST < 20 mm as alternative to surveillance
Decision to be discussed in multi-disciplinary team
Technique depends on size, location, local expertise
Resection does avoid surveillance/ follow-ups
(also for lesions of unknown histology after failure to obtain diagnosis)

NCCN:

gastric GIST < 20 mm without high-risk features
Can be followed-up periodically

ESGE Guidelines Deprez PH et al. Endoscopy 2022; von Mehren et al. J Natl Comp Network 2020

Principles of resection (e.g. surgery) ?

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

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

Definition of tumor rupture in GISTs

Ann Surg Oncol (2019) 26:1669–1675
https://doi.org/10.1245/s10434-019-07297-9

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

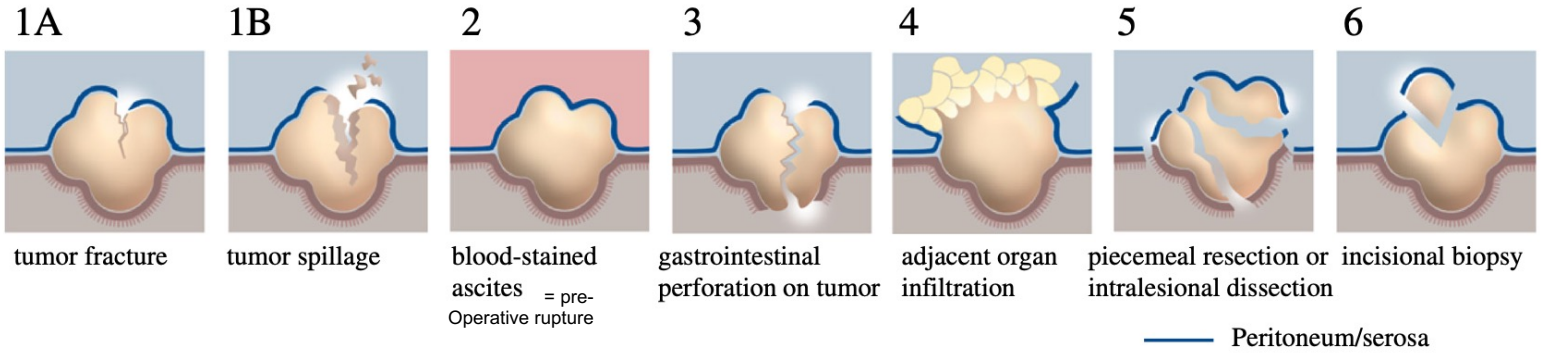
CONTINUING EDUCATION– SARCOMA

RFS in GIST stage-/mitosis adjustes

Without vs. With rupture 69-96% vs. 36-37%

Defining Tumor Rupture in Gastrointestinal Stromal Tumor

Toshirou Nishida, MD, PhD, FACS[1], Toto Hølmebakk, MD[2], Chandrajit P. Raut, MD, Msc[3], and Piotr Rutkowski, MD, PhD[4]



Risk stratification: e.g. after surgery for recurrence depends on ?

- **Tumor size:** < 2 cm, < 5 cm, > 10 cm
- **Mitotic index:** < 5/ 5 mm^2 > 10/ 5 mm^2
- **Location:** **small intestine (rectal) >>> gastric**

Plus:

- Tumor rupture at resection
- Nutritional status

1) [Miettinen M et al. Evaluation of malignancy and prognosis of gastrointestinal stromal tumors: a review. Hum Pathol 2002;33:478]
2) [Lasota J, Miettinen M et al. KIT and PDGFRA mutations in gastrointestinal stromal tumors (GISTs). Semin Diagn Pathol 2006;23:91]

Risk stratification

AFIP-Miettinen-Criteria

Gruppe	Größe	Mitosenzahl/5 mm² *	Lokalisation			
			Magen	Jejunum/Ileum	Duodenum	Rektum
1	≤ 2 cm	≤ 5	ø	ø	ø	ø
2	> 2–5 cm	≤ 5	Sehr niedrig	Niedrig	Niedrig	Niedrig
			(1,9 %)	(4,3 %)	(8,3 %)	(8,5 %)
3a	> 5–10 cm	≤ 5	Niedrig	Moderat	Hoch	Hoch
			(3,6 %)	(24,0 %)	(34,0 %)	(57,0 %)
3b	> 10 cm	≤ 5	Moderat	Hoch	Hoch	Hoch
			(12,0 %)	(52,0 %)	(34,0 %)	(57,0 %)
4	≤ 2 cm	> 5	ø[a]	Hoch[a]	–	Hoch
				(50,0 %)		(54,0 %)
5	> 2–5 cm	> 5	Moderat	Hoch	Hoch	Hoch
			(16,0 %)	(73,0 %)	(50,0 %)	(52,0 %)
6a	> 5–10 cm	> 5	Hoch	Hoch	Hoch	Hoch
			(55,0 %)	(85,0 %)	(86,0 %)	(71,0 %)
6b	> 10 cm	> 5	Hoch	Hoch	Hoch	Hoch
			(86,0 %)	(90,0 %)	(86,0 %)	(71,0 %)

Miettinen et al. Sem Diag Pathol 2006

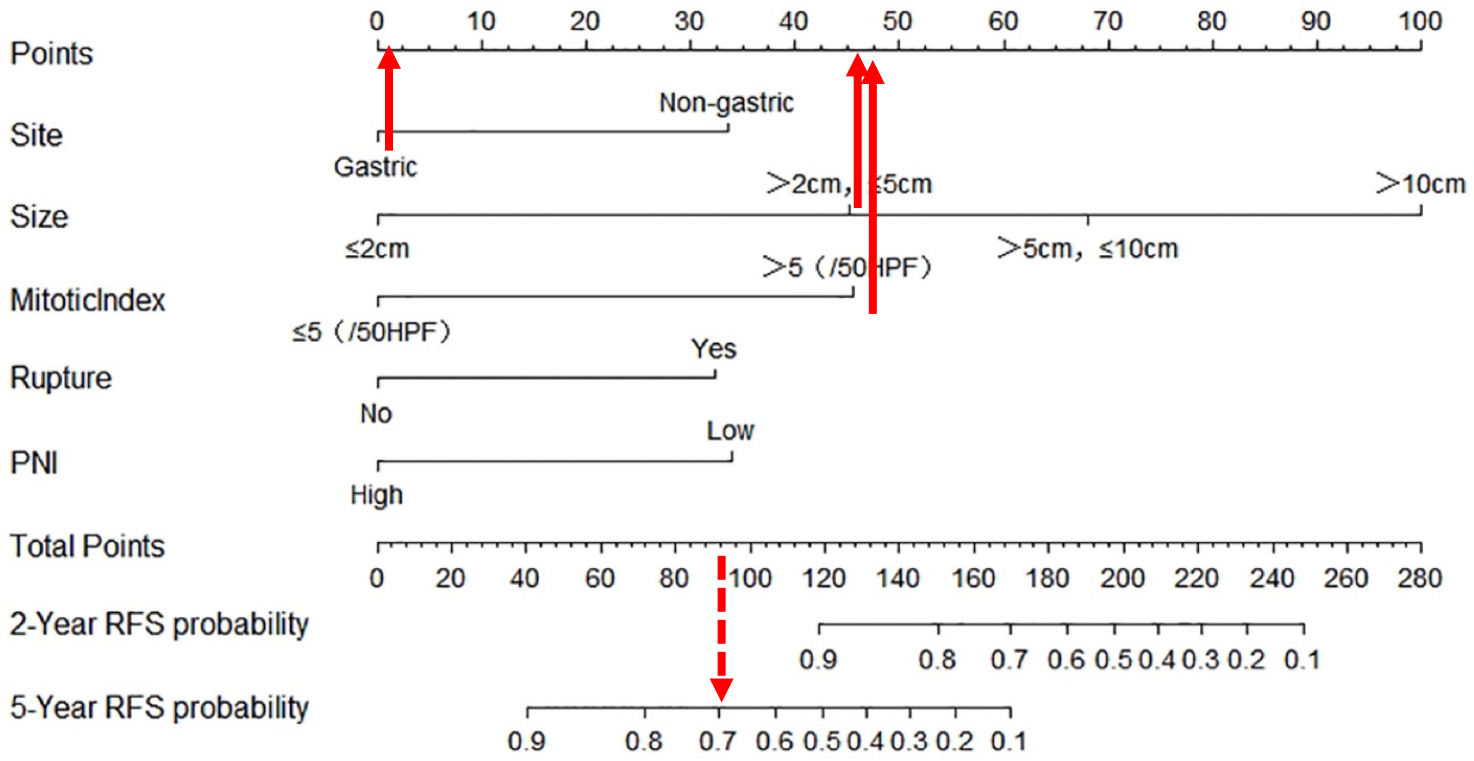
Risk Stratification Criteria ?

