

# Gastrointestinal stromal tumors (GIST)

Recommendations from the society for diagnosis and therapy of  
haematological and oncological diseases

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# Gastrointestinal stromal tumors (GIST)

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## Compliance rules:

- [Guideline](#)
- [Conflict of interests](#)

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## 1 Summary

Gastrointestinal stromal tumors (GIST) are of mesenchymal origin and belong to the rare malignant tumors. Men and women are affected with approximately equal frequency, and the median age of onset is 65-70 years. The most common primary sites are in the stomach and small intestine.

In resectable GIST, treatment is multimodal. For tumors with a high risk of recurrence, as determined by tumor size and mitotic rate, adjuvant therapy with imatinib is indicated.

In metastatic disease, systemic drug therapy is the treatment of choice. For imatinib-sensitive tumors, imatinib is available as first-line therapy, sunitinib as second-line therapy, and regorafenib as third-line therapy. Ripretinib, a new standard of care for fourth-line therapy, is available since 2021. Avapritinib is the therapy of choice if a *PDGFRA* mutation exon 18 D842V is detected.

The determination of the *KIT* or *PDGFRA* mutation status is an obligatory part of the initial diagnosis of GIST for which systemic treatment is indicated. Approximately 80-85% of all GIST have a mutation in the *KIT* gene, and approximately 10-15% have a mutation in the *PDGF receptor-alpha* gene (*PDGFRA*), both of which are considered to be predominantly imatinib-sensitive. Tumors with a *c-KIT/PDGFR-A* wild-type status or *PDGFRA* p.D842V mutations are considered imatinib-resistant.

## 2 Basics

### 2.1 Definition and basic information

Gastrointestinal stromal tumors (GIST) represent the most common mesenchymal tumors of the gastrointestinal tract and account for approximately 20-25% of all sarcomas. Their incidence is approximately 10-15 / 10<sup>6</sup> population and year. The median age at diagnosis is approximately 65-70 years (range: 16-94 years), and the sex distribution is almost equal.

The vast majority of GIST occur sporadically. Most frequent localizations are stomach (50-60%) and small intestine (20-30%); less frequently GIST occur in the colorectum (5-10%) and esophagus ( $\leq 1\%$ ), for Germany see also [Figure 4](#). The occurrence of extraintestinal GIST (E-GIST) is now increasingly in doubt, as more likely metastases of an undetected primary in the gastrointestinal tract are considered [1].

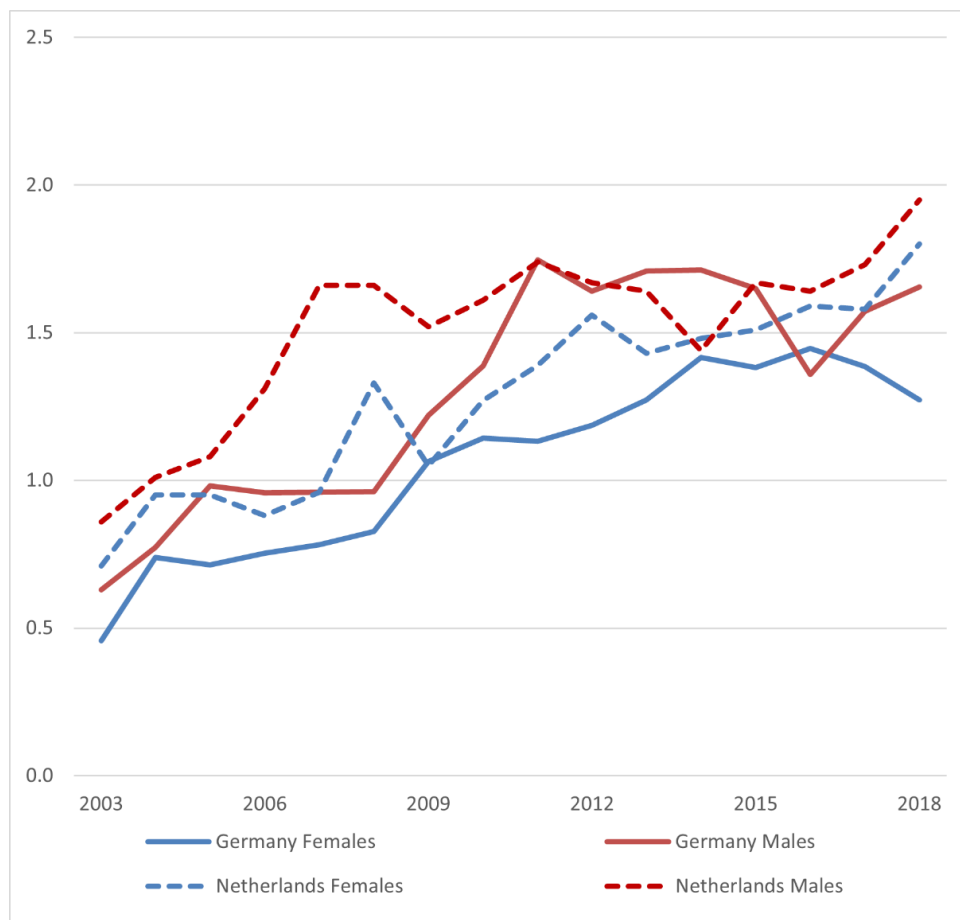
## 2.2 Epidemiology

The results presented here are based on data from population-based cancer registries in Germany. GIST were recorded using histology codes 8936/1 (gastrointestinal stromal tumor o.n.A.) and 8936/3 (gastrointestinal stromal sarcoma). Registries with a continuously high estimated completeness (>90%) for malignant tumors of the digestive organs in the studied period of 2003 to 2018 were selected. These registries cover approximately 36% of the German population. The disease rates thus determined were extrapolated to the population of Germany to estimate current nationwide case rates. Age- and sex-specific disease rates and the distribution of cases among the different localizations of the digestive tract were evaluated for the period 2016-2018. Relative survival rates, which take into account survival in the age-matched general population and can be considered a measure of disease-specific survival, were calculated using the period approach for the period 2014-2018. The epidemiology of GIST is not part of the standard evaluations of cancer registries; therefore, no area-wide figures are available for Austria and Switzerland. Results from the Dutch cancer registry were used as comparative values for incidence [54].

When assessing incidence trends and the temporal development of disease numbers, it should be noted that GIST were not recorded via histology with independent coding until the introduction of ICD-03 (from around 2003).

The age-standardized disease rates (per 100,000 persons, old European standard) more than doubled in Germany from 2003 to 2011, after which no further significant increase was observed. The course and level of the disease rates are largely consistent with the results from the Netherlands (Figure 1). The progression suggests that the initial increase in incidence is due to improvements in documentation and coding rather than an actual increase in the risk of disease.

