# Diplomarbeit

# Gastrointestinal stromal tumour-

# Literature review and retrospective analysis of 66 upper gastrointestinal GISTs


Eingereicht von

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# TABLE OF CONTENT

## Figures



## Tables

# Abstract

**Background/Aims**
Main objective of the literature review was to provide an overview on gastrointestinal stromal tumours, the most common mesenchymal tumour of the gastrointestinal tract. The results of the conducted retrospective analysis should show if the analysed cases and related data of upper GI-tract GISTs are comparable to those found in literature. We hope to draw conclusions with regard to follow-up care.

**Methods**
We retrospectively analysed 66 cases of upper GI-tract GISTs who were treated at the clinical department of general surgery, medical university of Graz. Inclusion criteria were operable GIST originating from the oesophagus, stomach or duodenum.

**Results**
Of the 66 analysed patients, 38 (57,6%) were male and 28 (42,4%) female, with a median age of 63 years (range 11 to 74) at the time of surgery. 3 patients were diagnosed with GIST related syndromes. Resection margin was R0 in 57 cases (86,5%), R1 in 2 cases (3%), and R2 in 5 cases (7,5%), respectively. Median tumour diameter was 4,1cm. Mitotic count was <5 in 46 cases (69,7%). For risk assessment the AFIP classification was used. 9 patients (13,6%) were administered adjuvant imatinib. 3 patients (4,5%) received neoadjuvant imatinib. 5 patients (7,5%) received imatinib after surgery because of disease progression. 5 patients (7,6%) had metastasis at the time of diagnosis, but where deemed resectable by the local tumour board Two other patients with metastatic disease received imatinib after surgery. Patients were followed for a median of 61 months (inter-quartile range 30 to 101 months). A total of 10 patients (15,2%) showed disease progression after surgery. The median time to recurrence was 38,5 months (2 to 69 months). The 5 year recurrence free survival rate was 86,4%. A total of 13 patients (19,7%) died during follow-up.

**Discussion**
Treatment and prognosis of GISTs has greatly improved in the past decade. Still, there is need for more research in some fields. The results series correlated well with information found literature. With regard to follow-up, we suggest that patients with no, very low, and low risk GISTs should not be followed-up regularly. Reliable conclusions are limited because of the retrospective design and the case number of our study.

# Zusammenfassung

**Hintergrund / Ziele**
Ziel der Literaturrecherche war es einen Überblick über gastrointestinale Stromatumoren, den häufigsten mesenchymalen Tumor des Gastrointestinaltrakts, zu geben. Die Ergebnisse der von uns durchgeführten retrospektiven Studie sollten zeigen, ob die untersuchten Fälle und die dazugehörigen Daten des GIST des oberen GI-Trakts mit denen vergleichbar sind, die in der Literatur zu finden sind. Wir hoffen, Schlüsse auf das Follow-Up zu ziehen.
**Methoden**
Wir haben 66 GISTs des oberen GI-Trakts retrospektiv analysiert, die in der klinischen Abteilung für Allgemeinchirurgie an der medizinischen Universität Graz behandelt wurden. Einschlusskriterien waren GIST des Ösophagus, des Magens oder des Duodenums.
**Ergebnisse**
Von 66 analysierten PatientenInnnen waren 38 (57,6%) männlich und 28 (42,4%) weiblich, mit einem medianen Alter von 63 Jahren (Bereich 11 bis 74) zum Zeitpunkt der Operation. Bei 3 PatientenInnen wurde ein GIST-Syndromen diagnostiziert. Die Resektion war R0 in 57 Fällen (86,5%), R1 in 2 Fällen (3%) und R2 in 5 Fällen (7,5%). Der mediane Tumordurchmesser betrug 4,1 cm. Die Zahl der Mitosen war <5 in 46 Fällen (69,7%). Für die Risikoabschätzung wurde die AFIP-Klassifikation verwendet. 9 PatientenInnen (13,6%) wurde adjuvant Imatinib verabreicht. 3 PatientenInnen (4,5%) erhielten Imatinib neoadjuvant. 5 Patienten (7,5%) erhielten Imatinib nach der Operation wegen fortschreitender Krankheit. 5 PatientenInnen (7,6%) hatten zum Zeitpunkt der Diagnose Metastasen, wurden aber als resektabel beurteilt. Zwei weitere Patienten mit metastasierter Erkrankung erhielten nach der Operation Imatinib. Das Follow-Up betrug im Median 61 Monate (Inter-Quartilen-Bereich 30 bis 101 Monate). Insgesamt 10 PatientenInnen (15,2%) zeigten eine Progression nach der Operation. Die mediane Zeit bis zum Rezidiv betrug 38,5 Monate (2 bis 69 Monate). Die 5-Jahres-Rezidiv-freie Überlebensrate betrug 86,4%. Insgesamt 13 Patienten (19,7%) starben während der Nachuntersuchung.
**Diskussion**
Die Behandlung und Prognose des GIST hat sich in den letzten zehn Jahren stark verbessert. Unsere Fallstudie korreliert gut mit der Information, die in der Literatur vermittelt wird.
Das Follow-Up betreffend schlagen wir vor, dass bei PatientenInnen mit no, very low und low risk GIST keine routinemäßigen Nachsorgeuntersuchungen durchgeführt werden. Verlässliche Schlussfolgerungen unserer Studie werden durch das retrospektive Design und die Fallzahl eingeschränkt.

# 1. Literature review

## 1.1. Overview

Gastrointestinal stromal tumours are the most common mesenchymal tumour in the gastrointestinal tract (1,2,3,4). It is assumed that GISTs either originate from the interstitial Cajal cells, which work as pacemaker cells, regulating the tone and movement of the smooth muscle tissue of the gastrointestinal tract (1), or from a KIT-positive spindle-cell population similar to stem cells and precursor of the Cajal cells (1). Most commonly, GISTs is found in the stomach (around 59-61%)(1). GISTs found in the small intestine make up approximately 30% of the cases, followed by duodenum with 5%. Esophageal GISTs and GISTs found in the colon and appendix have equal relative frequency with 1-2% (1). Fewer than 5% of GISTs are so-called extra-gastrointestinal, located either in the omentum, the mesentery, or the retro peritoneum. However many extra-gastrointestinal GISTs are found to be metastases of undetected gastrointestinal ones (1,2). By far the most common genetic aberrations of the tumour are either a KIT (75-80%) or a PDFGR (5-10%) mutation. These closely related proteins are receptor tyrosine kinases, which become ligand-independent through the mutation, leading to constant activation (3,4). GISTs are highly variable in with regard to their malignant potential, ranging from almost benign to highly aggressive. The first system to assess the risk given in an individual patient was the NIH (National Institutes of Health) consensus classification (6). Other frequently used assessment systems are the risk classification according to Miettinen and Lasota (1) and the risk classification according to Joensuu (9).

## 1.2 Epidemiology

It is estimated that GISTs represent 20% of soft-tissue sarcomas, which makes them the most common type of sarcomas (2). Incidence of clinical detected GISTs is estimated to be between 10 and 15 cases per million per year in Europe (2,4), while the estimated prevalence is about 129 per million (3). They may occur at any age, however 80% of the patients are older than 50 years when GIST is diagnosed

with a median age around 60-65 (2,8). In patients who are younger than 20 years, the GIST commonly is associated with a syndrome (2). Generally, there is no gender predilection (2), but specific tumour sites or syndromes often affect genders at a different rate (see below). These figures given, GIST is a rare disease. Asymptomatic micro-GISTs (0.2-10mm), on the other hand, appear to be far more common. *Kawanowa et al.* found microscopic GISTs in 35 of 100 stomachs (35%) they examined microscopically, which were retrieved by total gastrectomies because of gastric carcinoma (14). Furthermore, a German autopsy study by *Agaimy et al.* found palpable GISTs in 22 patients (22,5%) out of 98 consecutive performed autopsies (7). These findings were somewhat contradicted by the results of a Swiss autopsy study published by *Muenst et al,* which only found 17 palpable GISTs (2,9%) in the 578 patients that where examined (11). These figures are considerably lower as those given by the other two series before: *Muenst et al.* argue that this is because of the different approaches chosen to detect GISTs (11). Still, all figures given above are highly above the estimated incidence (11). Consequently, it is safe to assume that only a small minority of GISTs become clinically apparent. The majority of GISTs is sporadic. Familial GISTs, caused by germ-line mutations of KIT, are rare. Furthermore, there are familial cases of GISTs and syndrome-associated GISTs as the Neurofibromatosis Type 1, Carney´s triad and the Carney-Stratakis syndrome (2,4). Apart from these syndromes GISTs has no established risk factors (2).