Modified – NIH - Criteria

Risk category	Tumor size (cm)	Mitotic index (per 50 HPF)	Location
Very low	≤2.0	≤5.0	Any
Low	2.1–5.0	≤5.0	Any
Intermediate	≤5.0	6–10	Any
	5.1–10.0	≤5.0	Gastric
High	>10.0	Any	Any
	Any	>10	Any
	>5.0	>5	Any
	≤5.0	>5	Non-gastric
	5.1–10.0	≤5	Non-gastric

High-risk means:
after stopping adjuvant (or without)
within 1-3 years a relapse
(even after R0 resection)

Nomogram for predicting probabilities of 2- and 5-year recurrence-free survival



CAVE: for KIT-positive GIST (only)

Li S. et al. Frontiers Oncology 2021

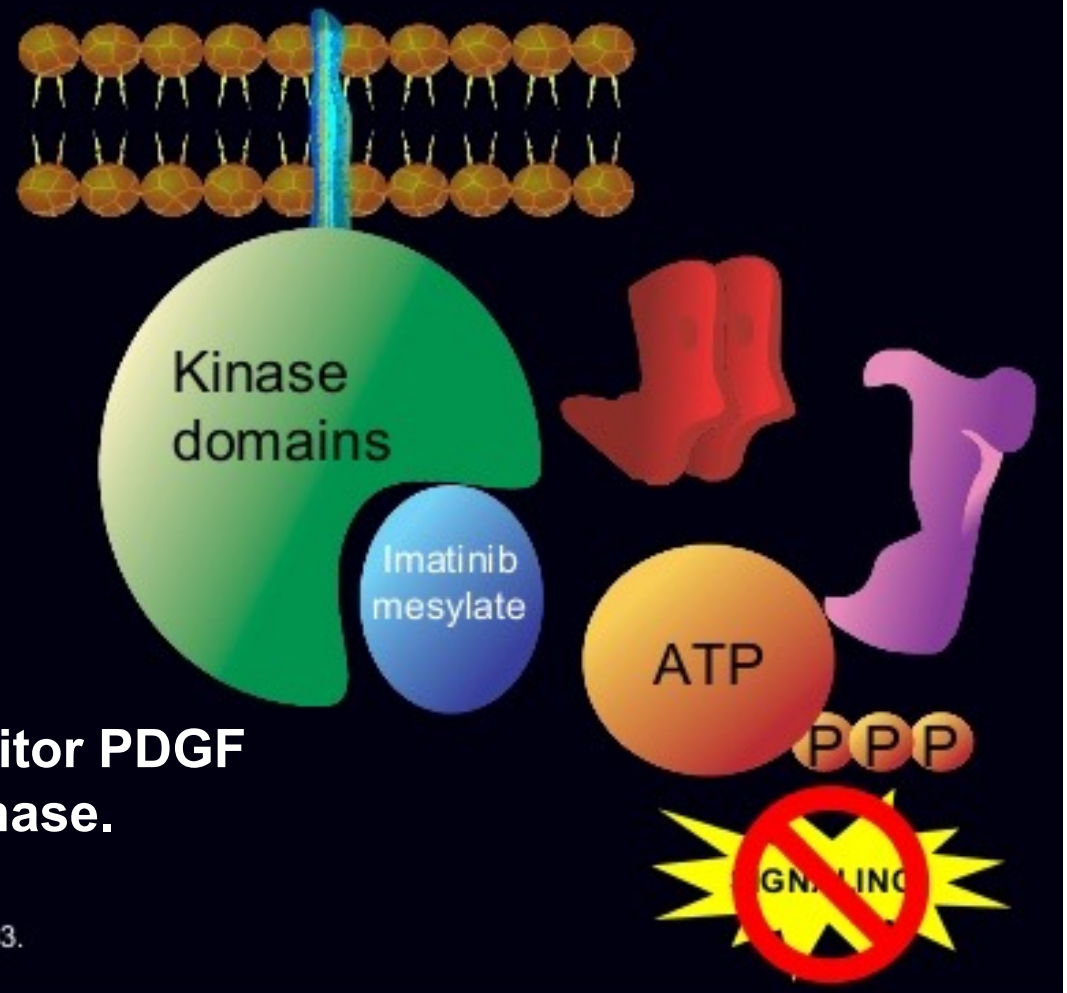
Adjuvant therapy after complete resection ?

What ?

Imatinib

Imatinib Mesylate: Mechanism of Action

- Imatinib mesylate occupies the ATP binding pocket of the KIT kinase domain
- This prevents substrate phosphorylation and signaling
- A lack of signaling inhibits proliferation and survival



Imatinib is also an inhibitor PDGF and Bcr-Abl tyrosine kinase.

Savage and Antman. *N Engl J Med*. 2002;346:683.
Scheijen and Griffin. *Oncogene*. 2002;21:3314.

Adjuvant therapy after complete resection ?

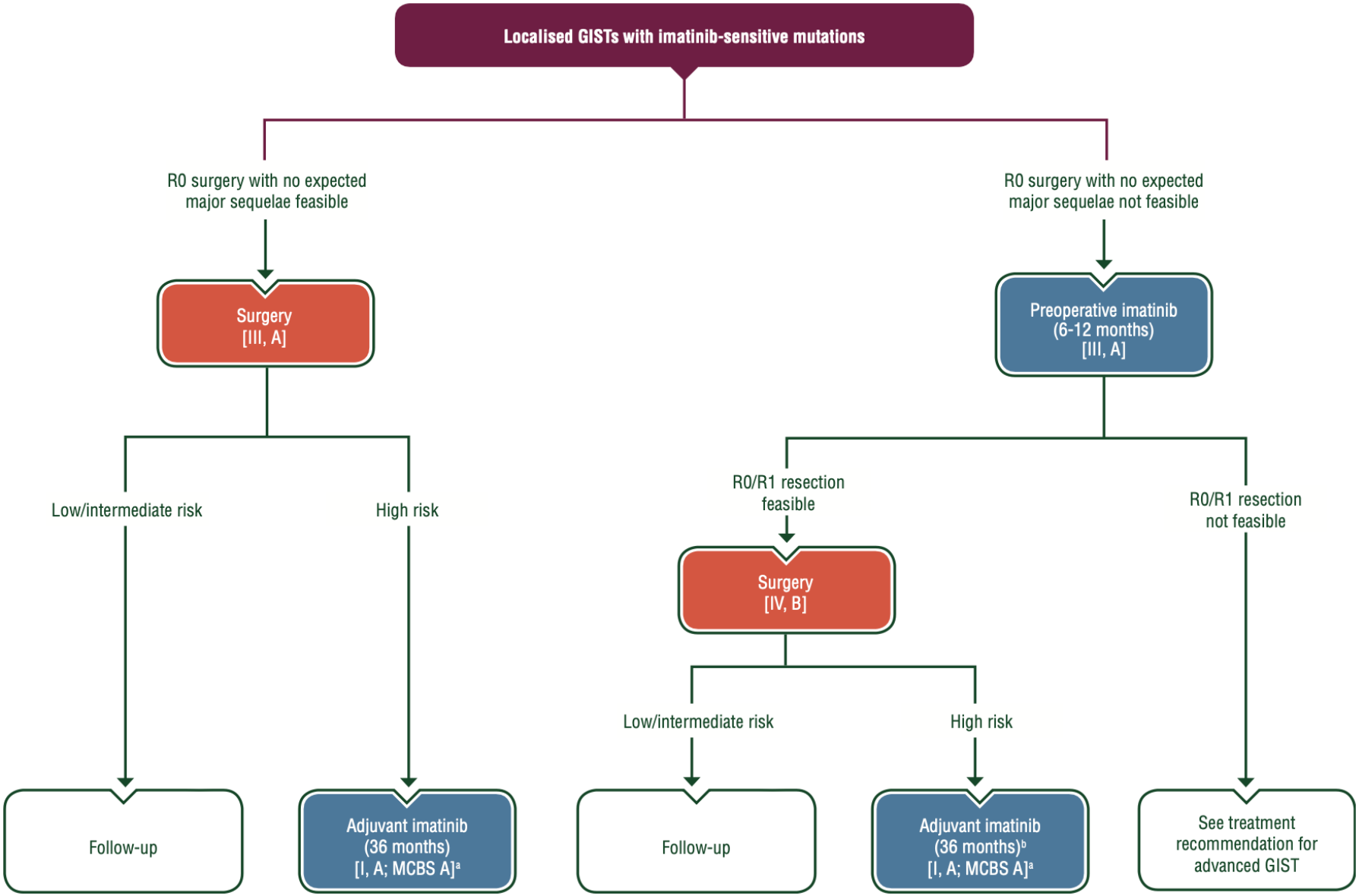
When ? How long ?