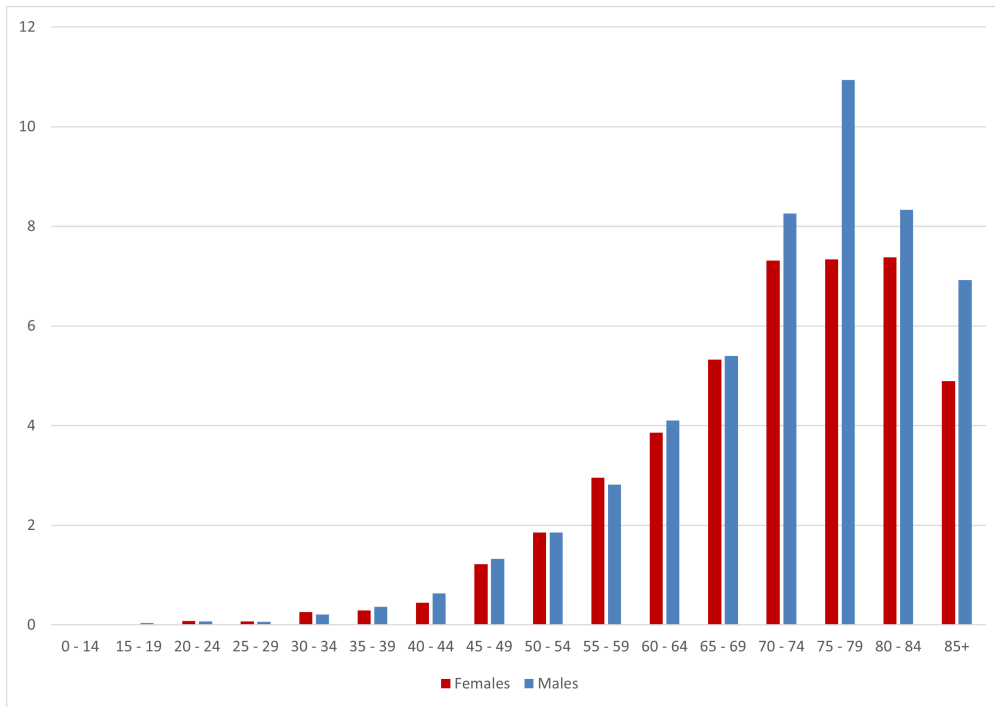
**Figure 1: Estimated age-standardized incidence rates of GIST in Germany and the Netherlands, 2003-2018 (per 100,000 persons, old European standard)**



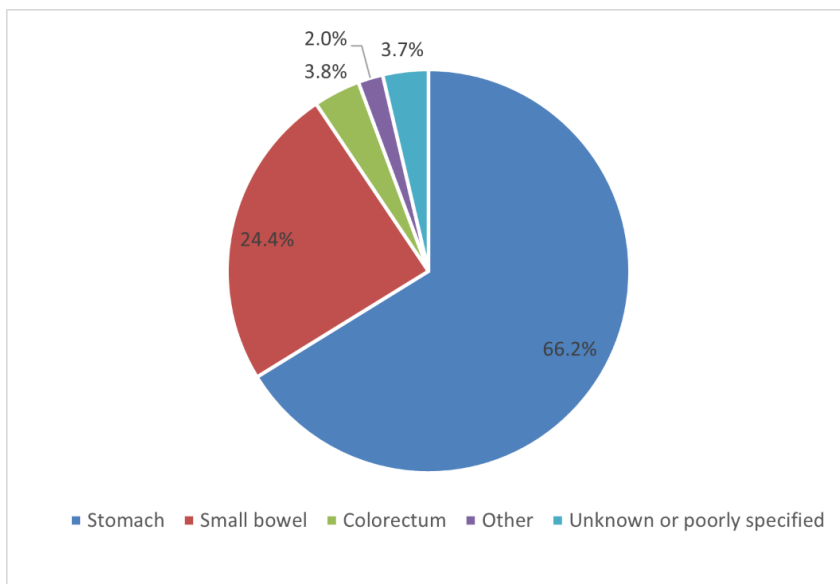
The mean (median) age of onset in Germany is currently 71 years for women and 70 years for men; only 8% of those affected are younger than 50 years at diagnosis. The age-specific incidence rates increase continuously with age in both sexes until the 8th decade of life and then decline again gradually (Figure 2). Men have a slightly higher risk of disease than women of the same age, which is compensated by the higher proportion of women in the older age groups: extrapolated, 970 women and 949 men were diagnosed with GIST per year in Germany in recent years. About two-thirds of cases involve the stomach, about one-quarter the small intestine, and just under 4% the colon or rectum (Figure 3). Differences in the distribution of localization between the sexes are not observed.

The 5-year relative survival rate for 2014-2018 is 82.7% (95% confidence interval: 79.5%-85.9%) for women (83.9%), slightly higher than for men (81.3%). For GIST of the stomach, the rate is higher at 87% compared with small bowel (81%), colorectum (75%), or other sites (57%) (Figure 4). For the Dutch Cancer Registry, an overall 5-year relative survival of 81% is currently reported for GIST [53, 54].

**Figure 2: Annual rates of GIST disease by age and sex (2016-2018, per 100,000 persons)**

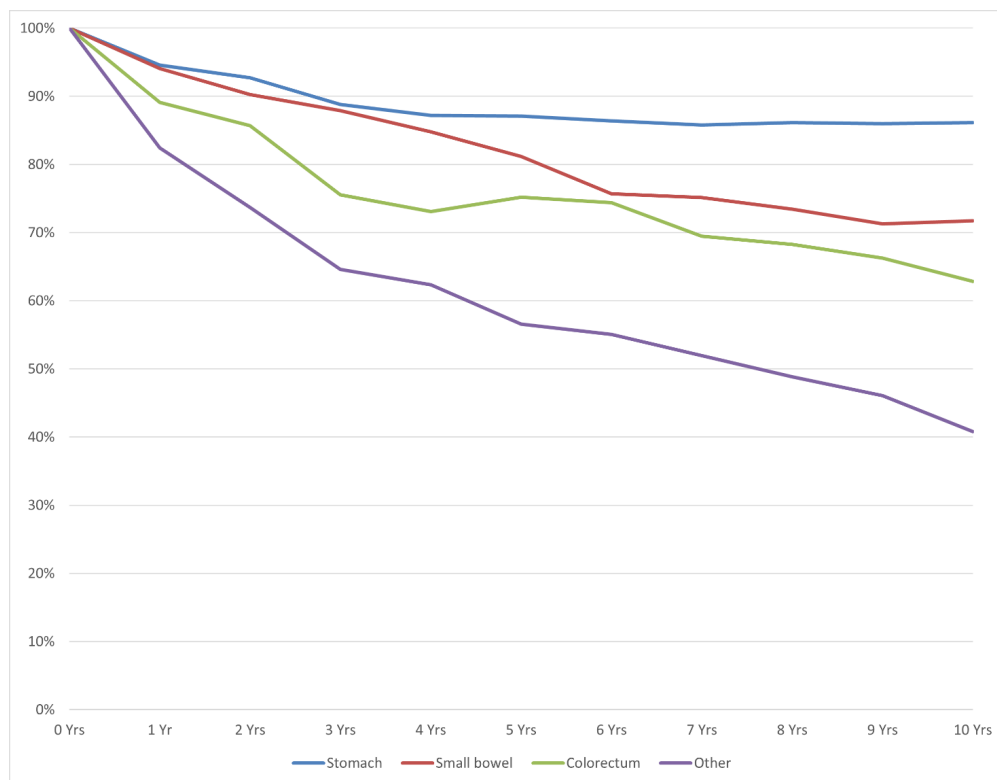


**Figure 3: Relative frequency of GIST locations (2016-2018)**





**Figure 4: Relative survival with GIST up to 10 years after diagnosis, by site (2014-2018)**



## 2.3 Pathogenesis

The histogenetic origin of GIST is considered to be the interstitial cells of *Cajal* (ICC) or corresponding progenitor cells. ICC are involved as "pacemaker cells" in the control of gastric/intestinal motility and express *KIT* (CD117) protein. Macroscopically, larger GIST in particular may show cystic areas and hemorrhage. Histopathologically, GIST usually present as spindle cell (60-70%), epithelioid (20-30%) or mixed tumors. The leading immunohistochemical feature of GIST is the expression of *KIT* [CD117] and *DOG-1*, which can be detected in approximately 95% of all GIST. *DOG-1* is also mostly expressed in *KIT*-negative GIST [1, 9].

A mutation of the *KIT* gene is found in about 80-85% of all GIST. The exon 11 coding for the transmembrane domain (approx. 70%) and the exon 9 coding for the extracellular domain (approx. 10-15%) are most frequently affected. The kinase I (exon 13) or the activation domain (exon 17) are rarely affected by primary mutations, with approximately 1% each [10]. In addition, an activating, imatinib-sensitive mutation in *KIT* exon 8 (p.D419del) occurs very rarely (<1%) and was first described as a germline mutation in a family with GIST and mastocytosis [11], but may also occur sporadically.