## 1.3 Pathology

### 1.3.1 Overview on macroscopic, microscopic and cellular pathology

The most popular theory on behalf of the origin of GISTs is that they originate from the interstitial cells of Cajal or their stem cell-like precursor. These cells are gastrointestinal pacemaker cells, intermediating between the vegetative nervous system and the smooth muscle cells of the GI-tract. As mentioned in 1.1, they regulate the tone and motility of the muscle tissue. They are located around the Auerbachian myenteric plexus and the muscularis propria throughout the GI-tract (2,3). The size of GISTs ranges from below 10mm in diameter (referred to as

micro-GISTs or tumourlets) up to 350 or even 400mm (1), with a median size of 50 mm (3). They present as well-circumscribed, intramural tumour nodules (4). These nodules are frequently singular, however may be as well multi-nodal. Although central cystic degeneration is possible, most tumours are fleshy and solid. Overlaying mucosa is intact in most cases, nevertheless central cavities and ulceration with subsequent bleeding are commonly seen in larger tumours (3,4). Histologically, GISTs can be separated into three different morphological types: Namely the spindle cell (70%), the epithelioid (20%), and the mixed type (10%) (4). Some authors divide gastric GISTs into further subtypes (see 1.3.4) (1,5,16). Due to these broad histological variations of the tumours a broad differential diagnosis, including immunohistochemically procedures, is necessary (3). Differential diagnosis includes sarcomas other than GIST, sarcomatoid carcinomas, and metastatic melanoma (2).
Metastases of GISTs are usually found in the liver, omentum, and peritoneum as well as other intra-abdominal locations, while extra-abdominal metastases are uncommon (37). Lymph node metastases are very rare (32).

### 1.3.2 Molecular Pathology

The most common mutation found in GISTs is the KIT mutation, also known as CD 117. The KIT-Kinase is usually activated by its ligand, the stem-cell-factor, which leads to dimerisation of the tyrosine-kinase. 75-80% of GISTs show mutations in this gene, which is typically affecting the juxtamembrane domain encoded by exon 11 (2). This helical domain, apparently an inhibitory region regarding to KIT activation, regulates the dimerisation of the kinase; hence a mutation in this region renders the regulatory function incapable (2,5). Other gene locations affected are exons 9, 13, and 17. While exon 9 encodes for the extracellular domain (prevalence 6%), exon 13 and 17 encode for kinase I and II domains respectively (prevalence 2%). Unlike mutations in the juxtamembrane domain, alterations in the kinase II domain change the activation loop, influencing the ATP binding pocket of the kinase (2). 20-25% of GISTs are KIT mutation negative, but only about 5% are negative for KIT expression (1,2,3). In about a third of these KIT mutation negative tumours, platelet-derived growth factor receptor alpha mutations are found

(prevalence 10%). The gene regions affected are homologous to these affected in the KIT-gene. As the KIT kinase, the PDGFRA-kinase is activated by its ligand, the platelet-derived-growth-factor, and activation leads to dimerisation. As with KIT mutations in kinase-domain II, PDGFRA alterations affect the activation loop and the ATP binding pocket. KIT and PDGFRA mutations exclude each other. About 10-15% of GISTs are negative for both KIT and PDGFRA mutations. These are usually referred to as “wild type” GISTs. These GISTs are usually found in neurofibromatosis 1, Carney’s triad, and Carney-Stratakis patients (see 1.3.3) (2).

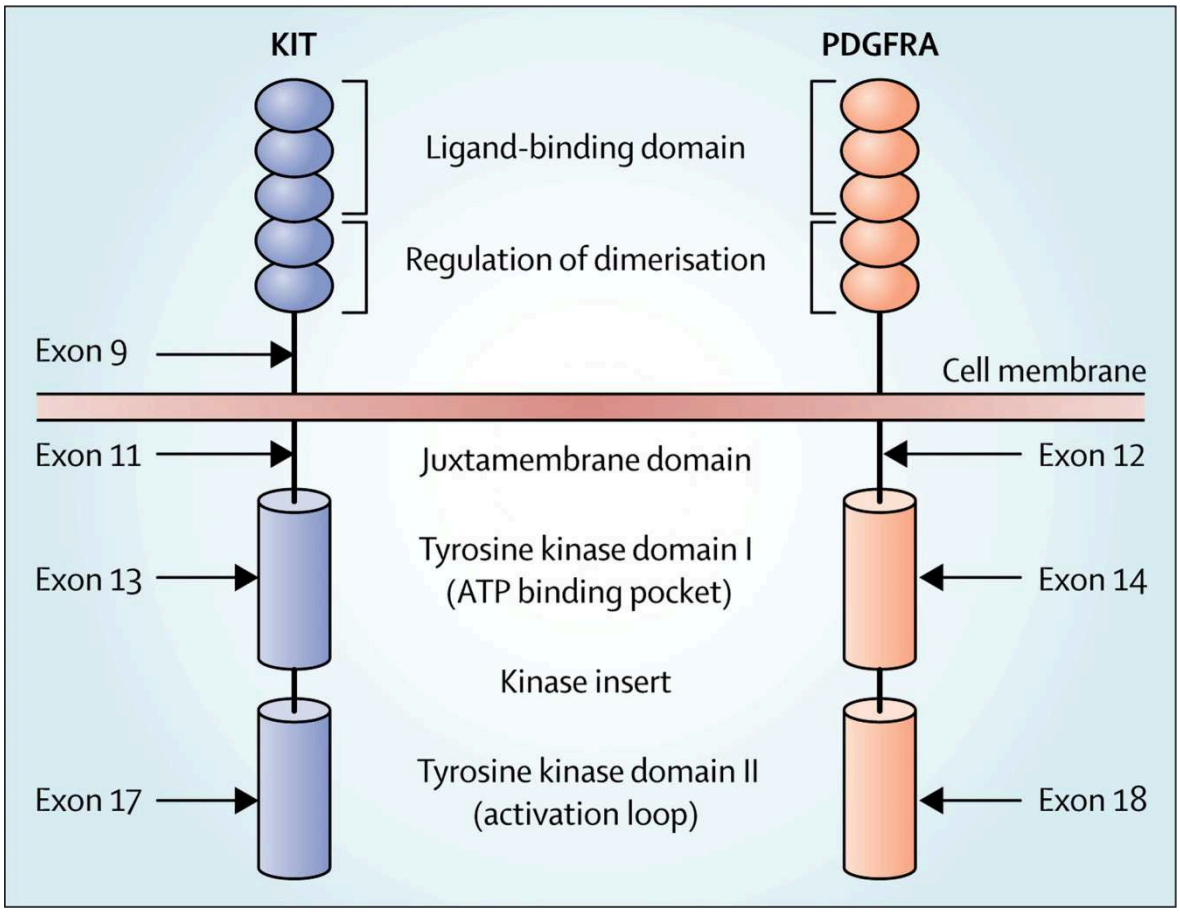


**Figure 1** Structure of KIT and PDGFRA receptor tyrosine kinases (2)

Another sensitive marker for GIST is anoctamin 1, also known as DOG1 (“Discovered on GIST”), which is positive in around 98%. Remarkably, of roughly 5% GISTs, who are negative for KIT expression, many about one third) are positive for ANO1 (2,4). Regarding the KIT expression, it has been stated that this characteristic of GISTs is a constitutional one. This is supported by the fact that even KIT mutation negative GISTs, as these that occur in NF1 patients, as mentioned above, are strongly positive for KIT expression (1). Other

immunohistochemical features of GISTs include CD 34 (60-70%), smooth muscle actin (30-40%), S-100 (5%), desmin (1-2%) ,and keratin (1-2%) (3).
The relative figures may differ in regard to specific tumour locations (1)

### 1.3.3 Familial and Syndrome related GIST

As mentioned before, the vast majority of GISTs are sporadic. However, about 5% are either related to a heritable mutation or a tumour syndrome (2,4).

**Familial GIST**

The mutations responsible for familial GISTs include KIT mutations on exon 8, 11, 13, or 17. Patients suffering from these mutations have a high probability of developing singularly or even multiple gastric or small bowel GISTs, often as early as at the age of 18 years (2,3). Furthermore, diffuse hyperplasia of interstitial Cajal cells is present in the adjacent gut wall occasionally (2,3). A germline mutation in exon 12 of the PDGFRA gene is also likely to cause GISTs. These patients often suffer from fibroid inflammatory polyps, both in the stomach and the small bowels (2,3).

**Neurofibromatosis 1**

A subset of patients with Neurofibromatosis 1 (von Recklinghausen's) develops GISTs, with a high predilection for the small intestine. These GISTs are often multiple and intensely KIT positive, although they are usually negative for KIT mutations (1, 2, 3). A Swedish study, including 70 patients, showed a prevalence of 7% of GISTs (15). Compared to the prevalence (129/1,000,000; see above) in the general population, the prevalence is more than 53,000 higher in NF1 patients.

**Carney's Triad**

Carney triad describes the combined appearance of pulmonary chondroma, paraganglioma, and GIST. This rare, uninheritable syndrome shows a strong female predilection (85%) (1,2,3). Associated GISTs seem to appear exclusively in the stomach. They are negative for KIT and PDGFRA mutations., but immunochemistry in Carney's Triad associated GISTs shows a loss of expression of succinate dehydrogenase subunit B (SDHB). Mutations in the gene encoding for

this enzyme are not recorded in these tumours, so that the cause for its deficiency is not known (2). The majority of these GISTs is biologically benign, and even patients who suffer from liver metastases manage to survive many years with stable disease (3).

**Carney-Stratakis syndrome**

Caused by a germline mutation in any of the subunits of succinate dehydrogenase (SDHA, SDHB; SDHC, SDHD) the Carney-Stratakis syndrome comes with a high risk for paraganglioma and GIST. The affected patient's GISTs have neither KIT nor PDGFRA mutations, but, similar to GISTs associated with Carneys triad, immunochemistry shows a loss of expression of succinate dehydrogenase subunit B (and subunit A, for those with SDHA mutations) (2).