Most/all data for „high (or at least intermediate)“ risk patients

- 1 year **imatinib** in GIST > 3 cm prolongs RFS (1)
- 3 years **imatinib** better RFS and OS than 1 year (2)
- benefit depends on type of KIT/PDGFRA-mutation:

  greater in KIT **exon 11 deletion** mutations (3)

1:Dematteo RP et al. Lancet 2009; 2: Joensuu H JCO 2016; Joensuu H JAMA Oncol 2017


Localised GISTs with imatinib-sensitive mutations
R0 surgery with no expected major sequelae feasible
R0 surgery with no expected major sequelae not feasible
Surgery [III, A]
Preoperative imatinib (6-12 months) [III, A]
Low/intermediate risk
High risk
R0/R1 resection feasible
R0/R1 resection not feasible
Surgery [IV, B]
Low/intermediate risk
High risk
Follow-up
Adjuvant imatinib (36 months) [I, A; MCBS A][a]
Follow-up
Adjuvant imatinib (36 months)[b] [I, A; MCBS A][a]
See treatment recommendation for advanced GIST

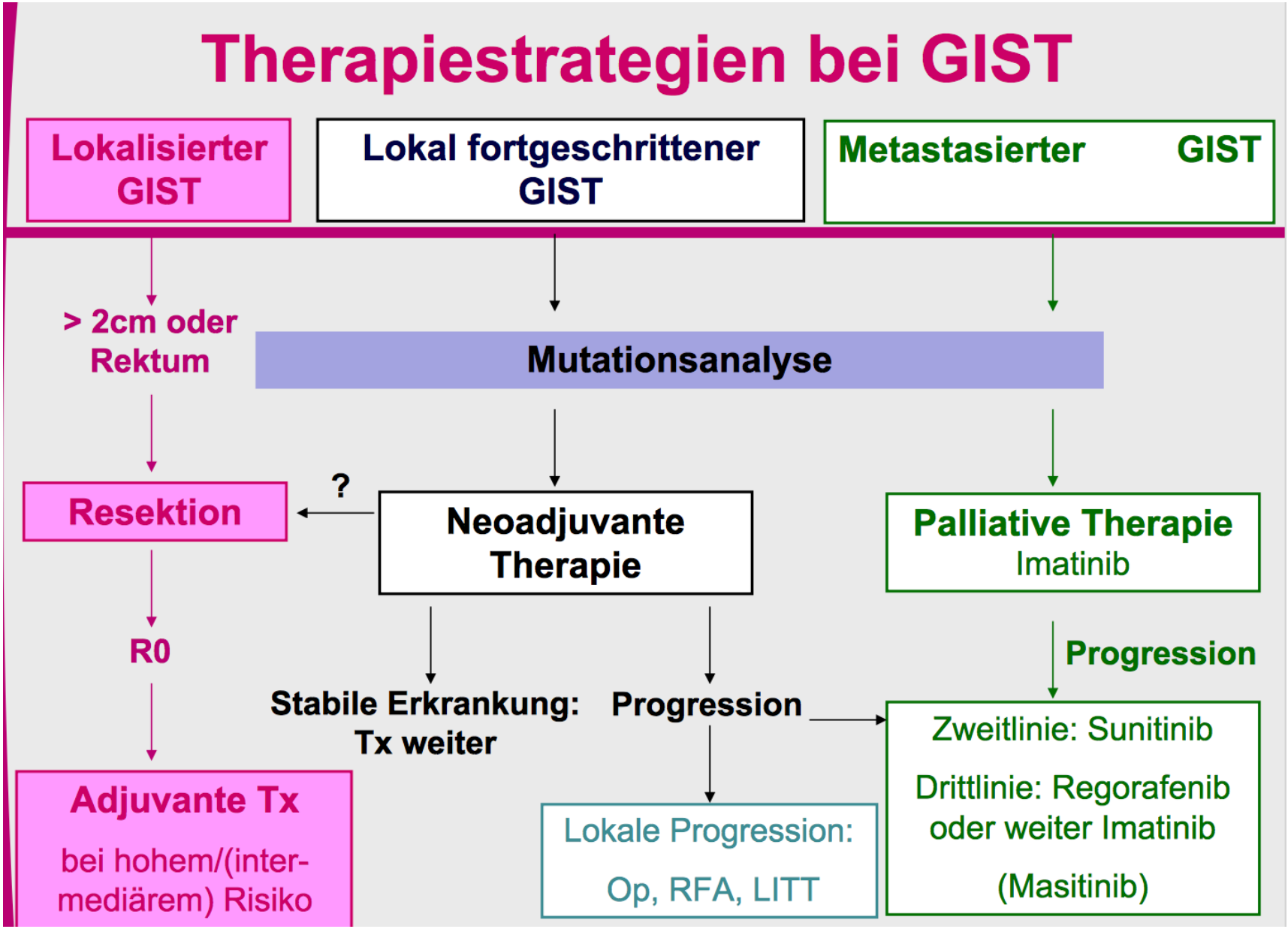
Follow up after complete resection and adjuvant treatment

Interval surveillance unclear (institution based SOPs)

Mostly in high-risk GIST: E.g. every 3-6 months for 3 years
CT scan (abdominal/pelvic) – then yearly

Most frequent sites of recurrence: liver and peritoneum

Therapiestrategien bei GIST



Mutational analysis: why - when - what ?

Predicts sensitivity to molecular-targeted therapy = prognosis

Mutational analysis in the diagnostic work-up of all GIST
should be considered standard
(with possible exclusion of non-rectal GIST < 20 mm)

Examples:

KIT exon 11 deletion codons 557-558 = high risk for relapse
PDGFRA mutation D842V generally good prognosis

Which mutations are „drug-able“ and by what ?

Genomic alteration	Drug	Evidence/ Literature
KIT mutations	Imatinib (adjuv.)	I-A (1,2)
PDGFRA D842V +other mutations	**Avapritinib (pre-op)** **Sunitinib**	I-B (3)
NTRK rearrangements	**NRTK-inhibitors (e.g. larotrectinib)**	I-C (4)
BRAF mutations	**BRAF-inhibitors (incl BRAF-MEK-comb)**	III-A (5)

1 Debiec-Rychter M et al. Eur J Cancer 2006; 2 Heinrich MC et al. J Clin Oncol 2008
3 Heinrich MC et al. Lancet Oncol 2020; 4 Drilon A et al. NEJM 2018; 5 Falchook GS et al. Oncotarget 2013

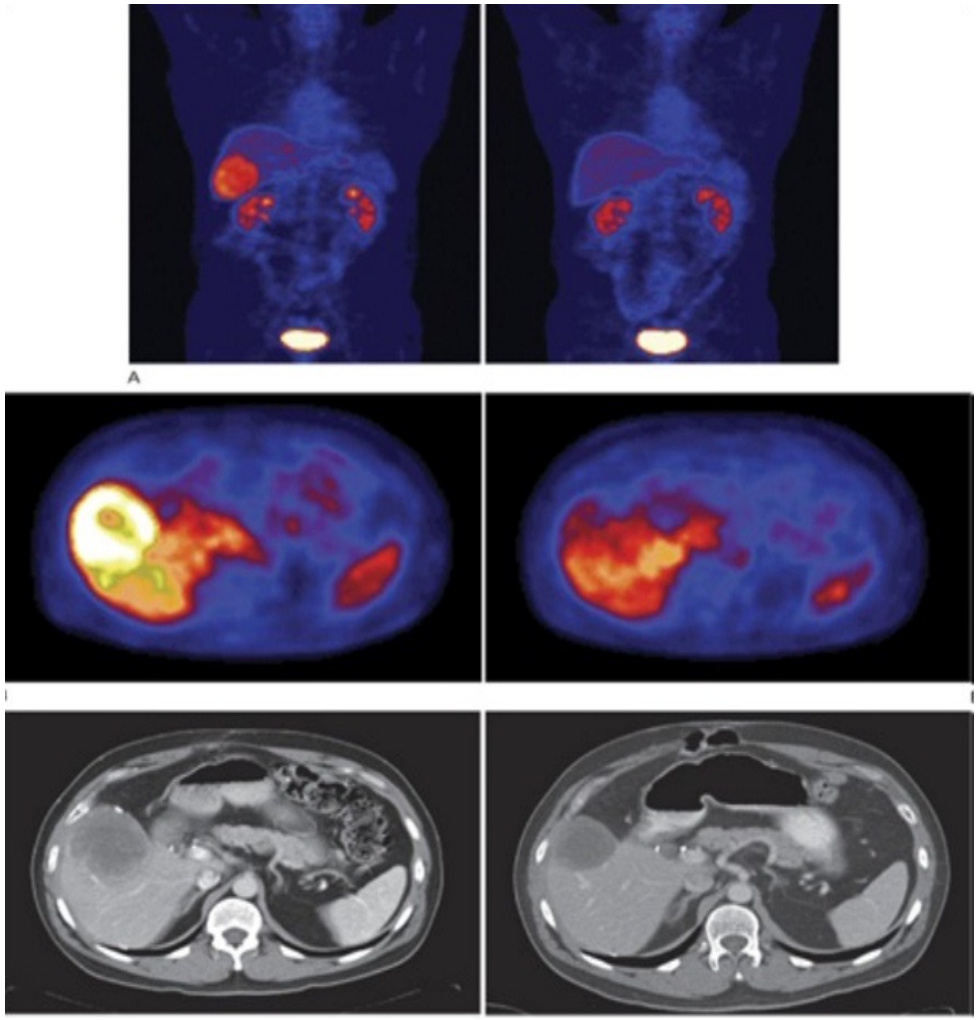
How to assess treatment response ? (e.g. neo-adjuv.)