In approximately 10-15% of all GIST, a mutation is found in the *PDGF receptor alpha* gene (*PDGFRA*), either in exon 12 encoding the juxtamembrane domain, exon 14 encoding the tyrosine kinase 1 domain, or exon 18 encoding the activation domain.

In the remaining approximately 10% of all GIST, no mutation of the *KIT* or *PDGFRA* gene can be detected, which is why these tumors have been simplistically referred to as "wild-type GIST" [10]. However, the term "wild-type GIST" is increasingly criticized because other rare mutations have now been found, for example, in *BRAF* [12], *NF1*, the *succinate dehydrogenase (SDH)* genes, and the *RAS* genes, which represent alternative pathomechanisms. The term "quadruple-negative (q-wt) GIST" (non-*KIT*, non-*PDGFRA*, non-*RAS*, non-*SDH*) describes the phenomenon that none of the known activating mutations can be detected.

A hereditary predisposition is observed only very rarely. These are either familial GIST with corresponding germline mutation of the *KIT* or *PDGFRA* gene, GIST in the context of *Carney-Stratakis* syndrome (with *SDH* mutations), or GIST associated with neurofibromatosis type-1 (NF-1; von Recklinghausen disease) (see [Table 1](#)) [13].

GIST occur very rarely in children/adolescents (1-2%); mostly girls are affected. In these pediatric GIST, which usually occur multifocally, mutations of the *KIT* or *PDGFRA* gene are found only exceptionally; *IGF-1* receptor amplification/overexpression can often be detected.

## 2.4 Risk factors

Risk factors for the development of GIST are not known to date.

## 3 Prevention and early detection

There is no evidence of effective measures for prevention or early detection of GIST in terms of a screening program.

## 4 Clinical image

### 4.1 Symptoms

Most frequent localizations of sporadic GIST are stomach (50-60%) and small intestine (20-30%); rarer localizations are rectum (5-10%), esophagus ( $\leq 1\%$ ) and mesentery/omentum (2-5%). The occurrence of extra-gastrointestinal GIST (E-GIST) has also been described but is now increasingly in doubt; metastases from an undetected primary to the gastrointestinal tract are considered more likely [8, 14].

Sporadic GIST almost always manifest as solitary tumors, whereas GIST in the context of rare familial genesis and NF-1 usually present as multifocal tumors in the stomach (q-wt, *SDH* deficiency) or small intestine (NF-1). In addition, sporadic GIST rarely occur at multiple sites synchronously or metachronously [15].

The clinical symptoms leading to the diagnosis are usually nonspecific (e.g., feeling of fullness, abdominal discomfort, increase in abdominal circumference). In up to 30% of patients, GIST is diagnosed incidentally during endoscopic examinations or surgery for other indications. 10% of patients are diagnosed as emergencies (6.4% small bowel mostly as obstruction, 3.2% stomach/duodenum as gastrointestinal bleeding [55]).

At diagnosis, metastasis is detectable in 20-50% of patients. The liver and peritoneum/omentum are most commonly involved. Extra-abdominal metastases are rare at  $<10\%$  but are found in advanced, refractory GIST in up to 20-25%. Lymph node metastases, with the exception of syndromal GIST, are so rare, as in the majority of other sarcomas, that they are usually of no clinical and thus surgical significance [1].

### 4.2 Incidental findings

In up to 25% of affected patients, the diagnosis of GIST is made incidentally during the increasing use of imaging such as endoscopy or during surgery for other reasons [1].

To be differentiated from these are the so-called micro-GISTs (GISTs with a diameter of less than 1 cm), which are also frequently found incidentally. Data from Japanese and German studies indicate that these occur primarily in the gastroesophageal junction and proximal stomach, and

are seen much less frequently elsewhere in the gastrointestinal tract. These lesions typically have no or very few mitoses and are therefore usually not clinically relevant [16, 17].

## 5 Diagnosis

### 5.1 Diagnostic criteria

**Table 1: Characteristics of sporadic and hereditary GIST\***

Syndrome	Sporadic GIST	Familial GIST	Carney's Triad	Carney-Stratakis syndrome	NF-1
Median age	~ 60 years	~ 40-50 years	< 35 years	< 25 years	~ 50 years
Sex predilection	none	none	w > m	none	none
Associated symptoms	none	hyperpigmentation, urticaria pigmentosa, mastocytosis, dysphagia	Paragangliomas pulmonary chondromas	Paragangliomas	Neurofibroma café-au-lait spots
Mutations	no germline mutation	<i>KIT/PDGFR</i> A	<i>SDHC</i> Hypermethylation	<i>SDHA SDHB SDHC SDHD</i>	NF-1 neurofibromin
Heredity	-	autosomal dominant	-	autosomal dominant	autosomal dominant
Histology	spindle cell > epithelioid > mixed cell	see sporadic GIST	epithelioid, multinodular	see sporadic GIST	spindle cell
Positive lymph node status	rare	rare	frequent	frequent	rare
ICC Hyperplasia	none	Mostly present	none	none	Mostly present
Localization	Stomach, small intestine, rectum, mesentery, other	Small intestine, stomach, rarely rectum	Stomach	Stomach	Small intestine
Clinical behavior	depending on size, mitosis number and localization	see sporadic GIST	Metastasis often already at diagnosis	unclear	Mostly indolent
Response to imatinib	depending on mutation type	depending on mutation type	unclear	poor	unclear

Legend:

\*according to [13]

### 5.2 Diagnostics

In addition to endoscopic or endosonographic diagnostics, computed tomography (CT) is of greatest importance for the diagnosis of spread, restaging/post-treatment control and follow-up. Positron emission tomography (PET) imaging may be helpful in individual cases to assess early response to drug therapy or to differentiate between benign and malignant changes [1, 9]. Response to therapy by CT can be determined according to the so-called Choi criteria. A size reduction of >10% and/or a density reduction (HU) of  $\geq 15\%$  are considered as response to therapy [18].

If necessary, biopsy can be performed by endoscopy or endosonography if this is technically feasible without risking intraabdominal dissemination of tumor cells [19]. GIST are usually fragile and highly vascularized tumors that originate from the muscularis propria and are therefore often difficult to access endoscopically. Evaluation of the SSG-AIO-XVIII study showed that transabdominal biopsy did not result in a worsened prognosis [20]. Percutaneous tumor biopsy

should be considered especially when other tumors, e.g., lymphoma, are considered for differential diagnosis or when neoadjuvant therapy is indicated due to tumor size or spread [21].

Molecular genetic testing to determine *KIT* or *PDGFRA* mutation status is now an obligatory part of initial diagnosis in GIST for which drug therapy is indicated [22].

An overview of the diagnostic procedures is given in Table 2.

**Table 2: Diagnostics and staging in GIST**

Diagnostic procedure	Note
Physical examination	
Laboratory (blood)	To assess organ functions (blood count, liver and kidney function parameters, coagulation, TSH).
Endoscopy, endosonography	Diagnostic for clarification of the spread pattern and histological confirmation
CT thorax, abdomen, pelvis with contrast medium	Survey of intra/extra-abdominal tumor manifestations. Before planned resection to vascular imaging
PET-CT	In individual cases for confirming the diagnosis and staging
Histology	For inoperable tumors prior to initiation of therapy. In operable, in unclear findings, cave intraabdominal tumor dissemination.
Molecular genetics	<i>KIT</i> / <i>PDGFRA</i> mutation status at initial diagnosis, in the course of disease in case of treatment failure

### 5.3 Classification

The current TNM classification [21] divides GIST localizations into the following anatomic districts and subdistricts (ICD 10):

- Esophagus (C15)
- Stomach (C16)
- Small intestine (C17)
  - Duodenum (C17.0)
  - Jejunum (C17.1)
  - Ileum (C17.2)
- Colon (C18)
- Rectum (C20)
- Omentum (C48.1)
- Mesentery (C48.1)

The regional lymph nodes correspond to the respective localization of the primary tumor but, as mentioned above, do not play a biological role in most GIST.