*Agarwal et al.* published a paper on inherited predispositions to GIST in which they provided an overview over the syndromes mentioned above (see table 1 below).

**Table 1: Syndromes associated with predisposition to GISTs** (34)

| Syndrome | Sporadic GIST | Familial GIST | Carney's Triad | Carney-Stratakis-Syndrome | NF-1 |
|---|---|---|---|---|---|
| **Average age at GIST** | approximately 60 years | approximately 40-50 years | < 35 years | < 25 years | approximately 50 years |
| **Gender predilection** | none | none | female > male | none | none |
| **Multicentric disease** | rare | yes | more or less | Yes | - |
| **Associated features** | none | Pigmentation, urticarial pigmentosa, mastozytosis, dysphagia | Paraganglioma pulmonary Chondroma | Paraganglioma | Neurofibroma, cafe-au-lait-spots |
| **Mutations** | no germ-line mutation | Kit/PDGFRA | unknown | SDHB SDHC SDHD | NF1 Neurofibromin |
| **Heredity** | - | autosomal dominant | - | autosomal dominant | autosomal dominant |
| **Histology** | spindle cells > epithelioid > mixed | similar to sporadic | epithelioid | see sporadic | spindle cells |
| **ICC Hyperplasia** | none | mostly present | none | none | mostly present |
| **Localisation** | all | small bowels, stomach, rarely rectum | stomach | stomach | small bowels |
| **Clinical behaviour** | depends on localisation, mitotic count and size | see sporadic | metastases often present at diagnosis | unknown | indolent |
| **Imatinib response** | depends on mutation | depends on mutation | unknown | poor | unknown |

### 1.3.4 Pathology of GISTs at different sites

**Oesophageal GISTs**

Overall, GISTs in the oesophagus are scarce, making up only around 1-2% of all GISTs, as mentioned before. Typically, these tumours are found in the lower third of the oesophagus. Patients are usually older adults, while the tumours range from small incidental ones to large masses. Larger tumours tend to cause dysphagia, although large mediastinal tumours have been described with no symptoms related to the oesophagus (1).

Most oesophageal GISTs are >5cm or >5 mitoses per 50HPF. Histologically, they range from spindle cell (75%) to epithelioid (25%), while some tumours resemble gastric GISTs. It has been shown immunohistochemically that these tumours are regularly positive for KIT as well as CD 34 (1).

Only few survivors are found in long-term follow up, most of which suffered from tumours with either size below 5cm or mitotic count below 5 per 50HPF (1).

**Gastric GISTs**

Gastric GISTs are by far the most common, with a relative frequency ranging from 59 to 61%. Patient cohorts show a mild male predilection with a relative frequency of 52 to55%, the median age ranging from 63 to 70 years (1,16).

Tumour size is very variable, ranging from microscopic nodules to gigantic masses with a diameter over 40cm. Smaller gastric GISTs are rather solid, subserosal, intramural or inward bulging than being intraluminal polypoid. Some larger GISTs are pedunculated, external masses attached to the outer side of the gastric wall, involving the muscularis propria. Central cysts are common among larger tumours; some only show a narrow rim of viable cells in the outwards parts. Furthermore, gastric GISTs have been found to form omental and lesser omental masses by extending outwards. Particularly, tumours of the lesser curvature may mimic hepatic tumours by impinging on the liver. In addition, malignant GISTs may be attached either to the spleen, pancreas or the transverse colon (1).

Regional differences have been described for gastric GISTs. Epithelioid are relatively more common in the antrum, while GISTs in the upper part of the stomach are more often clinically malignant (1).

Some authors, gastric GISTs may be further categorised in eight subtypes. Of 1765 GISTs, 1242 tumours were thus classified, in which the epithelioid and the spindle cell subtype each are represented by 4 further subclasses (1,5,16).

1.) Sclerosing spindle cell GISTs: These are paucicellular tumours, with extensive extracellular collagen. The spindle cells are slender and show no nuclear atypia and the mitotic count is usually low (see figure 1, A). Commonly, these tumours are small and incidental. The prognosis is excellent (1,5,16).

2.) Palisading-vacuolated spindle cell GIST: The cells are plump and homogenous, while the typical features are nuclear palisading and perinuclear vacuolisation. Cellular atypia is limited and mitotic activity rarely exceeding 10/50 HPFs, but the size regularly exceeds 10cm (see figure 2, B). These tumours are the most frequent ones in gastric GISTs and the prognosis is very good (1,5,16).

3.) Hypercellular spindle cell GISTs: The cells are uniform and densely packed without significant mitotic rate, usually ranging from 5 to 15 per 50HPFs, or atypia. They only show limited nuclear palisading and perinuclear vacuolisation, while the cellular arrangement is diffuse (see figure 2, C). This subtype imparts a moderate risk for metastasis (1,5,16).

4.) Sarcomatous spindle cell GISTs: Spindled or oval cells; which show diffuse atypia, demonstrated by nuclear enlargement and hyperchromasia. Pleomorphism, on the other hand, is limited. The tumour cells are often organised in bundles, separated by myxoid stroma. Mitotic activity exceeds 20 per 50HPFs (see figure 2, D). Almost all of them are larger than 5cm. Risk of metastasis and tumour associated mortality is high (1,5,16).

5.) Sclerosing epithelioid GIST: These are composed of cohesive, uniform polygonal cells with indistinct, nonvisible cell borders. The Matrix is diffuse-collagenous. Multiple nuclei are frequent; while the mitotic rate is low. This is the most common type of epithelioid gastric GIST (see figure 2, E). Metastatic rates, considering the tumour parameter, show an infrequent but somewhat unpredictable course (1,5,16).

6.) Dyscohesive epithelioid GIST: Tumour cells are large, polygonal, and dyscohesive. The cell borders are clearly visible, the cells themselves are surrounded by a lacunar space with little interstitial matrix. Focal atypia, in form of multiple nuclei and nuclear pleomorphism, is frequent (see figure 2, F). However,

this is without prognostic significance. The mitotic rate is low (below 5 per 50HPFs), as well as the metastatic rate (1,5,16).

7.) Hypercellular epithelioid GISTs: These tumours show high cellular density, while typically having well defined borders. Nucleocytoplasmic ratio is higher as in group six (see figure 2, G). Mitotic activity rarely exceeds 10 per 50 HPFs (1,5,16).

8.) Sarcomatous epithelioid GISTs: Cells have distinctly epithelioid morphology with well-defined borders. The nucleocytoplasmic ratio is high. Nuclei are uniform, often showing prominent nucleoli (see figure 2, H). The mitotic rate is commonly as high as 20 per 50 HPFs. An absolute majority of these tumours metastasise (1,5,16).

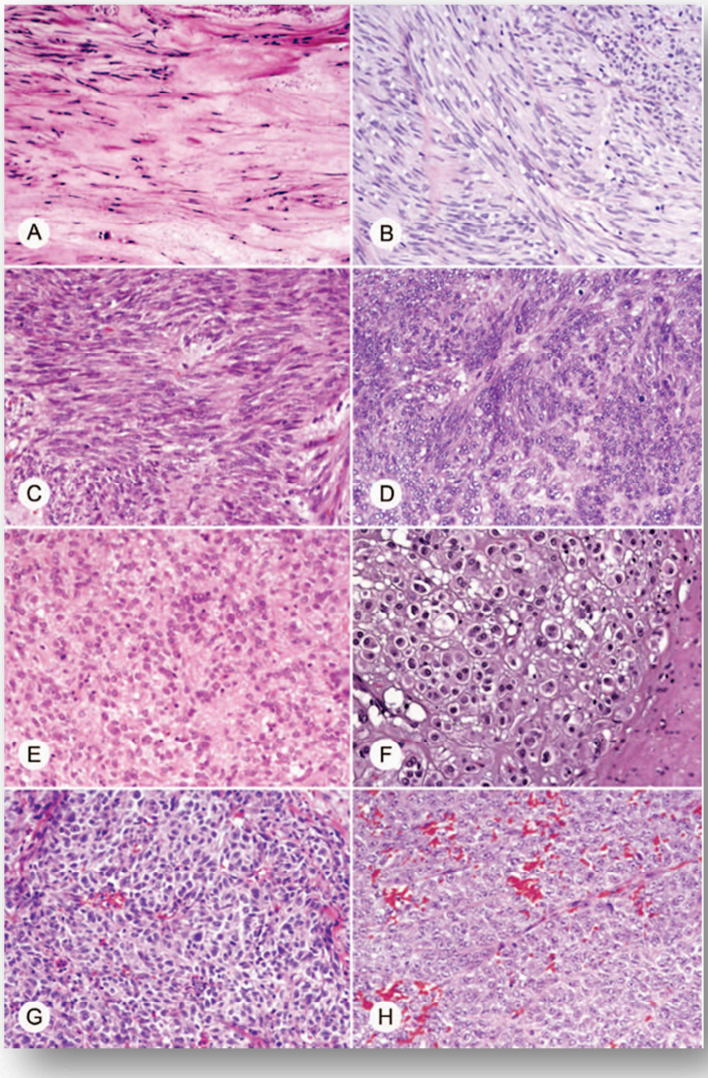


**Figure 2**: Histological examples of gastric GISTs (1)

**Duodenal GISTs**

Relative frequency of duodenal GISTs ranges from 4 to 5%. Tumours growing in the second part, which are more common, may clinically mimic a pancreatic tumour (1,21). A majority of duodenal GISTs show spindle cellular pattern and are similar to small intestinal ones, in around 50% of the tumours skenoid fibres are present. Epithelioid morphology seems to indicate malignant transformation, not an independent subtype, as with gastric GISTs. A somewhat exclusive characteristic of duodenal GISTs, present in around 20%, is haemangioma-like vascular proliferation. Prognosis is strongly dependent on both mitotic rate and tumour size. Almost all duodenal GISTs are KIT positive (1).