- **Aim: Do not miss early progression (avoid delay of surgery)**
- **Tumor size and tumor density:**
  changes can precede delayed shrinkage
  progression without increase in size
  e.g. „nodule within a mass“[1]
- **Contrast-CT and/or MRI and/or CEUS**
- **FDG-PET**

absence of tumor progression after 6 months = tumor response[2]

[1] Shankar S Radiology 2005 [2]Le Cesne A et al. J. Clin Oncol 2009

Use of FDG-PET-CT in GIST-Treatment

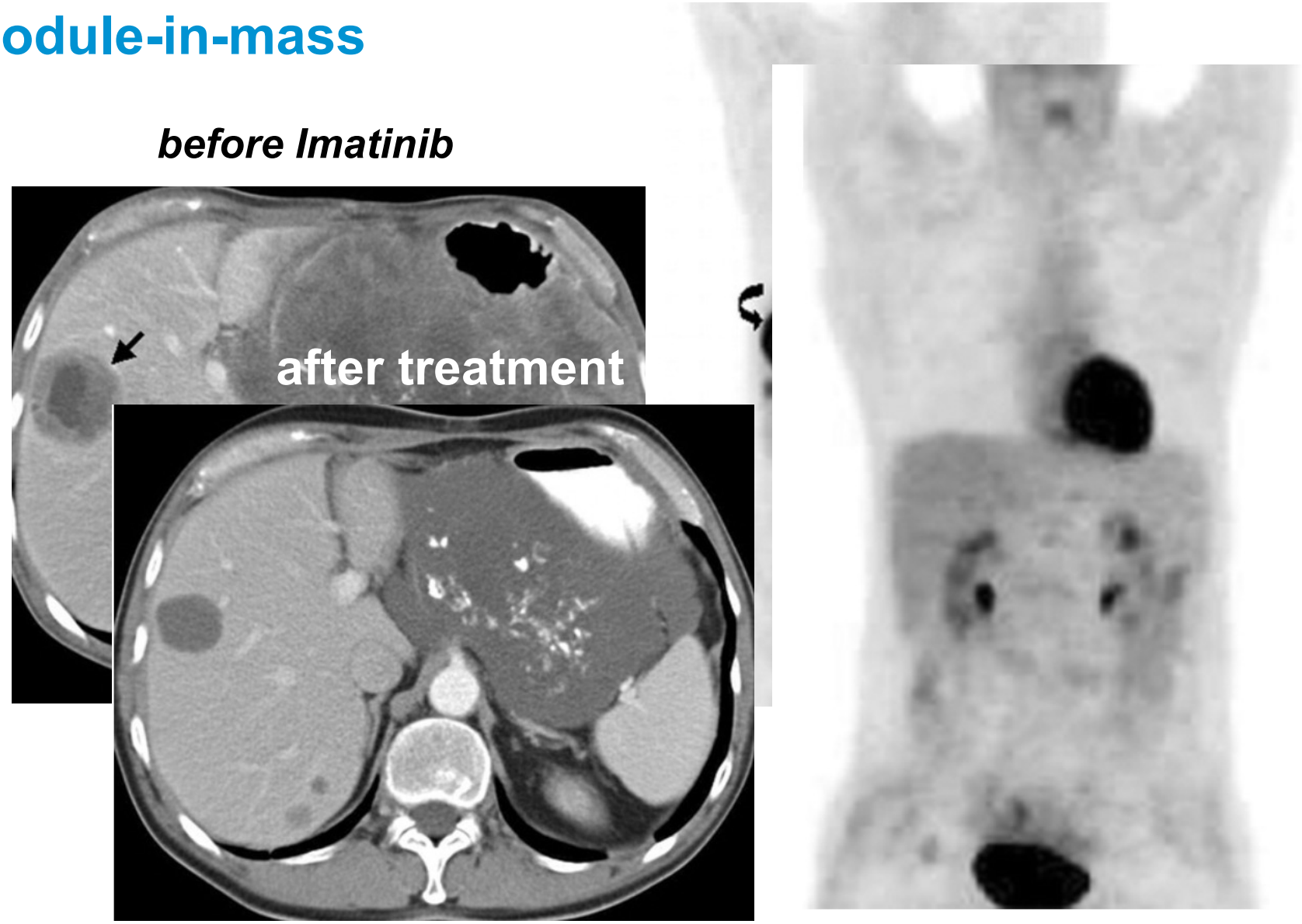


PET scan and CT scans
in a patient with a GIST

metastatic to the liver,
before (left)
after treatment (right)