Grading is based on the mitotic count:

- Low mitotic count: 5 or less per 5 mm<sup>2</sup>.
- High mitosis number: over 5 per 5 mm<sup>2</sup>

### 5.3.2 Stages and staging

Classification of the extent of the primary tumor and metastasis is based on the UICC/AJCC TNM criteria. Since January 1, 2017, the 8th edition has been used in Europe [23]. The TNM criteria are summarized in Table 3, and the staging is summarized in Table 4 and Table 5.

**Table 3: TNM classification - GIST [21]**

Classification	Tumor
<b>T</b>	<b>Primary tumor</b>
<b>T1</b>	Tumor ≤ 2 cm in largest extension
<b>T2</b>	Tumor 2-5 cm in largest extension
<b>T3</b>	Tumor > 5 cm but ≤ 10 cm in largest extension
<b>T4</b>	Tumor > 10 cm in largest extension
<b>N</b>	<b>Regional lymph nodes</b>
<b>Nx</b>	Regional lymph nodes cannot be assessed
<b>N0</b>	No regional lymph node metastases
<b>N1</b>	Regional lymph node metastases
<b>M</b>	<b>Distant metastases</b>
<b>M0</b>	No distant metastases
<b>M1</b>	Distant metastases

Regional lymph nodes are rare in GIST. Cases in which lymph node status is not determined clinically or pathologically may be classified as N0 rather than Nx or pNX. However, the usefulness of such a classification is questionable.

**Table 4: clinical staging according to UICC: GIST of the stomach [21]**

Stage	T	N	M	Mitotic rate
Ia	T1, T2	N0	M0	low
Ib	T3	N0	M0	low
II	T1, T2	N0	M0	high
	T4	N0	M0	low
IIIa	T3	N0	M0	high
IIIb	T4	N0	M0	high
IV	Each T	N1	M0	any
	Each T	Any N	M1	any

The criteria for the stages of gastric GIST can be applied to primary solitary GIST of the omentum, although there is no established evidence for this.

**Table 5: clinical staging according to UICC: GIST of the small intestine [21]**

Stage	T	N	M	Mitotic rate
I	T1, T2	N0	M0	low
II	T3	N0	M0	low
IIIa	T1	N0	M0	high
	T4	N0	M0	low
IIIb	T2, T3, T4	N0	M0	high
IV	Each T	N1	M0	any
	Each T	Any N	M1	any

The criteria for the stages of small bowel GIST can be applied to GIST in rarer locations such as the esophagus, colon, rectum, and mesentery.

## 5.4 Prognostic factors

Clinically significant prognostic factors include mitotic rate, tumor size, and primary tumor location. To estimate the probability of metastasis, different risk categories are distinguished, which are summarized in Table 6. Here, however, it is not possible to completely exclude the risk of metastasis on the basis of the prognostic parameters mentioned. The 5-year overall survival rate of patients with surgically resected primary tumor in the era before the introduction of imatinib has been about 50%, and in patients with tumor size > 10 cm it was 20-35%. The median survival of patients with metastatic disease is currently approximately 60 months, and the 5-year survival rate is approximately 45%.

It remains problematic that in the previous risk classifications the number of mitoses is applied dichotomized, (e.g., < or  $\geq$  5 mitoses), which does not completely represent the biological reality. Joensuu's classification uses so-called contour maps, where tumor size and mitotic count are applied as continuous variables [24]. This classification is nowadays considered to be the closest to clinical needs, however, the classification of Miettinen and Lasota from 2006 is still more commonly used [25]. There is general agreement that mitoses are counted in 5 mm<sup>2</sup> instead of 50 HPF (which currently corresponds to about 18 to 20 HPF on modern microscopes) [22].

*KIT* genotype represents both a prognostic and a predictive parameter. Thus, patients with a *KIT* exon 11 deletion have a higher risk of recurrence than those with exon 11 insertion or point mutation, *PDGFRA* mutation or wild type [26]. The prognostic relevance of *KIT* exon 9 mutations is controversial because they occur almost exclusively outside the stomach and the biology of intestinal GIST is mostly more aggressive than that of gastric GIST.

Patients who experience intraperitoneal tumor hemorrhage, rupture, or injury almost always develop peritoneal metastases [27].

**Table 6: Risk classification of primary GIST based on mitotic count, tumor size, and anatomic location (Armed Forces Institute of Pathology (AFIP)) [25]**

Mitosis number	Size (cm)	Risk of progression/recurrence							
		Stomach	%	Duodenum	%	Small intestine	%	Rectum	%
≤ 5 per 5 mm <sup>2*</sup>	≤ 2	no risk	0	no risk	0	no risk	0	no risk	0
	>2 ≤ 5	very low		low		low		low	
	> 5 ≤ 10	low		high	34	moderate	24	high	57
	> 10	moderate	12	high	high	52	high		
> 5 per 5 mm <sup>2*</sup>	≤ 2	no risk**	0**	N/A (high)	n.a.	high	50	high	54
	>2 ≤ 5	moderate	16	high	50	high	73	high	52
	> 5 ≤ 10	high	55	high	86	high	85	high	71
	> 10	high	86	high		high	90	high	

*Legend:*

*HPF = High Power Field (field of view at 400x magnification in the microscope; n.d.: not specified due to sparse data; \*the currently common counting of mitoses is in "5 mm" (corresponds to about 18-20 HPF depending on the microscope), in the original publication it was 50 HPF with, however, much older microscopes with smaller fields of view, which is why the area measure applies today; \*\*very small numbers of cases.*

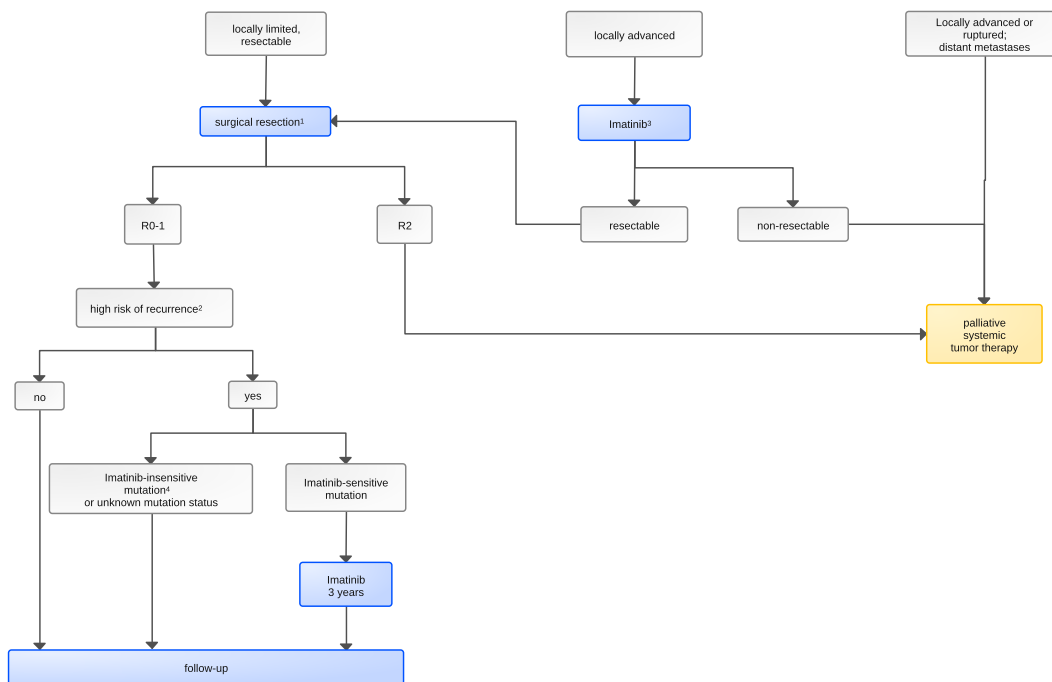
## 6 Therapy

### 6.1 Treatment structure

An optimal treatment strategy for gastrointestinal stromal tumors requires the cooperation of the different specialties already at diagnosis. It has two goals: locoregional tumor control and prevention/therapy of distant metastasis. The treatment strategy is determined by tumor stage, prognostic factors such as histology, mitotic rate, size and location, and patient-specific factors.