**Small intestinal GISTs**

GISTs arising in the jejunum and ileum make up around 30% of all GISTs. They are more often malignant than their gastric counterparts. The ratio of jejunal to ileal tumours is 1,6:1. Median age of the patients suffering from these GISTs is 59 years, with a slight male predominance (55%). Tumour size, as it is not unusual with GISTs in general, is highly variable, ranging from minuscule nodes to a diameter of over 20cm. Frequent gross patterns include dumbbell shaped masses, with both internal and external parts, solid outward bulging nodes, as well as external cystic formations. These in particular may fistulate into the bowels lumen, giving them a diverticular look. Because of that peculiar appearance, some of these have been considered arising from Meckel's diverticula. However, no evidence has been shown that a Meckel's diverticulum has been present in the first place. Therefore, it is assumed, that the diverticula is a secondary structure formed by the tumour (1,5).

On contrary to gastric GISTs, small intestinal GISTs do not form characteristic histological subtypes, most of them are spindle cell tumours. About half of these tumours contain skenoid fibres, which are either round, oval, or elongated eosinophilic and PAS-positive masses of collagen fibres with a concentric lamellar appearance. In non-malignant variants these structures are found more frequently, and, statistically, their presence is a favourable prognostic factor (1,22).

Sarcomatous characteristics, including a high mitotic rate, are only present in a minority of small intestinal GISTs, and pleomorphic patterns are rarely seen, despite the usually malignant course of the disease. Similar to duodenal GISTs,

small intestinal GISTs with an epithelioid pattern (5%) most likely characterize a morphological manifestation of tumour progression rather than a separate histological entity, the latter being the case with gastric GISTs. They differ both clinically and morphologically from each other. Almost all small intestinal GISTs are KIT positive (1).

**Colonic GIST**

GISTs arising in the colon roughly make up 1 to 2% of all GISTs. They can be found in every part of the colon, even if they appear to be more common on its left site (1).

*Tworek et al.* conducted a study of 20 cases of colonic GISTs. The patients were divided into two groups; one with metastasis and one without. It has been found, that the most significant adverse prognostic factors are mitotic count and invasion of the muscularis propria (17). However, other *Miettinen et al.* could not confirm the prognostic significance of the muscularis propria invasion in larger study of 44 cases (18). On the other hand, they did confirm that a separation into an unfavourable and a favourable group based on the mitotic count is reasonable (1,18). Only 2 of 11 patients with a mitotic count ≤5 per 50HPFs died, and both of these had a tumour size over 5cm (18). Tumours with low mitotic count (smaller than 5 per 50HPFs) tend to have a spindle cell pattern. Additionally, they are KIT positive and contain skenoid fibres in roughly half of the cases, similar to duodenal and small intestinal GISTs. Furthermore, these tumours frequently show an invasion of muscularis propria, but, as mentioned above, this circumstance is not associated with higher mortality rate (1). A mitotic count higher than 5 per 50HPFs is often found in explicitly sarcomatous tumours. These often show a mitotic count as high as 100 per 50HPFs, as well as infrequent skenoid fibres and variable histological features, regarding spindle cell, epithelioid, and pleomorphic cellular morphology. Macroscopically, they present themselves as large (over 10cm in diameter), fungating lesions. They are scarcely smaller than 5cm. Tumour related mortality is over 80% (1).

Positive for KIT were 19 out of 25 tumours (75%) in the study on 44 cases of colonic GISTs (18). However, the question is raised if the tumours which have been tested negative for KIT represent true GISTs. Subsequently, these KIT negative tumours show no mutations in PDGFRA or KIT, thus being unrelated to

GISTs. In conclusion, colonic GISTs are thought to be KIT positive just as frequently as other GISTs (1).

**Appendiceal GISTs**

These are very rare, with a relative frequency about 0,2%. They are similar to small intestinal and colonic GISTs, histologically. Appendiceal GISTs are spindle cell tumours, with low mitotic count and commonly contain skenoid fibres (1). A study on four cases by *Miettinen et al*. suggests that appendiceal GISTs are small, KIT positive, and incidental tumours (19).

**Rectal GIST**

It is estimated that rectal GISTs represent between 4 and 5% of all GISTs (1,20). As with other GISTs, they range from small, incidental tumours to sarcomas. Similar to gastric GISTs, rectal GISTs may have a hyalinised-calcified or palisading nuclear appearance, but commonly lack the perinuclear vacuolisation. Malignant variants sometimes possess a fascicular pattern, as seen in leiomyosarcomas. As the epithelioid gastric GISTs, rectal ones may be clinically indolent. However, epithelioid variants are rare in this location. Skenoid fibres, as seen in duodenal and small intestinal GISTs, do not appear in rectal GISTs. Rectal GISTs are frequently positive for KIT, and almost always CD 34 positive . On the other hand, expression of smooth muscle actin, as well as desmin and S100 protein, is rarely seen (1).

It seems to be the case, that only tumours with both a mitotic count below 5 per 50HPFs and a size below 2cm have a negligible metastatic risk. For example, tumours with a size below 2cm, but with a higher mitotic activity (>5/50HPFs) have been found to have a metastatic rate of over 50% (1,20). These kind of small, yet mitotically active tumours are most commonly found in the rectum. However, they are exceptionally scarce in the stomach or small intestines (1).

**Extragastrointestinal GISTs**

There have been reports of primary GISTs occurring outside of the gastrointestinal tract. However, the relative frequency of this tumour is estimated to be very low, not exceeding 1% (1). Furthermore, most extragastrointestinal GISTs, as they are often referred to (23,24,25), are believed to be metastases of undetected

gastrointestinal ones (1,2). A study, which examined 200 GISTs, found no substantial cases of EGISTs in their consecutive series. Consequently, the concept of EGIST was critically discussed (26).

A fact that's contradicts the sole metastatic origin of EGISTs is the good prognosis they have. This is particularly true for certain omental and retroperitoneal EGISTs, as reported in the series by *Miettinen et al.* as well as *Reith et al.* An issue regarding to these is the relatively short follow up. No overall median follow up is mentioned in the first one, it is merely stated that longer follow up is needed (23) The other series has a median follow up of 24 months, ranging from 4 to 84 (24). A more recent study by *Miettinen et al.* on 95 cases of omental GIST shows an exceptionally better prognosis for solitary (median survival 129 months) versus multiple (median survival 8 months) omental lesions(27).

An explanation for the genesis of some EGISTs may be that the origination from the external muscle layer of either the stomach or the small intestine is not discovered in examination and thus remains unnoticed . Another possible pathway may be the loss of the primary connection of some GISTs to the gastrointestinal wall, and, in a parasitic way, get attached to neighbouring organs (1). *Miettinen el al.* consider these two theories, combined with the circumstance that parts of the small intestines reach out into the pelvis and the retroperitoneum (1), to be the best explanation for reported EGISTs in somewhat peculiar locations, such as rectovaginal septum (28), urinary bladder serosa (29), and uterus (30).

### 1.3.5 Risk assessment of GIST

With beginning of the 2000s, a new targeted therapy, imatinib mesylate (Gleevec; see below), was introduced. This tyrosine-kinase inhibitor has proven to be an effective therapy, even for metastasised and advanced GISTs. Consequently, this beforehand neglected disease raised considerable attention. Thus, the necessity to assess the imposed risk by a GIST was greater than ever before (6). Back at that time, two predictive factors have been proven to be the reliable. These are mitotic count, measured in the total number of mitoses per 50 high power fields ($5mm^2$) and maximum tumour diameter in cm (6,10,12). The first classification system, the NIH consensus classification, was published by *Fletcher et al.* in 2002 (see table 1) (6). In 2006 *Miettinen et al.* proposed another system (AFIP-Armed

Forces Institute of Pathology classification), which includes tumour site (see table 3) (1,31). They argued that the "consensus criteria" proposed by *Fletcher et al.* overestimate the malignant potential of gastric GISTs. As it is clearly shown in table 3, gastric GISTs are way less likely to metastasise or cause tumour related death. Furthermore, the "consensus criteria" are not based on specific series, which account for the different origins of GISTs regarding to anatomic location (1). The AFIP (Armed forces institute of Pathology) classification, on the other hand, is based on four specific series, including 1055 gastric (16), 629 small intestinal (22), 144 duodenal (21), and 111 rectal GISTs (20). This system has been adapted by the National Comprehensive Cancer Network (NCCN) (31). *Joensuu et al.* published another scheme in 2008, the main objective being able to identify patients who benefit the most from adjuvant therapy (see table 3) (9). The 7$^{th}$ edition of *TNM-classification of malignant tumours* by the American joined committee of cancer (AJCC), and the Union of international cancer control (UICC) included GISTs for the first time (see table 5.1, 5.2) (32). To predict the individual risk, *Gold et al.* developed a nomogram for recurrence free survival (see figure 3) (33).