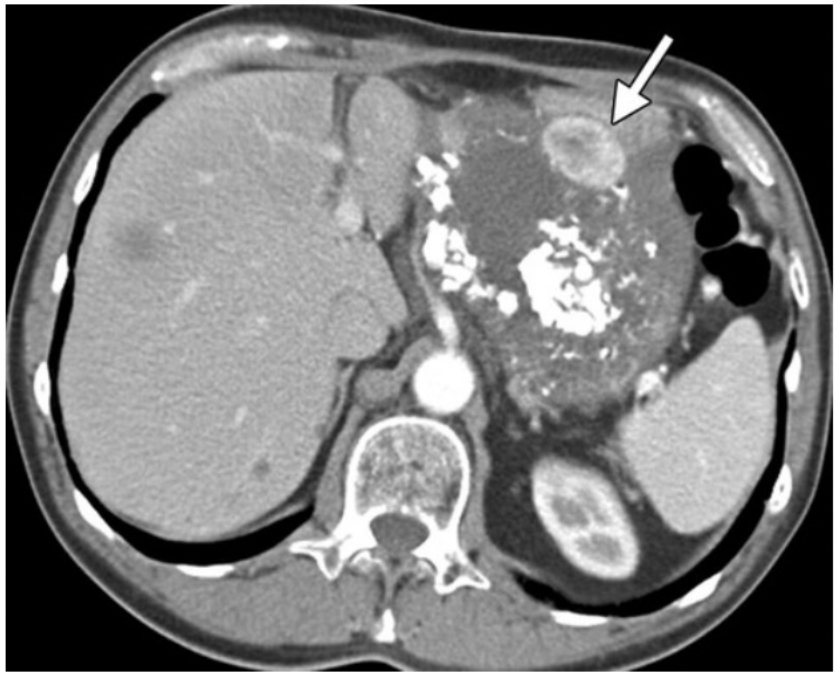
with imatinib mesylate

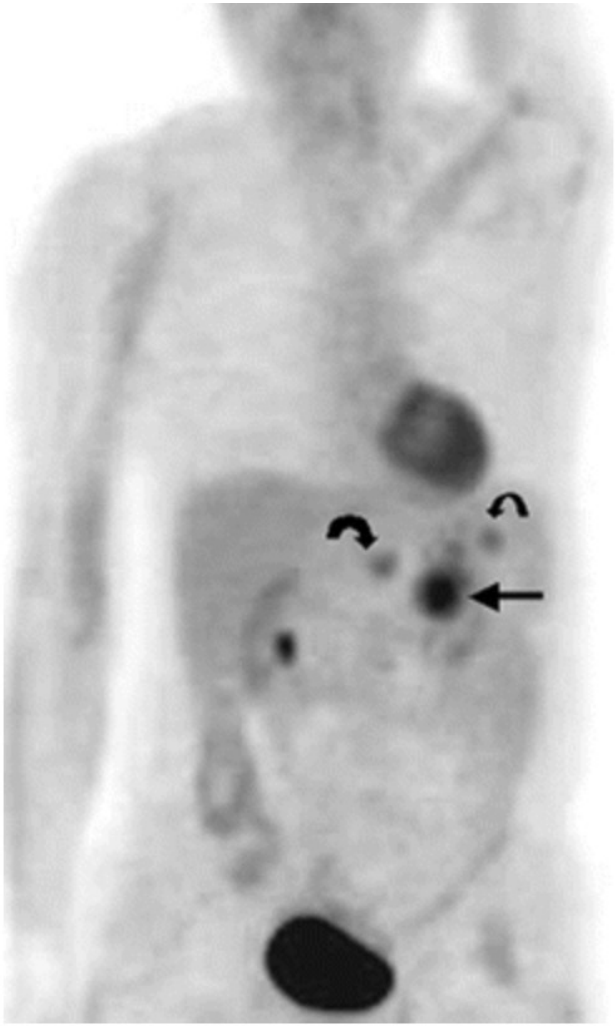
Nodule-in-mass



Nodule-in-mass

= relapse - evidence





Shankar S et al. Radiology 2005

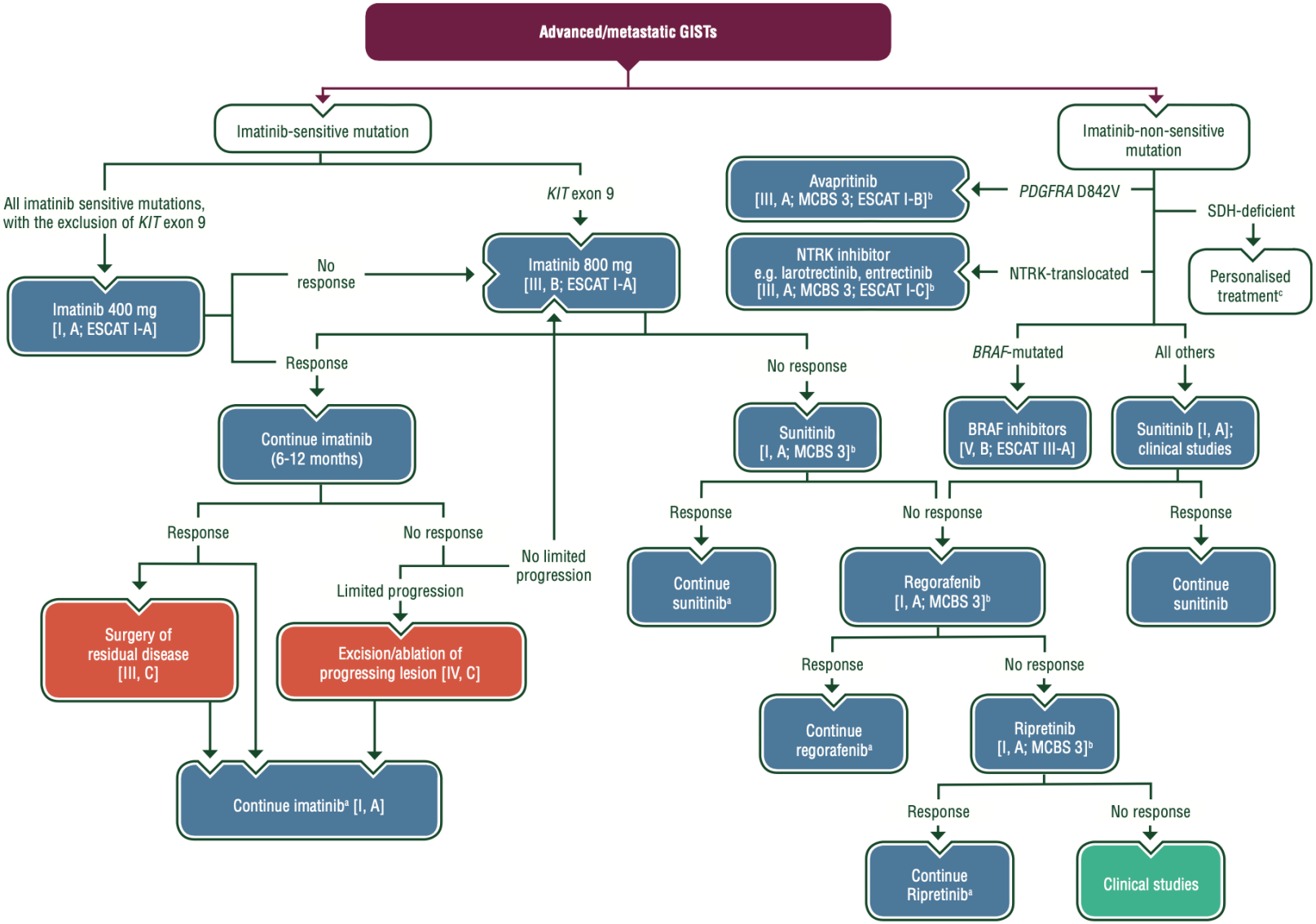
What is standard 2nd line treatment in GIST after/ failing imatinib (even at dose-escalation)?

Sunitinib[1]

What to do when sunitinib is failing 3rd line therapy in advanced GIST ?

Regorafinib[2]

[1] Demetri GD et al. Lancet 2006 [2]Demetri GD et al. Lancet 2003


Advanced/metastatic GISTs
Imatinib-sensitive mutation
Imatinib-non-sensitive mutation
All imatinib sensitive mutations, with the exclusion of KIT exon 9
KIT exon 9
Imatinib 400 mg [I, A; ESCAT I-A]
No response
Imatinib 800 mg [III, B; ESCAT I-A]
Response
No response
Continue imatinib (6-12 months)
Response
No response
Limited progression
No limited progression
Surgery of residual disease [III, C]
Excision/ablation of progressing lesion [IV, C]
Continue imatinib[a] [I, A]
Avapritinib [III, A; MCBS 3; ESCAT I-B][b]
PDGFRA D842V
SDH-deficient
NTRK inhibitor e.g. larotrectinib, entrectinib [III, A; MCBS 3; ESCAT I-C][b]
NTRK-translocated
Personalised treatment[c]
BRAF-mutated
All others
Sunitinib [I, A; MCBS 3][b]
BRAF inhibitors [V, B; ESCAT III-A]
Sunitinib [I, A]; clinical studies
Response
No response
Response
Continue sunitinib[a]
Regorafenib [I, A; MCBS 3][b]
Continue sunitinib
Response
No response
Continue regorafenib[a]
Ripretinib [I, A; MCBS 3][b]
Response
No response
Continue Ripretinib[a]
Clinical studies

Pediatric GISTs

- fundamentally different clinicopathologic entities (1-2% of all GISTs).
- typically lack *KIT/PDGFRA* mutations
- frequently affected genese encoding for SDH (succinate dehydrogenase)
- 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

Syndromes linked to GISTs ?