The treatment algorithm is shown in [Figure 5](#).

**Figure 5: Treatment algorithm for GIST**



Legend:

■ curative intention, ■ non-curative intention

<sup>1</sup> gastric GIST < 2 cm: consider „watch & wait“

<sup>2</sup> see Table 4

<sup>3</sup> for imatinib-sensitive mutations; in case of PDGFRA D842V-mutation consider neoadjuvant avapritinib therapy (see chapter 6.2.4.1)

<sup>4</sup> c-KIT/PDGFR-A wildtype, PDGFRA D842V-mutation

## 6.2 Treatment modalities

### 6.2.1 Therapy-free monitoring („watch & wait“)

Small GIST of the stomach (< 2 cm) are - after resection - associated with a very low recurrence rate, so that in individual cases (e.g., age, comorbidities, perioperative risks), after discussion with the patient, they can initially also be progress-controlled, provided that the size does not exceed 2 cm and no significant tumor growth is detected during endoscopic/endosonographic controls (initially 3-6 monthly). Small GIST of other locations (especially rectal) have a significantly higher risk of progression/metastasis and should be treated surgically as a rule.

### 6.2.2 Surgical treatment

#### 6.2.2.1 Primary tumor surgery

If the primary tumor appears initially resectable, primary resection is indicated. In gastric GIST, this is usually performed as a wedge resection, if technically possible with a safety margin of 1-2 cm. If necessary, a segmental resection (small/ large bowel) or an 'en bloc' resection is performed. For esophageal GIST smaller than 3 cm, enucleation may also be sufficient to perform a low-morbidity tumor removal [56]. Lymphadenectomy is not regularly required due to the rarity of lymph node metastases. If primary R0 resection does not appear possible or requires mutilating surgery, preoperative (neoadjuvant) therapy with imatinib is indicated (see chapter 6.2.4.1) [19, 21, 56].



### 6.2.2.2 Surgery of metastases

Data from prospective studies on surgical resection of metastases are not available. Some, but not all, retrospective analyses showed a more favorable prognosis of patients who underwent secondary resection, usually after imatinib pretreatment with treatment response. However, it is unclear to date whether the more favorable survival data of operated patients are due to surgical resection or to patient selection. Unfortunately, a prospective study set up to clarify this question had to be discontinued due to poor recruitment [28].

If complete tumor/metastasis resection seems possible and is considered, it should be performed in the phase of therapy response (partial remission or stable disease). Even limited tumor progression under ongoing drug therapy worsens the prognosis; in the case of generalized progression, surgery is not indicated due to the unfavorable prognosis except to control complications. Continuation of drug therapy is mandatory even in case of complete removal of metastases [29].

### 6.2.2.3 Secondary tumor/metastasis resections after imatinib induction chemotherapy

To date, there are no prospective, randomized studies demonstrating that resection of residual unilocular or oligotopic tumor manifestations after imatinib induction therapy is of prognostic benefit. However, retrospective analyses from various institutions suggest that secondary resections are associated with a better prognosis when performed in patients with tumor response (tumor shrinkage or arrest), possibly still in focal progression, and R0 resection can be achieved [30, 31, 32]. In multifocal progression and/or anticipatory R2 resection, elective tumor resection is usually not indicated.

### 6.2.3 Radiotherapy

There are no conclusive data on radiotherapy of GIST. Possible indications for palliative radiotherapy are (rare) bone metastases or irresectable tumors of unfavorable localization (e.g., rectum, esophagus) with refractoriness to drug therapy.

### 6.2.4 Systemic drug treatment

#### 6.2.4.1 Neoadjuvant therapy (with imatinib)

If complete tumor resection is not or only questionably possible due to primary tumor size or location, or mutilating surgery appears necessary, preoperative/neoadjuvant therapy with imatinib for achieving tumor shrinkage should be evaluated. For GIST of the stomach, a rate of partial response to imatinib of 75%, a reduction in median tumor diameter of nearly 50%, and an R0 resection rate of 94% can be expected. In a quarter of patients, the residual tumor can also be resected laparoscopically, if necessary, and gastric continuity can be preserved in 96% of patients [57]. Knowledge of the *KIT/PDGFR*A genotype as a predictive factor for treatment response to imatinib is determining treatment in these cases, which is why mutation analysis should definitely be performed. In the case of a *PDGFRA-D842V* mutation associated with imatinib resistance, neoadjuvant therapy with avapritinib can be considered according to the current ESMO guidelines [22]. In contrast, if a *KIT wild-type* tumor is present, neoadjuvant therapy with imatinib is not an option, as no tumor shrinkage can be expected in this case.

Resectability is evaluated at 3-4 monthly intervals during ongoing imatinib therapy. When maximum response is achieved, tumor resection (see above) is followed (usually within 6-12 months).

#### **6.2.4.2 Adjuvant therapy (with imatinib)**

The value of adjuvant therapy with imatinib was investigated in three randomized trials. First results were obtained in a double-blind, placebo-controlled American phase III study (ACOSOG Z9001) with 713 patients. Patients with a completely excised *KIT*-positive GIST of at least 3 cm in size were eligible for inclusion, and mitotic count was not considered. The duration of therapy was 1 year. Initial results showed a significant improvement in recurrence-free survival (RFS) with imatinib treatment for 1 year compared with placebo (98% vs. 83%,  $p < 0.0001$ ). The study was stopped early due to its unequivocal outcome. Retrospectively, it was shown that high-risk patients in particular benefited: at 2-year follow-up, relapse-free survival was 77% vs. 41% for high-risk ( $p < 0.0001$ ), 98% vs. 76% for intermediate-risk ( $p = 0.05$ ), and 98% for low-risk with imatinib and placebo, respectively ( $p = 0.92$ ). Based on these data, the U.S. authorities approved imatinib for adjuvant treatment for 1 year in December 2008 [33].

Approval for adjuvant therapy with imatinib in Europe by the EMA was granted in April 2009. In contrast to the U.S. label, which does not specify which patients should be treated, the EMA specifies approval for patients "at significant risk of relapse." Patients with a low risk of relapse should not receive adjuvant imatinib treatment.

In the Scandinavian-German study SSGXVIII, a total of 400 patients at high risk of relapse were studied. A treatment duration of 1 year was compared with a duration of 3 years. Results showed a significant improvement in relapse-free survival and overall survival with 36 months of treatment compared to 12 months. In 2020, published data on the 10-year follow-up of the study showed an overall survival in the intention-to-treat population of 65% at 10 years for the group receiving 1 year of therapy and 79% with 3 years of therapy [34]. Based on these results, 3 years of therapy is internationally considered the gold standard for adjuvant therapy in patients at high risk of recurrence.

The third randomized trial is a phase III EORTC intergroup study with 900 patients. Randomization was to a treatment arm with imatinib 400 mg/day for 2 years vs. an observation arm. Patients at intermediate and high risk of relapse according to consensus criteria were included. The primary endpoint was "imatinib failure-free survival," i.e., time to progression with new imatinib treatment after relapse occurred despite or without adjuvant therapy. Here, there was a trend for the group at high risk of relapse, but it did not reach significance. For the secondary endpoint "relapse-free survival", however, the difference was highly significant ( $p < 0.0001$ ) [35].

The question of the optimal duration of treatment has not been conclusively resolved. The currently ongoing SSG XXII trial is investigating in high-risk patients whether two additional years of therapy after 3 years of treatment will result in an advantage over no further therapy. Recruitment has just been completed.

Mutation analysis with regard to a *KIT* or *PDGFRA* mutation is an essential component of the therapy decision in the adjuvant situation. On the one hand, the mutation status represents a prognostic factor, on the other hand, not all mutations respond to imatinib. Therefore, the mutation status must be determined in an experienced laboratory before starting adjuvant therapy.