**Table 2. Approach proposed by *Fletcher et al.* for defining risk of aggressive behaviour of GISTs** (6)

| | **Size** | **Mitotic Count** |
|---|---|---|
| **Very low risk** | <2cm | <5/50HPFs |
| **Low risk** | 2-5cm | <5/50HPFs |
| **Intermediate risk** | <5cm | 6-10/50HPFs |
| | 5-10cm | <5/50HPFs |
| **High risk** | >5cm | >5/50HPFs |
| | >10cm | Any mitotic rate |
| | Any size | >10/50HPFs |

**Table 3. Approach Proposed by *Miettinen et al.,* modified by NCCN, for Risk Stratification of Primary GIST by Mitotic Index, Size, and Site** (1,31)

| Tumour Parameters | | Risk for Progressive Disease*(%), Based on Site of Origin | | | |
|---|---|---|---|---|---|
| **Mitotic Rate** | **Size** | **Stomach** | **Jejunum/Ileum** | **Duodenum** | **Rectum** |
| **≤5/50HPFs** | ≤2cm | None (0%) | None (0%) | None (0%) | None (0%) |
| | >2≤5cm | Very low (1,9%) | Low (4,3%) | Low (8,3%) | Low (8,5%) |
| | >5cm≤10cm | Low (3,6%) | Moderate (24%) | Insufficient data | Insufficient data |
| | >10cm | Moderate (10%) | High (52%) | High (34%) | High (57%) |
| **>5/50HPFs** | ≤2cm | None× | High× | Insufficient data | High (54%) |
| | >2≤5cm | Moderate (16%) | High (73%) | High (50%) | High (52%) |
| | >5cm≤10cm | High (55%) | High (85%) | Insufficient data | Insufficient data |
| | >10cm | High (86%) | High (90%) | High (86%) | High (71%) |

***** Defined as metastasis or tumour-related death
× denotes small number of cases

**Table 4: Proposed modification by *Joensuu et al.* of Fletcher's classification for selecting patients with GISTs for adjuvant therapy** (9)

| Risk category | Tumour size (cm) | Mitotic index (per 50HPFs) | Primary tumour site |
|---|---|---|---|
| **Very low risk** | <2.0 | ≤5 | Any |
| **low risk** | 2,1-5,0 | ≤5 | Any |
| **intermediate risk** | 2,1-5,0 | >5 | Gastric |
| | 2,1-5,0 | 6-10 | Any |
| | 5,1-10 | ≤5 | Gastric |
| **high risk** | Any | Any | Tumour rupture |
| | >10 | Any | Any |
| | Any | >10 | Any |
| | >5 | >5 | Any |
| | 2,1-5,0 | >5 | Non-gastric |
| | 5,1-10,0 | ≤5 | Non-gastric |

| **Table 5.1: GIST - TNM staging system** (32) | |
|---|---|
| **T-Primary tumour** | |
| T0 | no signs of tumour |
| T1 | tumour ≤2cm |
| T2 | tumour >2cm ≤ 5cm |
| T3 | tumour >5cm≤10cm |
| T4 | tumour >10cm |
| **N - regional lymph nodes** | |
| Nx | lymph nodes cannot be evaluated |
| N0 | no spread to regional lymph nodes |
| N1 | regional lymph node metastases |
| **M - distant metastases** | |
| M0 | no distant metastases |
| M1 | distant metastases |

N: N1 is rare in GISTs (1%). Thus, if it is not possible to evaluate lymph node status, N0 may be assumed (32)

M: Extra-abdominal metastases are rare in GISTs (10%) (32)

| **Table 5.2. GIST - TNM histopathological grading system** (32) | | | | |
|---|---|---|---|---|
| **Gastric GIST** | **T** | **N** | **M** | **Mitotic count*** |
| Grade I | T1, T2 | N0 | M0 | low |
| Grade II | T3 | N0 | M0 | low |
| | T1 | N0 | M0 | high |
| Grade IIIA | T4 | N0 | M0 | low |
| Grade IIIB | T2, T3, T4 | N0 | M0 | high |
| | any | N1 | M0 | any |
| Grade IV | any | any | M1 | any |
| | | | | |
| **Small intestinal GIST** | | | | |
| Grade IA | T1, T2 | N0 | M0 | low |
| Grade IB | T3 | N0 | M0 | low |
| Grade II | T1, T2 | N0 | M0 | high |
| | T4 | N0 | M0 | low |
| Grade IIIA | T3 | N0 | M0 | high |
| Grade IIIB | T4 | N0 | M0 | high |
| Grade IV | any | N1 | M0 | any |
| | any | any | M1 | any |

* Low defined as ≤5/50HPFs; high defined as >6/50HPFs

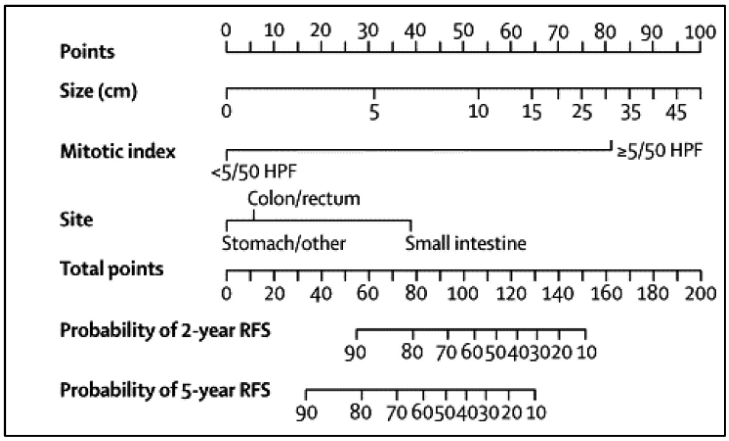


**Figure 3:** Nomogram for individual risk assessment by *Gold et al.* (33)

The ESMO (European society of medical oncology) guidelines do not recommend the use of the TNM system, as they see several limitations. Furthermore, they mention that mitotic count and tumour side are non-continuous, linear factors. Consequently, the authors propose a careful interpretation of the given thresholds (8). The Austrian GIST panel recommends the AFIP classification to be used as a standard. They suggest that the TNM system may be used complementarily in pathological reports, and the Gold nomogram to assess individual risk of relapse. In the case of local recurrence, they recommend to use the same classification system as the one used in the first place(4).

## 1.4 Diagnosis & staging

Up to two thirds of GIST patients suffer from nonspecific symptoms. Symptoms reported include abdominal pain (most frequent with about 50-70%), anaemia, dysphagia, dyspepsia, frequent urination, fatigue, gastrointestinal or abdominal cavity bleeding (2$^{nd}$ most frequent), nausea, and vomiting (2,4,32). In 25% up to one third of the cases, GISTs are found incidentally during endoscopic procedures, radiologic imaging, and other therapeutic procedures performed on behalf of other diseases (2,3,4): Around 5 % are found during autopsies (2). For proper diagnostics and staging, investigation of several tumour related parameters is essential. These include histological assessment, immunohistochemicall analysation, radiological assessment, and mutational analysation. For histological assessment, endoscopically retrieved biopsies are favoured over transcutaneous ones because of the risk of tumour cell dissemination (2,4). Endoscopic ultrasound (EUS), including a biopsy retrieved by fine needle aspiration is particularly useful because GISTs tend to leave the organs mucosa, which covers the luminal aspect of the tumour, intact. Thus, biopsies retrieved by standard endoscopy are often negative. Characteristic presentations of GISTs, in regard to EUS, include: hypoechoic lesions, possibly heterogeneous with small cystic or hyperechoic patterns, emerging from the tumour from the muscularis mucosa or muscularis propria (second and fourth layer on EUS), and reproducible margins to neighbouring organs (2,4). Mitotic count, as stated before, has been found to be the most important histological parameter (see 1.3.5).

Immunohistochemistry is essential to all GISTs diagnosis, especially because of the inhomogeneous nature of the GISTs and the broad diversity of differential diagnoses. Highly sensitive and specific diagnostic markers, and that for the most important ones, are KIT and ANO1 (DOG1) (see 1.3.2 for further reference) (1,4).
On behalf of radiological assessment and staging, computed tomography is well established as standard. MRI and PET may be used complementarily. Small tumours usually present themselves as dense, homogenous nodules (32). Standard radiological staging examinations regarding metastases are abdominal and chest CT. Positron emission tomography, using Fluorodeoxyglucose, is, apart from detection of metastases, important to verify a metabolic response to imatinib, which can be measured with PET within a few days (4). Although, limited availability and high costs make it impractical for standard use (32).
Mutational analysis is necessary to assign the patients to the correct therapy regimes, particularly regarding adjuvant or neoadjuvant treatment with imatinib mesylate. It has been shown that different mutations in KIT or PDGFRA respond differently to imatinib. For example, a tumour with a KIT mutation in exon 11 is associated with high imatinib sensitivity, while those with a mutation on exon 9 show a considerably lower sensitivity. An outstanding specimen is a PDGFRA mutation in exon 18 (D842V), which is resistant to imatinib (see 1.5 for further reference) (2,4,8,32).
All parameters taken together, in synopsis with the information of the classification systems listed in 1.3.5, are necessary to properly plan individual treatment.
The Austrian GIST panel recommends EUS for diagnosis and local staging with FNA for retrieving biopsies, where available. Excluding very low risk GISTs, an abdominal CT, including the pelvic region, is recommended as well. They state that mutational analysation is currently not crucial for diagnosis (4). The ESMO recommends core needle biopsies, either obtained by EUS or through a percutaneous ultrasound/computed tomography (CT)-guided procedure (8).