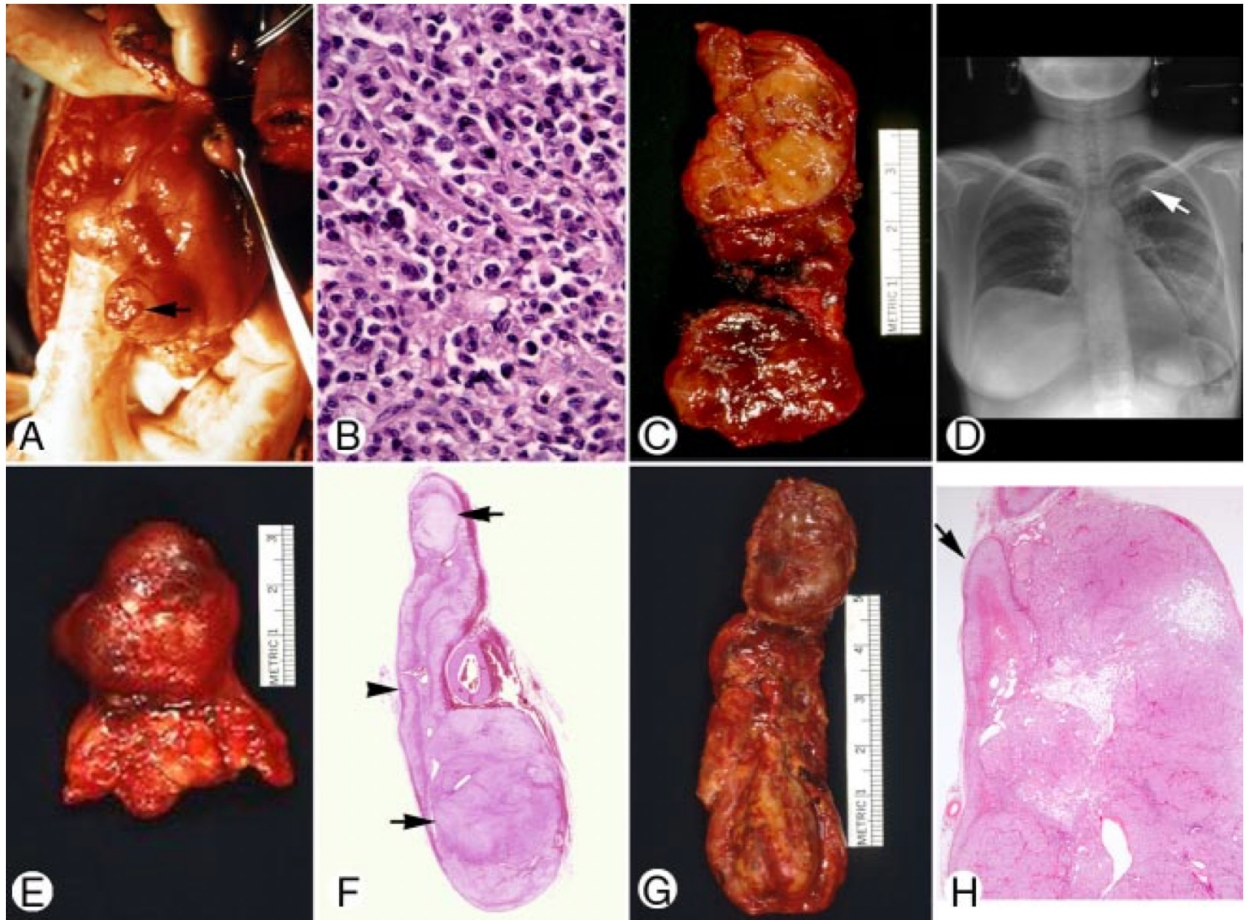
- **Carney triad syndrome:**
  gastric GISTs, paraganglioma + pulmonary chondromas

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

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

- Families with germline autosomal dominant mutations of KIT are extremely rare (about 10 families worldwide)
  – → presenting with multiple GISTs at an early age

Carney Triad Syndrome



A: **gastric tumors** on serosal surface
B: **GIST**- histology spindle-cell-like
C: Aorto-Pulmonary **Paraganglioma**
D: Calcified nodule at **pulmonary chondroma**
E: Extra-adrenal **para-ganglionoma**
F: **Cortical adenomas** in right adrenal gland
G: Extra-adrenal para-ganglionoma with **pheochromocytoma**
H: histology of pheoch.

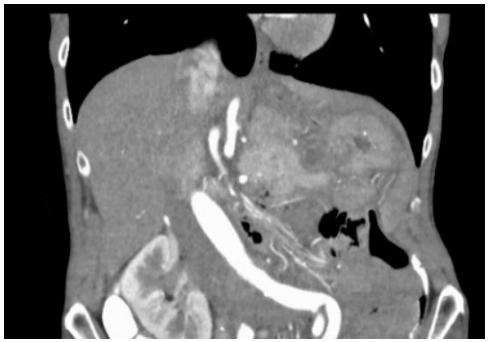
Carney et al. J Clin Endo Metabol 2009

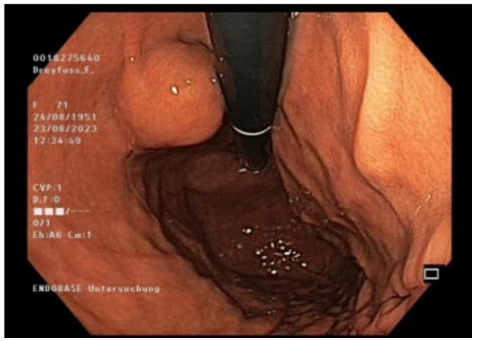
What tumor-associated factors do determine prognosis ?

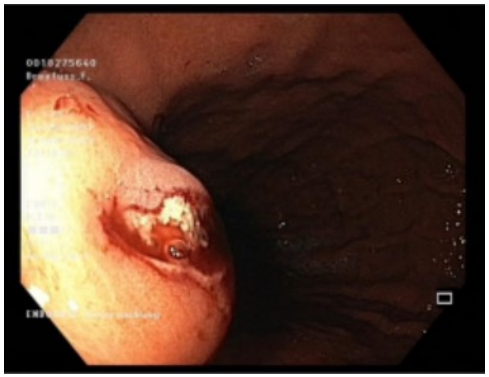
- **Size: the bigger the worse (> 10 cm)**
- **Mitotic index: the more the worse (> 10/ 5 mm^2)**
- **Site: small intestine (rectal) >>> gastric**
- **Tumor rupture: e.g. infiltrative plus hemorrhagic ascites**
- **Genotype**

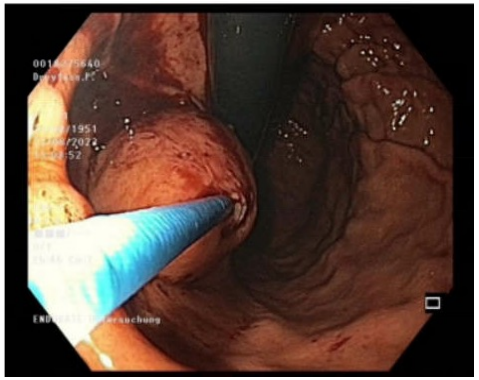
Welcome to Sarcomboard

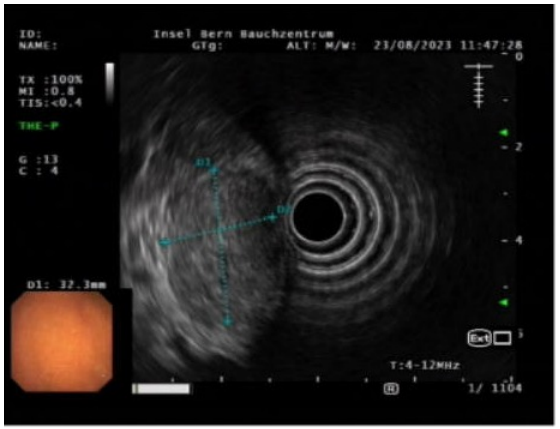
Dreyfuss, F. 24.8.1951 ?











23.08.2023 ÖGD und obere EUS:
Hoch Vd.a auf GIST (4. Schicht).
needle knife deroofing

Histologie (B2023.33051):
GIST mit spindelzelliger Morphologie
Mitoserate am 0/5 mm2.

typische Exon 11 Mutation
Keine PDGFR-/ BRAF Gen-Mutationen

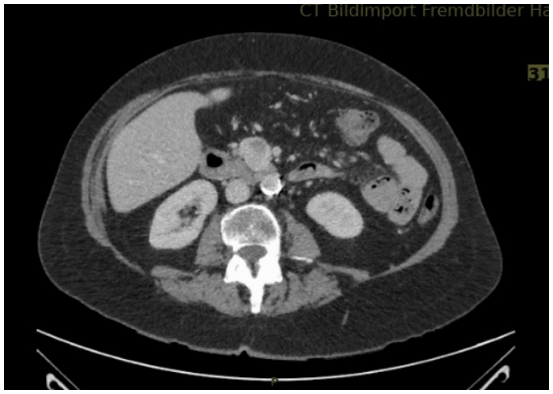
Primäre Resektion

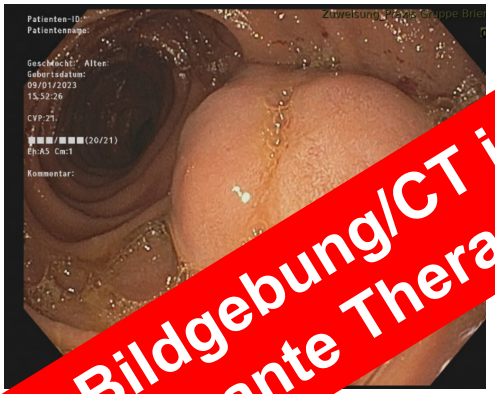
?

maximal 3,5 cm messenden gastrointestinalen Stromatumor
Mitoserate < 5 pro 5 mm²
TNM-Klassifikation (UICC, 8. Auflage, 2017)
pT2 pNX L0 V0 Pn0 R0