The best dosage of imatinib in adjuvant in patients with a *KIT* exon 9 mutation remains unresolved. Considering that a higher dosage of 800 mg/day approximately triples the response rate and progression-free survival compared with a dosage of 400 mg/day in patients with

metastatic GIST, this would also argue for a higher imatinib dose in the adjuvant setting. According to many experts, patients with an exon 9 mutation benefit from higher dosing, but this has not yet been investigated in randomized trials.

Patients with a D842V mutation in exon 18 of *PDGFRA* should generally not be treated adjuvantly, regardless of the risk of relapse. This genotype does not respond to imatinib either in vitro or in vivo and is also characterized by a mostly rather indolent course. Patients with other mutations in *PDGFRA* receive adjuvant therapy according to their risk of relapse.

Wild-type GIST is a heterogeneous subgroup without evidence of an activating mutation in *KIT* or *PDGFRA*. In the SSGXVIII trial, with a small number of cases, none of the treatment arms proved superior. If *SDH* deficiency or an association with neurofibromatosis type 1 is detected, imatinib is not expected to have a beneficial effect. In patients with "wild-type GIST" who do not fall into the typical age group, a complementary reference pathology examination should always be performed to exclude technical errors in molecular pathology.

#### **6.2.4.3 Additive imatinib therapy after metastasectomy.**

After metastasectomy, tumor progression/recurrence can be expected within a few months in the majority of patients, unless surgery is followed by systemic drug treatment. Therefore, according to current knowledge, imatinib therapy should also be given after metastasectomy. This also applies to patients who received preoperative imatinib therapy and did not show (oligotopic/generalized) tumor progression thereunder. The optimal duration of this therapy is not known. Typically, imatinib therapy is continued until progression is demonstrated.

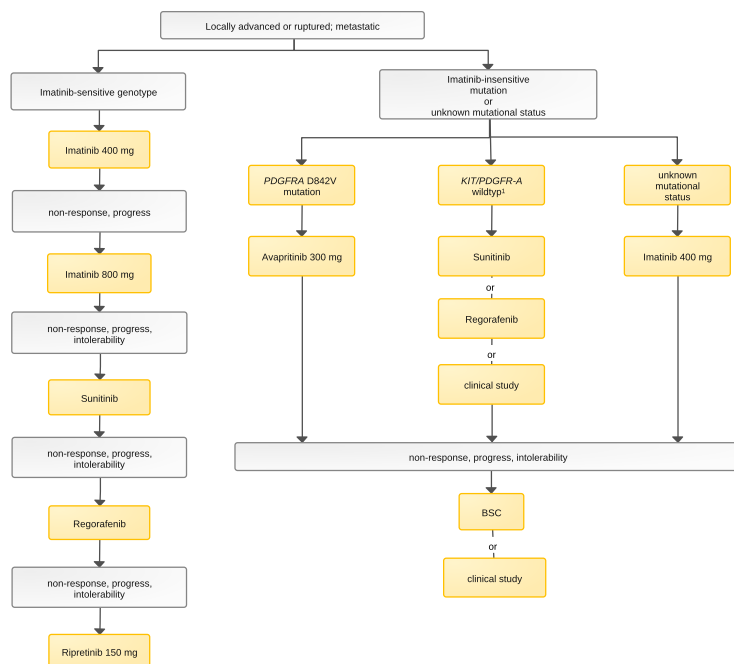
#### **6.2.4.4 Pre- or intraoperatively ruptured GIST**

A special situation results from pre- or intraoperative rupture of the GIST. Here, the „universal definition“ of 2019 [70] should be applied. After (true) rupture, a very high recurrence rate must be expected [27], irrespective of adjuvant therapy with imatinib for 3 years [71, 72, 73]. Therefore, international guidelines recommend to treat a ruptured GIST in analogy to a metastatic GIST for an unlimited time period [22, 74].

#### **6.2.4.5 Metastatic GIST**

Systemic drug treatment is the first-line treatment for advanced GIST, see [Figure 6](#).

**Figure 6: Systemic drug treatment for GIST**



**Legend:**

non-curative intention;

<sup>1</sup> look for other molecular alterations: *BRAF*, *KRAS*, *NRAS*, *SDH*, *NF1* (see text); in case of *SDH*-deficiency consider regorafenib

**6.2.4.5.1 First-line therapy with imatinib**

Initial therapy with the tyrosine kinase inhibitor imatinib is the therapy of choice for patients with metastatic GIST [36, 37, 38]. In the first large trials of imatinib, a median overall survival of approximately 52 months was reported for patients with metastatic/irresectable GIST. Depending on the genotype, median survival times of 66 months were observed for tumors with *KIT* exon 11 mutation, 38 months for those with *KIT* exon 9 mutation, and 40 months for tumors with *KIT/PDGFR-A wild-type*. The 10-year survival rates are reported as around 20%. Median progression-free survival in the SWOG S0033 trial was 25 months for GIST with *KIT* exon 11 mutation, 17 months for those with *KIT* exon 9 mutation, and 13 months for imatinib-treated patients with *KIT/PDGFR-A wild-type* GIST [39].

The rate of objective remissions (according to RECIST) achievable with imatinib is approximately 50-60% and the rate of prognostically equivalent tumor stabilizations is approximately 30%. For patients with *KIT* exon 11 aberrations, the response rate with imatinib dosing at 400 mg/day is approximately 70-90%. An initial higher imatinib dose does not result in significantly higher response rates or improvement in progression-free survival in this patient group. In contrast, the response rate in patients with *KIT* exon 9 mutation at 400 mg imatinib/day is only about 20% versus 50-65% at a dose of 800 mg/day. Progression-free survival is also improved in patients with *KIT* exon 9 mutation by a higher imatinib dose (400 mg: 6 months; 800 mg: 19 months; p=0.017); for overall survival, a risk reduction of 31% for higher-dose imatinib was found, probably not significant due to crossover.

The treatment response of patients with *KIT/PDGFR-A wild-type* has been assessed very divergently in older studies. In the B222 phase II trial, the PR rate was 0% and the SD rate was 33% [40]. In the 'North American Intergroup' study of imatinib, a PR rate of 33% and an SD rate of 28% were reported [41]. Majority of the group of patients with *KIT/PDGFR-A wild-type* GIST are likely to be those with *SDH*-deficient GIST, and less frequently *NF1*- or *BRAF*-mutated tumors.

Objective response to imatinib is expected in only 2-8% in SDH-deficient GIST [39], but is likely to be somewhat more favorable for sunitinib and regorafenib.

The recommended dosages are summarized in Table 7.

**Table 7: Imatinib dosing in first-line metastatic GIST according to primary KIT/PDGFR A genotype**

Genotype / Genotypic aberrations at initial therapy	Imatinib dose per day
<i>KIT</i> exon 11, 13, 17	400 mg
<i>KIT</i> / <i>PDGFRA</i> wild type*	400 mg
<i>KIT</i> exon 9	800 mg
<i>PDGFRA</i> exon 12, 14	400 mg
<i>PDGFRA</i> exon 18 (D842V) mutation	Imatinib-resistant

Legend:

\*mostly SDH-deficient GIST with very low response rate to imatinib (2-8%).

#### 6.2.4.5.2 Duration of therapy with imatinib

The results of the French BFR14 trial [42] showed that discontinuation of imatinib therapy leads to progression after a relatively short interval even after several years of treatment in patients with advanced stable GIST, including those with complete response (CR) or no evidence of disease. After 3 years of therapy, 2-year PFS rates were 16% after discontinuation of imatinib and 80% for continued therapy, respectively. Even after 5 years, the progression/recurrence rate was still 45% after discontinuation of imatinib. Of the patients with CR and partial response, respectively, at the time of imatinib discontinuation, only 41% and 56% achieved CR and PR, respectively, again as the best treatment response after restarting imatinib. Accordingly, therapy should not be interrupted or stopped for a prolonged period of time, if possible, even after several years of treatment.