## 1.5 Therapy

The treatment of GISTs requires a multidisciplinary team to be properly performed. This involves pathologists, radiologists, surgeons, and medical oncologists, as well as gastroenterologists, nuclear medicine specialists, and others. Naturally, within reference centres for sarcomas and GISTs, or within reference networks who share multidisciplinary expertise and treating a high number of patients annually, are most suitable for such a complex assignment (8).

**Targeted therapy with tyrosine kinase inhibitors**

GIST have been reported to be resistant to chemotherapy, and there was no effective pharmacotherapy before imatinib mesylate was discovered (2,6).

Imatinib mesylate is a small molecule tyrosine kinase inhibitor, whose structure closely mimics ATP. It binds competitively to the ATP binding pockets of some tyrosine kinases, including KIT and PDGFRA, and thus preventing their signalling (3).

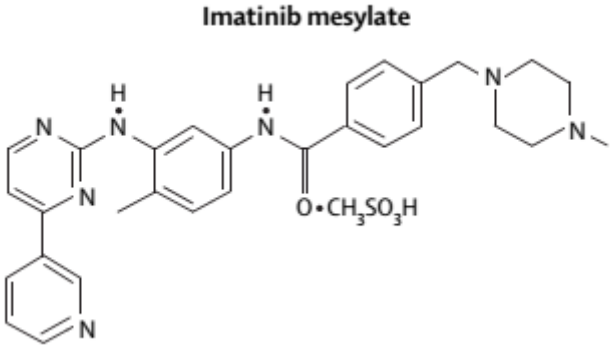


**Figure 4:** Chemical structure of imatinib mesylate (3).

Besides imatinib, other TKI are used in the therapy of GIST, especially in advanced and metastatic GIST (see below for further reference).

The introduction of tyrosine kinase inhibitors, imatinib in particular, has vastly improved the prognosis of GISTs. Before, the median overall survival of metastasised/ unresectable GIST was 10-20 months, after the introduction of TKI 51-57 months (2,32). The 10-year survival rate in palliative care is 22% (32).

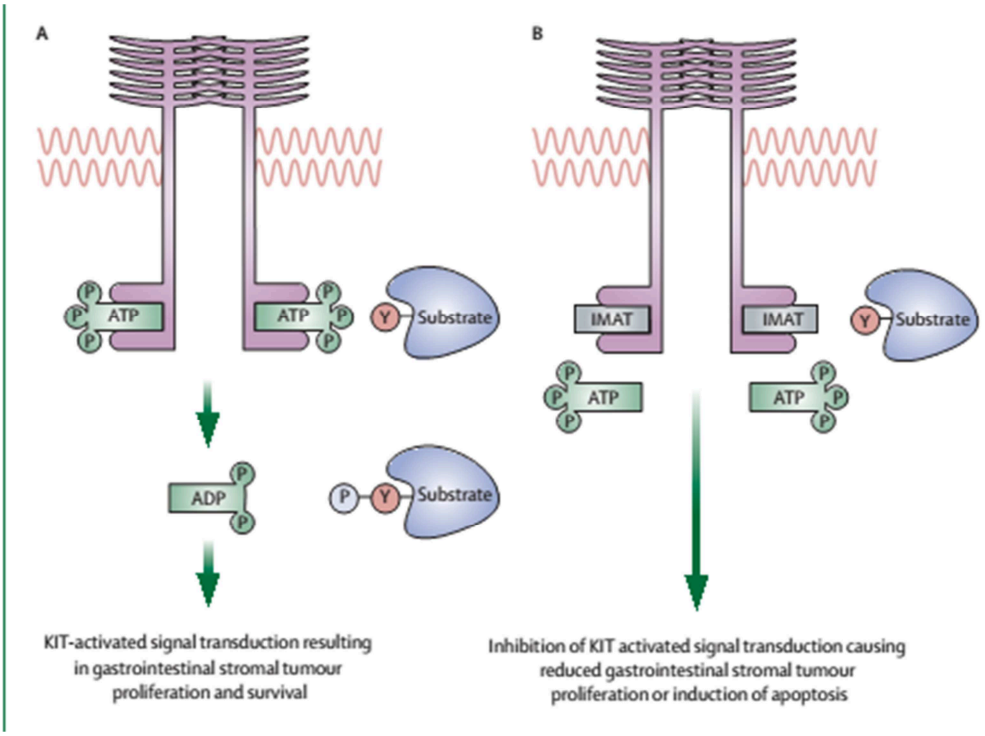


**Figure5:** Mechanism of action of imatinib mesylate (3).

## 1.5.1 Localised GIST

### Surgical treatment

GISTs, suspected or detected, which are larger than 2cm should be removed. Tumours with a diameter below 2cm may be excised or, by the “watchful waiting” approach revaluated endoscopically every 6-12 months, preferably by EUS (2,4). Main objective of surgical treatment is complete resection of the tumour with tumour-cell free resection margins (R0). Currently, this is the only curative therapy available (32). To achieve a microscopically tumour–cell free resection margin, a macroscopic margin of 1-2 cm could be sufficient (2). Generally, GISTs are soft and fragile with a thin pseudocapsule, which is prone to rupture if not handled with appropriate caution (2,4). Tumour rupture during surgery should be avoided at all cost, because tumour cell spillage is associated with a high risk of tumour recurrence, regardless of any other tumour parameters (2,4,9,32,35). The benefit of peritoneal lavage in case of tumour rupture is uncertain (4). Of course, preoperative tumour rupture is possible as well (35). If tumour rupture occurs, it should be recorded if it was before or during surgery (8).. As mentioned in 1.4 (see also table 5.1), lymph node metastases are very rare (<1%), and therefore

lymphadenectomy is not indicated, except they show macroscopic signs of tumour invasion (2,4,32).

Laparoscopic surgery is feasible with smaller gastric tumours (<5cm), if the procedure is carried out in a specialised centre, who routinely perform laparoscopic resections in the upper GI-tract (4). *Hohenberger et al.* describe intraoperative and postoperative complications in laparoscopic resected patients, being 6,8% and 7,7%, respectively. In 99% (n=473), negative resection margins were achieved (36). However, larger GISTs or those located in areas of the abdomen which are difficult to access laparoscopically, should be removed via laparotomy (4). Small bowel tumours are usually resected with a bowel segment (2).

Regarding R1 settings (resection margins contain tumour cells), literature is somewhat inconclusive. *Fuchs et al.* state, that R1 is associated with a poor prognosis without treatment. Consequently, they suggest to either perform re-resection or additive imatinib therapy (32). On the other hand, *Joensuu et al.* deem it unclear, if R1 affects the outcome negatively (2). Furthermore, *Bareck et al.* call R1 margins acceptable, especially with regard to low-risk GISTs (4). However, they see an indication for preoperative imatinib, if R0 cannot be achieved certainly (4). For further reference on neoadjuvant (preoperative) imatinib, see below.

**Outcome after surgery**

*Joensuu et al.* published an analysis from ten population based series and 2459 patients. They estimated the 5 year recurrence-free survival with surgery-only treatment to be 70,5%, the 15 year recurrence-free survival to be 59,9%. Furthermore, they found that only a few tumours recur after the first 10 years of follow-up. Thus, they estimate that around 60% of patients with operable GIST are cured with surgery (38).

**Adjuvant treatment**

Three randomised, controlled trials have been published on the adjuvant use of imatinib mesylate. *DeMatteo et al.*(ACOSOG Z9001 trial) analysed the recurrence-free survival of Patients with histologically verified (defined as KIT positivity), operable GISTs over 3cm after complete resection. From July 2002 to April 2007 713 patients were randomised to either 400mg imatinib daily (n=359) or placebo

(n=354) for one year. Accrual to the study was stopped in April 2007 because interim analysis crossed the efficacy boundary for recurrence-free survival. It was found that imatinib reduced recurrence rate significantly. 98% of patients in the imatinib group were recurrence free after 1 year, while in the placebo group 83% suffered no relapse (overall hazard ratio 0.35; one-sided p<0.0001). However, overall survival after 1 year was very similar with 99.2% and 99.7%, respectively (hazard ratio 0.66; p=0.47) (39).

*Joensuu et al.* (SSG XVIII trial) compared 12 vs. 36 months of 400mg imatinib daily after surgical removal of GIST. Inclusion criteria were either high risk (defined as: tumour size over 10cm, *or* mitotic count over 10/50HPFs, *or* tumour size over 5cm and mitotic count over 5/50HPFs) *or* tumour rupture. In total, 400 patients were randomised between February 2004 and September 2008. It was shown that patients assigned for 36 months of imatinib had longer recurrence free survival and overall survival compared with those assigned for 12 months. In the 36 months group 5-year RFS was 65,6% vs. 47,9% in the 12 month group (hazard ratio 0.46; 95% CI, 0.32-0.65; p<0,001). Overall survival, specified as 5-year survival was 92.0% and 81.7%, respectively, has been found to be better as well (hazard ratio 0.45; 95% CI, 0.22-0.89; P=0,02). Median follow up was 54 months (inter-quartile range 41-66 months) (40).