Keine adjuvante Therapie
Verlaufs-MRI in 1 Jahr

Ammacher Silvia 1948: GIST Pars III duodeni





Nachsorge Bildgebung/CT in 3 Monaten
Keine adjuvante Therapie aktuell

, R0
n/mm2

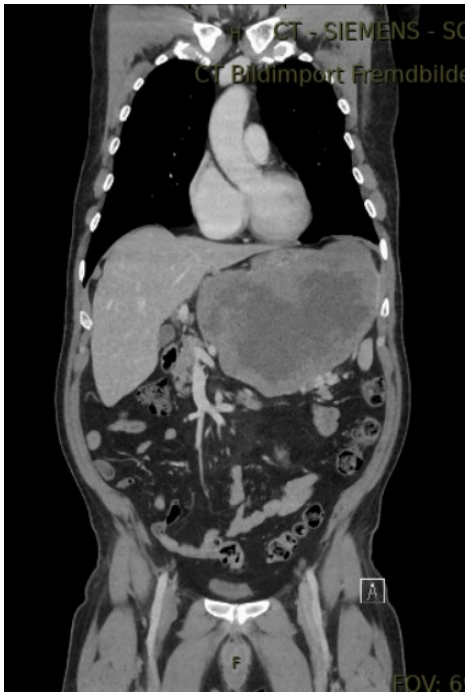
ezidivrisiko nach
Miettinen 8.3%

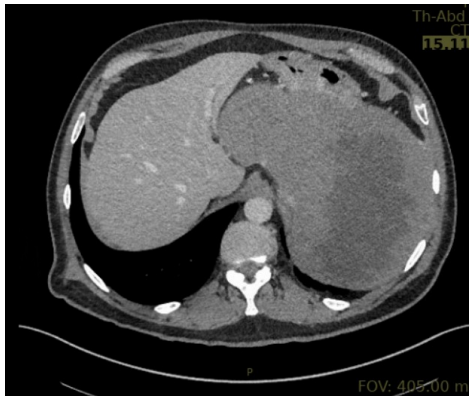
?

Exzisat, Duodenum[illegible]naler Stromatumor (GIST, siehe Kommentar)
überwi[illegible]eiliger Morphologie, vollständig reseziert,
[illegible]Abstand zur Serosa 0,1 cm.
K[illegible]weis einer Lymph- oder Blutgefässinvasion.
Keine Perineuralscheideninfiltration

pT2 pNx L0 V0 Pn0 R0
AFIP-Kategorie: 2 (4.3% Progressionsrisiko)

SALI Shefshet, geb. 15.10.1953





Histologie (Path. Uni Bern Z22.6477):
GIST

erhaltene Expression von SDHB
Mutation KIT EXON 11 p.W557R
keine Mutation im PTGFR Alpha

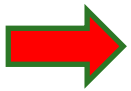
Neoadjuvante Systemtherapie mit Imatinib

darunter autoimmun hämolytische Anämie
kurzfristige Therapiepause

?

19.10.2023 Diagnostische Laparoskopie, mediane Laparotomie, Resektion des Tumors, Splenektomie, proximale Gastrektomie und Double Tract Reconstruction; keine Perforation

cT4 cN0 cM0, ypT4 ypNx cM0, R0 (22 cm)
Mitose: 2/5mm2; Durchmesser 21,5 cm
etwa 50% vitaler Tumor

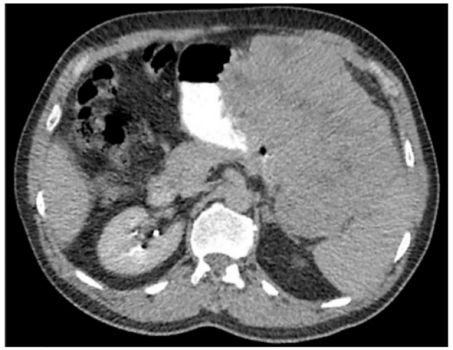
? 

12/23 - 04/24 Adjuvante Systemtherapie mit Imatinib
Aktuell: Keine Hinweis für Tumorrezidiv

Thank you!

GIANT GIST

we suspected it was a GIST with necrotic areas.



gure 2 – ***Abdominal CT scan showed a large mass of ×15×14 cm, with numerous necrosis and cystic areas, using a mass effect on the spleen. Also, it suggested at the point of origin might be the stomach wall. CT: mputed tomography.***

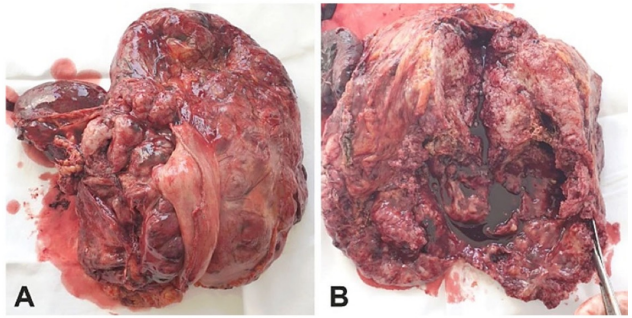


Figure 3 – ***(A and B) Macroscopic image of the resection specimen (22×10 cm) with hemorrhage spots, cystic and necrotic areas.***

In the thickness of the muscular tunic of the gastric wall, a partially encapsulated tumor proliferation was noted, with a pseudonodular appearance, composed of fusiform cells,

Review

How to measure your microscope's HPF. A critical guide for residents

Salvatore Lorenzo Renne[1,2]

[1] *Department of Biomedical Sciences, Humanitas University, Milan, Italy;* [2] *IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy*


Restricted access | Case report | First published online February 19, 2023

A Rare *PDGFRA* Exon 15 Ge
Concerning for GIST-Plus

Chiyun Wang, MD, Rhonda K. Yanti

Volume 31, Issue 6 | https://doi.org

Contents | Get access

Case Reports > Rev Esp Enferm Dig. 2023 Dec;115(12):741-742.
doi: 10.17235/reed.2023.9927/2023.

Multiple GIST and pheochromocytoma – A rare association in neurofibromatosis type 1

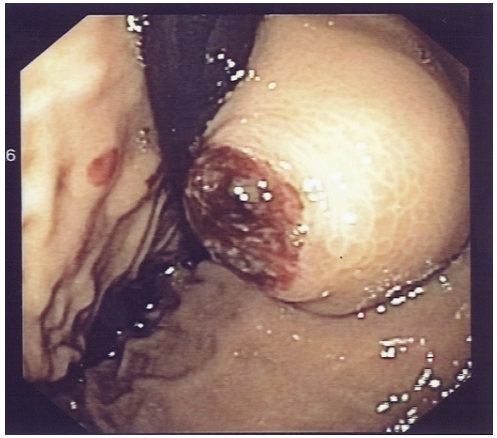
Maria Manuela Estevinho [1], João Varanda [2], Rolando Pinho [1], Fernando Viveiros [2], Susana Graça [2], Carlos Soares [2], Antónia Póvoa [2], Manuel Oliveira [2]

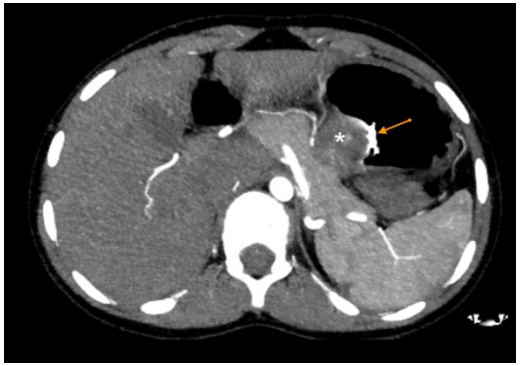
Affiliations + expand

PMID: 37732354 DOI: 10.17235/reed.2023.9927/2023

Free article

GIST





aenger Romain, 10.6.199, die Endoskopie liegt allerdings schon länger zurück (3.8.2012), die Zeit vergeht…

Imatinib

- **Settings / Indications?**
  - **Adjuvant setting: effect of imatinib**
  - **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 qd at least 1y**

      High risk GIST: better RFS / OS with therapy 3y[2)]