#### 6.2.4.5.3 Imatinib resistance

Primary imatinib resistance is seen in approximately 10% of GIST patients [43]. This is defined by tumor progression in the first 3-6 months of therapy. At this point, at the latest, the expertise of a sarcoma/GIST center should be consulted to verify the histopathological diagnosis and to exclude possible therapy-associated pseudoprogression.

Primary resistance to imatinib is found in *PDGFRA* mutations (D842V, D1842-843IM, R841-842KI), in most primary exon 17 mutations, and in rare genotypes with KIT/*PDGFRA*-independent oncogenic mechanisms (BRAF mutations, NF1, SDH deficiency) [58]. Early progression is also seen, particularly in patients with primary exon 9 mutation, under a standard dose of 400 mg [59]. Patients who have a primary *KIT* exon 11 mutation are generally always considered to be imatinib-sensitive, and early progressions almost always have pharmacokinetic causes (interactions, absorption, compliance).

In about 40-50% of patients, tumor progression, i.e., secondary imatinib resistance, is observed after an average of 2 years. In about half of the cases, this initially manifests itself in the form of newly appearing, hyperdense "nodules" within existing, mostly hypodense metastases ("nodule in a mass"). Further progression according to conventional criteria is then subsequently observed usually after about 5 months. Secondary mutations are detectable in about 50-80% of cases, mostly affecting the ATP-binding domain (exon 13/14) or the kinase domain (exon

17/18). Secondary *KIT* mutations are mostly found in tumors with primary exon 11 mutation, less frequently in primary exon 9 mutation. Different secondary mutations in different metastases are typical, and about one-third of cases show two different secondary mutations within one metastasis. Other mechanisms of imatinib resistance include *KIT* amplifications, loss of the wild-type allele, or mutations leading to *KIT*-independent constitutive activation of downstream signal transduction pathways (e.g., aberrations of *PI3K*, *PTEN*, *NF1*, *TSC1* or *2*, *NRAS*, *KRAS*) [60].

Pharmacokinetic resistance should also be considered. Examples include reduced binding affinity of imatinib in *KIT* exon 9 mutant tumors, *KIT* gene amplification, and comedications (via CYP3A4), which may lead to changes in imatinib plasma levels. Low plasma levels are associated with significantly shorter progression-free times than higher imatinib levels. It is also important to review patient compliance in this context.

If tumor progression is detected during ongoing therapy with imatinib at a dose of 400 mg/day, a dose increase of imatinib to 600-800 mg/day can be considered [44]. However, as the response or 'clinical benefit' rate after dose escalation is only about 7% in patients with exon 11 mutation, this is often not done in clinical practice. However, dose escalation may be useful after extensive gastric resection or gastrectomy, as often only subtherapeutic blood levels of imatinib are achieved. If a dose increase does not lead to renewed tumor stabilization or is not feasible in the longer term due to intolerance, a change in therapy to sunitinib is indicated.

Based on *in vitro* as well as *in vivo* data, the different sensitivity of secondary *KIT* mutations to the various tyrosine kinase inhibitors used in GIST is nowadays well characterized [61]. Nevertheless, considering tumor heterogeneity, a repeat molecular *KIT* analysis of tumor tissue progressing under imatinib and a therapy choice based on this analysis is not recommended outside of trials. In order to overcome the problem of tumor heterogeneity in the future, intensive research is currently being conducted to establish liquid biopsy diagnostics in GIST [62]. GIST, in contrast to lung and colon carcinomas, unfortunately secrete only very small amounts of ctDNA, mostly only at a very advanced tumor stage. The optimal preanalytical handling of the samples as well as the interpretation of the results must therefore be further investigated on the basis of studies [63] before this technique can be used in clinical practice.

#### **6.2.4.5.4 PDGFRA-D842V mutation**

Patients whose tumors have a valine substitution in codon 842 (p.D842V) of *PDGFRA* should be treated with avapritinib in case of non-resectable or metastatic disease.

Avapritinib is a highly potent *PDGFRA* inhibitor that achieved a remission rate of 91% in 56 patients with D842V mutation and clinical benefit in 98% of patients in the NAVIGATOR trial. Median progression-free survival was 34 months and median overall survival has not been achieved to date [64, 65]. Avapritinib is well tolerated overall with predominantly mild side effects. Of particular concern, however, are neurocognitive side effects, which can occur in more than 50% of cases, especially in elderly patients. Education on these side effects should always include persons from the immediate social environment in order to sensitize them to the multi-layered symptoms (disturbance of memory and movement, psychiatric symptoms, behavioral changes, etc.). Immediate discontinuation of therapy for at least two weeks, even for mild disorders, is mandatory and an important prerequisite to ensure long-term treatment with avapritinib [66]. To date, treatment is without alternative for patients with this genotype and discontinuation due to side effects is prognostically very unfavorable.

Patients with this mutation do not respond to imatinib, sunitinib, regorafenib, and ripretinib, and therefore these agents should not be used. Local treatment modalities may be considered, particularly in cases of focal progression on avapritinib, which may allow prolonged disease



control with avapritinib. The median life expectancy after discontinuation of therapy due to progression is only a few weeks [67].

Avapritinib resistance develops by selecting clones with secondary mutations in exon 13, 14, and 15, in analogy to the mechanisms in *KIT*-mutated GIST. In particular, mutations in the solvent front region (p.G680R) lead to absolute avapritinib resistance, for which no alternative inhibitors are available to date [67].

Patients with the presence of a *PDGFRA-D842V* mutation should be treated in clinical trials and/or presented at a sarcoma center when possible.

#### **6.2.4.5.5 Second-line therapy with sunitinib**

Sunitinib is approved for second-line therapy after imatinib failure and for patients with imatinib intolerance [46, 47, 48]. Phase I-III trials have demonstrated its efficacy in imatinib-refractory GIST. A placebo-controlled phase III trial found a tumor stabilization rate of 58% and a remission rate of 7%. Median progression-free survival was 6.8 months with sunitinib versus 1.6 months with placebo. Overall survival was also significantly improved with sunitinib despite the "cross-over" design. Treatment response to sunitinib correlated with *KIT* mutation status. Thus, progression-free and overall survival are significantly higher in patients with (pre-imatinib) exon 9 mutation and *KIT* wild-type than with *KIT* exon 11 mutation (PFS: 19 vs. 5 months; OS: 28 vs. 12 months). Sunitinib may be effective for secondary mutations in the ATP-binding domain (c-*KIT* exon 13/14), whereas imatinib typically shows no activity here. For secondary mutations in the kinase activation domain (exons 17/18), sunitinib is usually ineffective, so that alternative treatment options should be considered.

The dosage of sunitinib tested and approved in initial studies is 50 mg/day for 28 days, followed by a 14-day break in therapy. In a phase II trial, continuous dosing of 37.5 mg was tested. The median progression-free survival was 34 weeks and overall survival was 107 weeks, making this route of administration an option for patients in whom 50 mg/day for 4 weeks is poorly tolerable.

#### **6.2.4.5.6 Third-line therapy with regorafenib**

Regorafenib is approved as third-line therapy after failure of imatinib and sunitinib. In the 'GRID' phase III trial, regorafenib was compared to placebo/'best supportive care' with a 'cross-over' to regorafenib upon progression on placebo. Similar to sunitinib, regorafenib is found to have a low rate of objective remission of only 4.5%. Median PFS was 4 months longer than placebo (4.8 vs. 0.9 months); survival benefits were probably not apparent as a result of cross-over. Regorafenib showed efficacy in patients with primary *KIT* exon 11 or exon 9 mutations, as well as in *KIT/PDGFRA* wild-type (SDH deficient) GIST and certain secondary *KIT* exon 17 mutations [49].

The standard dosage is 160 mg/day for 3 weeks, followed by a 1-week break. Similar to sunitinib, regorafenib should be administered in a personalized, toxicity-adapted manner.