*Casali et al.* compared imatinib failure-free survival (IFFS) between 24 months of 400mg imatinib daily with observation only. At first, overall survival was chosen as primary end point. Although, at a planned interim analysis in March 2009, it was shown that due to likely overall duration of the trial overall survival as primary end point was not viable. Therefore, IFFS was selected instead. Furthermore, the authors argue that IFFS is more sensitive in regard to imatinib resistance, which is seen as the main adverse prognostic factor in advanced GISTs. Between December 2004 and October 2008, at total of 904 patients underwent randomisation. In the imatinib arm, results showed a 5-year IFFS of 87% versus 84% IFFS in the control arm (hazard ratio, 0.79; 98.5% CI, 0.50 to 1.25; P=0,21). Recurrence free survival was 84% and 66% at 3 years, at 5 years 69% and 63%, respectively (log-rank P<.001). Overall survival at 5-year was 91.8% and 92.7%, respectively. Median follow-up was 4.7 years ((inter-quartile range 4.0 to 5.3 years) (41).

All three studies show either a significant benefit in recurrence free survival for adjuvant use of imatinib over no imatinib, or, with the findings of the SSG XVIII trial, show a clear advantage for 3 years adjuvant treatment over 1 year. Therefore, 3 years adjuvant treatment is standard for GISTs with higher risk of relapse (*moderate* and *high* risk according the AFIP criteria; see above) (2,32,42). However, as pointed out by *Serrano et al.*, the difference in recurrence free survival appears to be more significant during imatinib treatment and shortly thereafter. This is shown in the increase of relapse 6-12 months after the completion of adjuvant treatment. Consequently, the question is raised if adjuvant treatment with imatinib prevents relapse or merely postpones it. Thus, they argue that future studies should emphasise on this matter (42).
In conclusion, the beneficial effect of imatinib in an adjuvant setting is considered proven. This data given, the standard adjuvant therapy regimen is 400mg imatinib daily for 3 years (32).

**Adverse events and toxicity**

In all three studies, adverse events and toxicity of imatinib were analysed. *Joensuu et al* used the *National Cancer Institute Common Toxicity Criteria* version 2.0, while the other two used the *Common Terminology Criteria for Adverse Events* version 3.0.
In the imatinib arm of the series of *DeMatteo et al.* a dose reduction and/or therapy interruption due to adverse events occurred in 14.5% (n=52) of patients. Furthermore, almost all the patients suffered from at least one adverse event. Grade 1 and 2 events affected 68.0% (n=229) of patients on the imatinib arm, and mostly involved gastrointestinal effects (mild diarrhoea, nausea, and flatulence), headache, rash, periorbital or peripheral oedema, fatigue, or myalgia/arthralgia. 30.9% (n=104) of patients on the imatinib arm suffered from Grade 3 and 4 adverse events, including abdominal pain, diarrhoea, and dermatitis. It has to be noted that the patients in the placebo arm suffered from adverse events as well. Grade 1 and 2 adverse events occurred in 72.8% (n=251) of patients, while Grade 3 or 4 events occurred in 18.3% (n=63) (39).
*Joensuu et al.* reported that a larger percentage of patients discontinued imatinib treatment in the 36-month group for reasons other than GIST recurrence compared with the 12-month group, namely 25,8% (n=51) and 12,6% (n=25),

respectively. Adverse events lead to treatment discontinuation in 13,6% (n=27) in the 36-month group and in 7,5%(n=15) in the 12-month group. Other reasons named for treatment discontinuation are patient preference, tumour histology not GIST, and other or unspecified reasons. Similar to the series of *DeMatteo et al.*, almost all study patients had at least 1 adverse event recorded; most of them graded as mild in severity. Grade 3 or 4 adverse events occurred in 32.8% (n=65) of patients in the 36-month group and 20.1% (n=39) patients assigned to the 36-month and 12-month groups, respectively. Frequently reported adverse events in this series were anaemia, periorbital oedema, and diarrhoea, among others (40).
*Casali et al.* had a drop-out of 12,5% (n=56) because of toxicity. They categorized Grade 3 and 4 toxicities, which occurred in more than 2,5% of patients in the imatinib group as "main toxicities". These are neutropenia (6.2% of patients affected in the imatinib arm), weight loss or gain (3.3%), infections (3.1%), and ALT increase (2.8%) (41).

In summary, imatinib was deemed well tolerable and with a low incidence of severe side effects (39,40).

For further information on the *National Cancer Institute Common Toxicity Criteria* version 2.0, and the *Common Terminology Criteria for Adverse Events* version 3.0, see the respective websites named in References (43,44).

**Selection of patients for adjuvant treatment**

For patients with either a "moderate" or "high" risk GIST, adjuvant therapy should be considered (2). However, as mentioned in 1.4, mutational analysis is significant if imatinib therapy is considered, because the different mutations do respond differently to therapy. In regard to patients in the "moderate" (="intermediate") risk group, some authors argue that the decision, whether adjuvant therapy should administered or not, ought to be on an individual basis (4,8,32). The NCCN guidelines for "Soft Tissue Sarcoma" (version 2.2017) recommend adjuvant therapy for both risk groups (51). *Joensuu et al.* point out that the percentage of patients in these two risk categories may differ depending on what risk assessment system (see above) was used. With AFIP criteria, about 36% of patients with operable GIST have intermediate-risk tumours, and 22% have high-

risk GIST. Estimated 10-year recurrence-free survival is 46–80% and 9–25%, respectively. With the modified NIH criteria, fewer patients (14%) have intermediate-risk GIST and more patients (46%) have high-risk tumours, with 10-year recurrence-free survival of 87% and 36%, respectively. According to the authors, these findings suggest that with the modified NIH classification only patients in the high risk group should receive adjuvant imatinib, and therefore is suited best to identify those (38).

For wild type GIST, lacking KIT and PDGFRA mutations (see 1.3.2), adjuvant treatment with imatinib remains controversial (2,4,8). *Joensuu et al.* deem the evidence for a beneficial effect unconvincing (2), while *Fuchs et al.* state that this decision should be made in an individual basis (32).

**Neoadjuvant treatment**

Several studies have been published to assess the neoadjuvant use of imatinib, none of them were randomised, controlled clinical trials.

*Eisenberg et al.* published the first prospective phase 2 trial (RTOG 0132) that analysed preoperative imatinib therapy in 2009. Their objective was to assess the safety and efficacy of neoadjuvant imatinib (dose 600mg daily). Two groups were formed out of the 52 patients that were accrued to the study and deemed analysable. Group A (n=30) with primary GIST (tumour size >5cm) and Group B (n=22) with metastasized or recurrent GIST (tumour size >2cm). Imatinib was given for a median of 9.9 weeks before surgery. After surgery, imatinib therapy was maintained for 2 years. Therapy response was evaluated with RECIST guide lines (*Response Evaluation Criteria in Solid Tumors*) (52). Group A showed 7% partial, 83% stable, and 10% unknown response. Group B showed 4.5% partial and 91% stable response, while 4.5% showed progression. Two year progression free survival was 83% and 77%, respectively. Two year overall survival was estimated to be 93% for Group A, and 91% for Group B. They called both imatinib toxicity and surgical complications minimal, the latter being comparable with any series of patients with extensive abdominal surgery. Thus, they concluded that neoadjuvant imatinib therapy is feasible (46).

Another phase 2 trial by *McAuliffe et al.*, also published 2009, examined the pre- and postoperative safety and efficacy of imatinib. Therefore, they randomised 19 patients to 3, 5 or 7 days and administered 600mg imatinib daily. Response was

assessed by 18-fluorodeoxyglucose positron emission tomography (18FDG-PET), and dynamic computed tomography (DCT). Response rates measured were 69% and 71%, respectively. This is remarkable, considering the very short duration of preoperative therapy. After surgery, imatinib therapy was continued for 2 years. Median disease free survival was 46 months. In this series, tumour size was found to be a predictive parameter for recurrence. Again, it was deemed safe to administer imatinib prior to surgery (47).

*Hohenberger et al.* conducted a prospective trial for neoadjuvant imatinib with locally advanced, non-metastasised GIST. The distribution among locations in this study was: 5 oesophageal GISTs, 17 gastric GISTs, 2 duodenal, 3 small bowels, and 3 rectal GISTs. Yet again, the study was published in 2009. 36 patients with histologically verified GISTs were accrued. Patients were treated with 400mg of imatinib daily for a median duration of 11 months (range 2-31 months), and dose was adjusted to 800 mg of imatinib for 2 patients due to exon 9 mutation. Median tumour size shrank to 55 mm after treatment (median size before: 10,5cm; range 4-28cm). Out of six patients deemed inoperable before treatment 5 were deemed resectable after treatment, and in 21 out of 25 patients a less extensive surgical procedure was performed in comparison to recommendations by previous tumour boards. Consequently, authors argued that locally advanced GIST can be treated successfully with 400mg imatinib daily (800 mg in exon 9 mutations) before surgery, and that substantial tumour shrinkage makes radical, but organ preserving surgical procedures possible in the majority of examined cases (48).