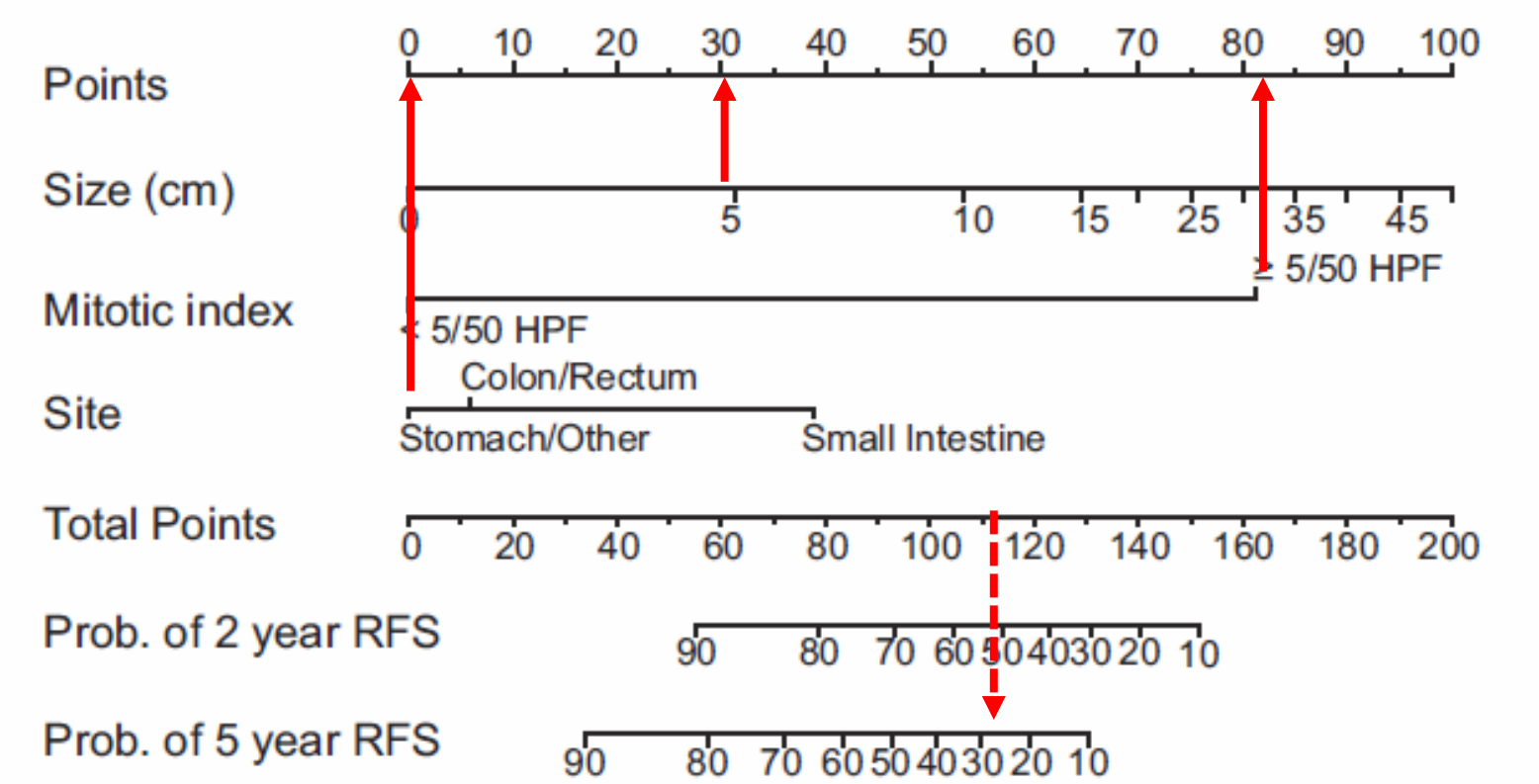
  - **Additive setting: incomplete resection (R1/2), intraoperative tumor perforation**

- **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]

Nomogram for predicting probabilities of 2- and 5-year re…)

CAVE: for KIT-positive GIST (only)



1) [Gold JS et al. Development and validation of a prognostic nomogram for recurrence-free survival after complete surgical resection of localised primary gastrointestinal stromal tumour: a retrospective analysis. Lancet Oncol 2009;10:1045]

EUS +/- biopsy – advantages:

Most accurate and reliable method to secure a diagnosis of GIST

- **Tissue sampling: any tumor ≥ 2 cm**
- **Diagnostic rate using EUS-FNB ???%**

  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 only for masses of > 1 cm
- **Helps assessing malignant potential**

- ***Diameter*** **(i.e. >3-4cm)**
- **Echogenic foci**
- ***Irregular borders***
- **Cystic spaces**
- **Lymph nodes**

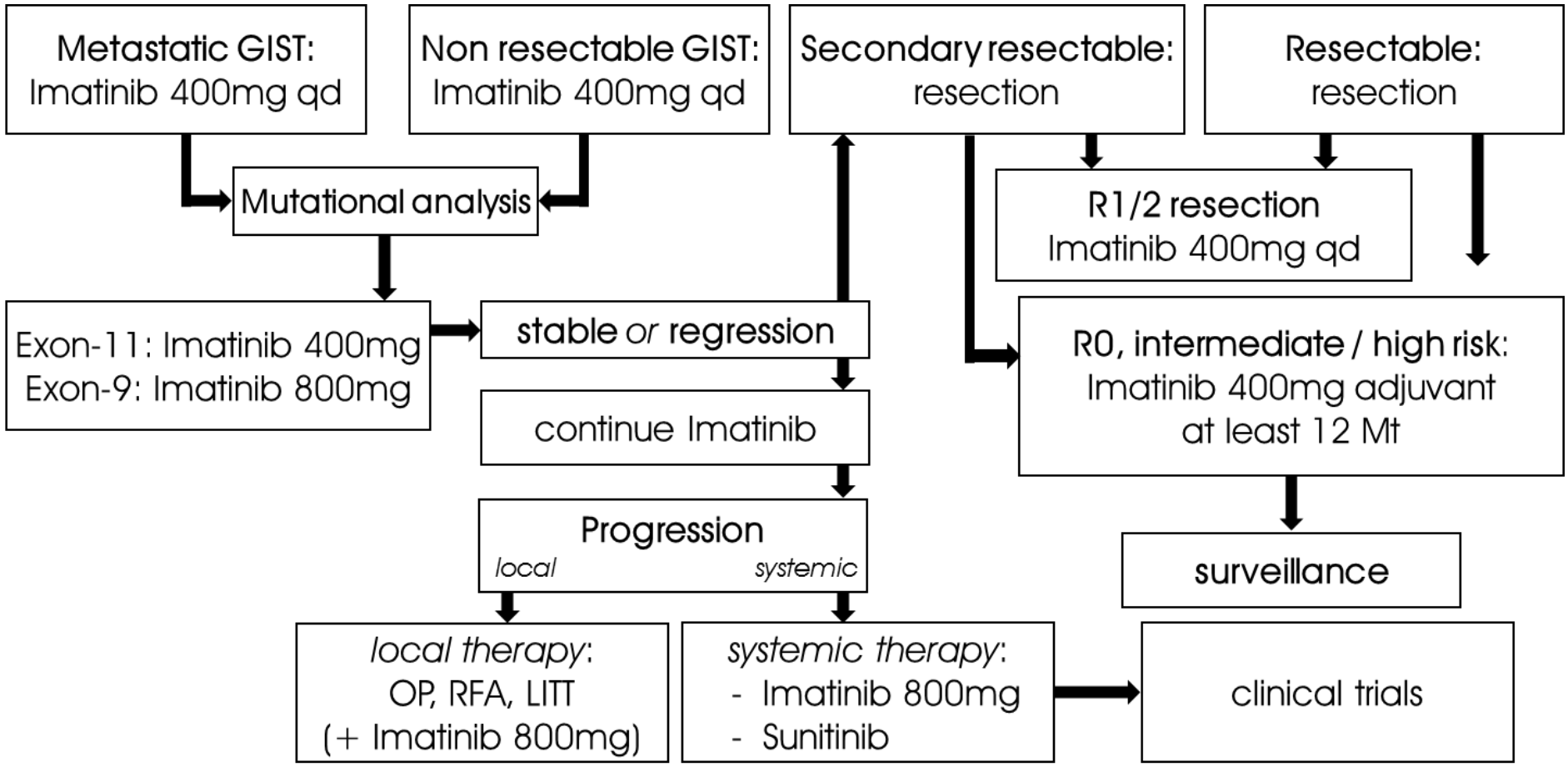
≥ 2 criteria met: sensitivity 80-95%

≥ 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]

Therapeutic algorithm



Where do most relapses occur ?

- Peritoneum
- Liver

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.

In the metastatic setting, treatment with imatinib should be continued indefinitely, until clinically relevant disease progression or intolerance, because treatment interruption is generally followed by relatively rapid tumour progression, even when lesions have been previously excised surgically [I, A].[54] The patient should be informed about the importance of complying with imatinib therapy, as well as interactions with concomitant medications and food, and the best ways to

Prognosis

- **Localized GIST: mean survival *5y 85-90% overall***

- **Incomplete Resection or metastatic GIST: 5y-survival <*35-50%***