#### **6.2.4.5.7 Fourth-line therapy with ripretinib**

Ripretinib is approved after pretreatment with three therapies, including imatinib. In the INVICTUS trial, ripretinib 150 mg was compared with placebo in patients who had received at least three prior therapies, including imatinib. One-third of patients had received 4-7 prior therapies.

Patients in the control arm had the option to receive therapy with ripretinib via crossover if progression was documented. Ripretinib had a significantly better median progression-free survival of 6.1 months than placebo (1.0 months). In addition, patients in the ripretinib arm had significantly better median overall survival (hazard ratio: 0.36). One-third of patients in the control arm were unable to crossover due to worsening general condition or death [68].

The standard dosage is 150 mg daily without interruption. Dose reduction, if indicated, is done in 50 mg steps.

#### **6.2.4.6 Therapy after failure of imatinib/sunitinib/regorafenib/riporetinib**

If no study options are available in this situation, kinase inhibitor therapy should be continued to avoid tumor 'flare' after kinase inhibition is discontinued. The rapid deterioration of patients in the placebo arm of the INVICTUS trial dramatically underscored the risk of life-threatening flare. There is no robust evidence for effective therapeutic alternatives for treatment after ripretinib failure.

Conceptually, imatinib resistance develops clonally - so that usually, when initial resistance occurs, imatinib-sensitive metastases are still present alongside resistant clones. This also explains that, particularly in earlier lines of therapy, continuation or rechallenge with imatinib can partially control the disease [50, 51]. Imatinib is ineffective in cells harboring secondary mutations of *KIT*. In a 5<sup>th</sup>-line situation, one must assume complete imatinib resistance, and repeat imatinib therapy has no relevant prospect of efficacy. Preclinical studies show that sunitinib is active against mutations in the ATP-binding domain as well as against the gatekeeper mutation (T670I), whereas regorafenib, but especially ripretinib, show very broad efficacy against exon 17 and exon 18 mutations. For patients who do not experience general progression with ripretinib, the first option is to continue ("beyond progression") ripretinib or even rechallenge with sunitinib. This preserves the chance to control still responding metastases. Here, local therapies should also be evaluated, if necessary, to treat focal progression. Efficacy data for other TKIs, such as pazopanib, must be evaluated in the temporal context of their publication [52], as studies were conducted in much earlier lines of therapy. Preclinically, there is no evidence that pazopanib covers an additional spectrum of mutations compared with sunitinib and ripretinib. Based on evidence of *KIT*-independent resistance mechanisms, such as mutations that activate the *PI3K* pathway, some centers are using combinations with *mTOR* inhibitors. Imatinib combinations are not useful in this context due to the presence of imatinib resistance; however, there are safety data for combinations of sunitinib and sorafenib with, for example, sirolimus [69].

#### **6.2.5 Locoregional procedures for uni-/oligolocular progression**

In case of uni- or oligolocular progression especially in symptomatic GIST, additional locoregional treatment procedures may be considered. Surgical resection, radiofrequency ablation (RFA), transarterial embolization (TAE) and/or selective internal radiation therapy (SIRT) may be considered as debatable therapeutic procedures. If tumor tissue is obtained in this context, another mutation analysis may be considered for further targeted drug treatment. The selection of suitable patients can only be done in a multidisciplinary approach.



## 6.2.6 Substances

### 6.2.6.1 Imatinib

Imatinib is a competitive inhibitor of ATP binding to the kinase domains of the *KIT* and *PDGFRA* receptors, leading to inhibition of signal transduction of these pathogenetically relevant tyrosine kinases. Imatinib is approved for the treatment of *KIT*-(CD 117)-positive unresectable and/or metastatic malignant gastrointestinal stromal tumors and for the adjuvant treatment of adults at significant risk of recurrence following resection of *KIT*-(CD 117)-positive GIST. The most commonly reported treatment-related adverse events ( $\geq 10\%$ ) are vomiting, diarrhea, abdominal pain, fatigue, myalgia, muscle cramps, skin redness, and edema. These should be treated consistently to maintain long-term compliance. Hematologic adverse events (neutropenia 10%, thrombocytopenia 1%, anemia 6%) occur less frequently than in patients with CML. Gastrointestinal bleeding occurs in up to 5% of patients during treatment.

### 6.2.6.2 Sunitinib

Sunitinib is an inhibitor of the tyrosine kinases *KIT*, *PDGFR-A and -B*, *VEGFR1-3*, *FLT3*, and *RET* and is approved for the treatment of unresectable and/or metastatic GIST following treatment with imatinib.

The most common side effects are loss of appetite, impaired sense of taste, hypertension, fatigue, gastrointestinal complaints (e.g., diarrhea, nausea, stomatitis), and the occurrence of hand-foot syndrome. Endocrine (hypothyroidism), hematologic, or cardiac side effects may occur in patients treated long-term with multikinase inhibitors.

### 6.2.6.3 Regorafenib

Regorafenib is an inhibitor of the tyrosine kinases *VEGFR1-3*, *KIT*, *RET*, *TEK*, *RAF1*, *BRAF*, *PDGFRA and B*, and *FGFR* and is approved as a third-line therapy for advanced GIST after failure of imatinib and sunitinib. Common side effects in CTCAE grade 3/4 include fatigue, diarrhea, hand-foot syndrome, and hypertension. Side effects occur after a median of 14 days and therefore require close monitoring (e.g., weekly) at the start of therapy and consistent dose reduction if necessary. The occurrence of changes in liver function tests (ALT, AST, bilirubin) are common, severe liver dysfunction is rare.

### 6.2.6.4 Ripretinib

Ripretinib is a potent inhibitor of the tyrosine kinases *KIT*, *PDGFRA*, *TIE2* as well as *VEGFR2* and the serine/threonine kinase *BRAF*. Ripretinib binds in the posterior portion of the ATP binding pocket (back pocket) and exhibits high potency, particularly against secondary *KIT* mutations in the activation loop (exon 17 and 18). Ripretinib is approved for the treatment of patients with GIST who have received prior treatment with three or more kinase inhibitors, including imatinib. The most common ( $>2\%$ ) higher-grade (grade 3-4 by CTCAE) adverse events include anemia (7%), fatigue (2%), diarrhea (2%), loss of appetite (2%), dehydration (2%), hyperkalemia (2%), acute renal failure (2%), and pulmonary edema (2%). More common mild adverse events included alopecia (49%), myalgias (27%), nausea (25%), fatigue (24%), and hand-foot syndrome (21%). In contrast to sunitinib and regorafenib, arterial hypertension is rarely observed (5%).

### 6.2.6.5 Avapritinib

Avapritinib is a highly potent type I *PDGFRA* inhibitor. Avapritinib is overall well tolerated with predominantly mild side effects (mild nausea, fatigue and periorbital edema). However, patients must be monitored with special vigilance for neurocognitive side effects, which can occur in more than 50% of cases, particularly in elderly patients. When explaining these side effects, people from the immediate social environment should always be included in order to sensitize them to the complex symptoms (impaired memory, movement disorders, psychiatric symptoms, behavioral changes, etc.).

## 8 Follow-up/Control examinations

After complete tumor resection, clinical controls including CT abdomen/pelvis - depending on the risk - should be performed every 3-6 months during the first 5 years, then once a year. For small tumors (<2 cm), longer intervals may be selected if necessary. MRI examinations may also be performed after a longer recurrence-free period and when the risk of recurrence is low to reduce abdominal radiation exposure. Abdominal ultrasonography is not recommended because the sensitivity for peritoneal metastases is too low. Regular endoscopic follow-up is currently no longer recommended because the local recurrence rate after complete resection is very low.

For follow-up of existing metastases, intervals of about 3-4 months are usually chosen. Here, too, CT abdomen/pelvis examinations are the method of choice, especially for the detection of peritoneal metastases and for the follow-up of hepatic metastases also by means of density measurement [22].

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## **16 Disclosure of Potential Conflicts of Interest**

according to the [rules of the supporting professional societies](#).