In 2012, *Tielen et al.* published a retrospective analysed series, in which they examined progression-free and overall survival for 57 patients with locally advanced, non-metastasised GIST treated with preoperative imatinib and surgery. Surgery was performed after a median imatinib treatment of 8 months (range 1 to 55 months). Median tumour size before treatment was 12,2cm (range 5,2 to30 cm), and reduced to 6,2cm (range 1 to 20 cm) before surgery. No tumour perforation occurred and R0 resection was achieved in 84% of patients (n=48). 33 patients received adjuvant imatinib, and showed a non-significant trend to higher progressive free survival (p=0,11). Five-year progression free survival and overall survival were 77% and 88%, respectively. Similar to the authors cited above, it was concluded that imatinib in locally advanced GIST is feasible and enables a high complete resection rate without tumour rupture. Furthermore, the authors

consider the combination of imatinib and surgery in patients with locally advanced GIST to improve PFS and OS in comparison to historically reported, available series (49).

The so far largest series in this regard was published by *Rutkowski et al.* in 2013. In a pooled analysis they retrospectively investigated overall, disease free survival, and disease specific survival in 161 patients with locally advanced, non-metastasised GIST who received neoadjuvant imatinib. Median time on therapy was 40 weeks (range 6 to190 weeks). 80,1 % of patients (n=129) showed a documented response to neoadjuvant therapy and 18.6 % of patients (n=30) showed stable disease before surgery, while only two patients suffered progression under neoadjuvant therapy. Tumour resection thereafter was R0 in 83%. Five-year DSS and DFS rates were 95 and 65 %, respectively, while median OS was 104 months, and median DFS was not reached. 56 % of patients continued imatinib therapy after resection. 37 GIST recurrences were diagnosed, with only 5 local relapses. According to the authors, this analysis indicates excellent long-term results of combined therapy in locally advanced GISTs. Furthermore, they see indications for preoperative imatinib treatment in locally advanced tumours, which are not resectable without mutilating operation, and/or if negative resection margins around the organ of origin are difficult to obtain, and/or if function-sparing surgery and minimising the extent of surgical procedures is possible after tumour downsizing (50).

According to the ESMO guidelines neoadjuvant imatinib is standard if R0 resection is highly unlikely, or could be achieved through less extensive surgical procedure in the case of cytoreduction of the tumour. Furthermore, neoadjuvant therapy should be considered, if surgical conduct is believed to be safer after cytoreduction, for example by reducing the risk of bleeding and tumour rupture. Surgery should be performed at maximum point of tumour response, usually after 6 to 12 months of therapy (see below for further reference). Again, mutational analysis is of the essence because it helps to exclude less sensitive or resistant genotypes (see below for further reference). It is pointed out that data on behalf when to stop imatinib before surgery is scarce. However, they deem it safe to stop imatinib a few days or even 1 day before surgery, and that it may be resumed promptly after (8).

The NCCN guidelines for “Soft Tissue Sarcoma” (version 2.2017) recommend the use of neoadjuvant imatinib for GISTs deemed resectable if R0 resection would be associated with significant risk of morbidity. Before neoadjuvant imatinib is started, “base line” imaging is recommended, namely a CT and/or MRI of the abdomen and pelvis using contrast. Furthermore, chest imaging should be considered, either with CT or x-ray. Response should be assessed (see below for further reference), followed by surgery, if feasible.

However, the final statement of the NCCN guidelines in regard to neoadjuvant imatinib is that at the present time, with the data available, the decision whether a patient with primary resectable (or locally advanced or recurrent) GIST should be administered neoadjuvant imatinib or not should be taken individually (51).

**Response evaluation**

According to NCCN guidelines, evaluation of response is indicated every 8-12 weeks under tyrosine kinase inhibitor therapy (52). While most of the GISTs shrink under therapy, tumour shrinkage is not the only sign of response. Often, tumours show response by decreasing in density, even if the size itself remains unchanged or even increases due to haemorrhage or cystic changes (4). Thus, a mere increase in size is not always a sign of progression (4). Even the appearance of new lesions may be due to the fact that they became less dense (8). Inversely, an increase in density is often an indication for progression, even if the lesions size is unaffected (4). A typical radiological image in this regard is the “nodule within the mass” (4,8,32). Consequently, density measurement is just as essential is response assessment as tumour size (2,4,8).

Commonly used tools for measurement of response evaluation are the RECIST and modified RECIST criteria, and the Choi criteria, the latter being developed for metastatic GISTs (52,53,54). However, it is controversial which criteria should be used. *Bareck et al.* argue that the RECIST criteria are not always useful to assess response to pharmacotherapy, but are excellent to evaluate target lesions. They state that the Choi criteria (table 5) have greater practical value, but do not recommend to generally using them outside of clinical trials (4).The NCCN guidelines point out that experts have deemed the Choi criteria to be considerably better than the RECIST criteria. Although, they point out as well that Choi criteria are not broadly accepted and that it is unknown whether their use is feasible

outside of specialised centres (51). On the other hand, *Fuchs et al.* generally recommend the use of Choi criteria, because they see inaccuracies regarding to GISTs in the RECIST criteria (32).

**Table 6: Choi criteria**. (54)

| Response | Definition |
|---|---|
| Complete Remission (CR) | Disappearance of all lesions<br>No new lesions |
| Partial response (PR) | No new lesions<br>A decrease in size of ≥ 10% or a decrease in tumour<br>density (HU) ≥ 15% on CT<br>No new lesions<br>No obvious progression of non-measurable disease |
| Stable Disease (SD) | Does not meet the criteria for CR, PR, or PD<br>No symptomatic deterioration attributed to tumour<br>progression |
| Progression of Disease (PD) | An increase in tumour size of ≥ 10% and does not meet criteria of PR by tumour density (HU) on CT<br>New lesions<br>New intra-tumoural nodules or increase in the size of the existing intra-tumoural nodules |

### Imatinib resistance

Several mechanisms may be the cause for imatinib resistances. First, it may be due to the tumours genotype, thus the mutation that is present in the tumour. These are KIT mutations in exon 9, PDGFRA mutations in exon 18 (D842V), and also wild type GISTs, the latter usually found in syndrome related GISTs (2). Between 10 to 15% of patients are affected by these mutations (4).

Second, mutations acquired during treatment in KIT and PDGFRA may cause resistances: Secondary KIT mutations mostly occur in exons 13, 14, 17, and 18 (4).

Third, it has been found that pharmacokinetics vary significantly between patients. Thus, imatinib resistance may be due to low amounts of imatinib in tissue. Low plasma levels (<1100 µg/l) were associated with a shorter time to disease progression than higher plasma levels (2).

## 1.5.2 Advanced and metastasised GIST

**First line therapy**

First line therapy for advanced and metastatic GIST is imatinib. If the disease is progressive under standard dose, it may be increased to 600mg or 800mg daily. With this imatinib dose escalation stable disease may be achieved in about a third of patients, while 2% respond. Furthermore, of those who respond or have stable disease with 800mg of imatinib, little less than two thirds remain progression free for more than 2 years (2,55). Treatment is continued until the occurrence of intolerable toxicities or until disease progression, otherwise it is continued indefinitely (2,32,56). This is due to the findings of *LeCesne et al.*. In this open-label phase 3 trial patients with GIST without progression after 3 years of imatinib 400 mg/day were randomly assigned to continue or interrupt imatinib. The primary endpoint was progression-free survival. 434 patients were enrolled in this trial between May 27, 2002, and May 5, 2009. Between June 13, 2005, and May 30, 2007, 50 patients with non-progressive disease who had received 3 years of treatment with imatinib were randomly assigned to continue or interrupt their treatment, 25 patients in each group. By Dec 7, 2009, after a median follow-up of 35 months (95% CI 33-38) after random assignment, 2-year progression-free survival ) in the continuation group was 80% (95% CI 58-91 and in the interruption group ($p < 0{\cdot}0001$) 16% (5-33). They did not record differences in adverse events grade 3 or higher between the two groups. Thus, it was concluded that imatinib interruption after 3 years in responding patients results in a high risk of rapid progression in patients with advanced GIST. Therefore, they recommended not to interrupt imatinib treatment outside clinical trials, except the occurrence of intolerable toxicities (56).

**Second line therapy**

Standard therapy for advanced GIST progressing with 800mg of imatinib is sunitinib, an inhibitor of several tyrosine kinases including KIT, PDGFRs and VEGFRs (vascular endothelial growth factor receptors) (57).

In 2006 *Demetri et al.* published a randomised, double-blinded, placebo-controlled trial to assess safety and efficacy of sunitinib in patients with advanced GISTs who were resistant to previous imatinib treatment or suffered intolerable toxicities. The

primary endpoint was time to tumour progression. A total of 312 patients were randomised 2:1 to either 50mg of sunitinib (n=207) or placebo (n=105) given daily in 6-week cycles, with4 weeks on and 2 weeks off regime. The trial was conversed to open-label early when a planned interim analysis showed significantly longer time to tumour progression in the sunitinib arm, with a median time to tumour progression of 27,3 weeks (95% CI 16·0–32·1) and 6·4 weeks (4·4–10·0) in the placebo arm (hazard ratio 0·33; p<0·0001). They deemed the tolerability acceptable; the most common adverse events being fatigue, diarrhoea, skin discolouration, and nausea. In summary, they found a significant clinical benefit, including disease control and superior survival, with sunitinib compared with placebo (57).

A phase 2 trial by *George et al.* found that a continuous sunitinib therapy with 37,5mg daily was equally effective, but that tolerability was better (58). Thus, the continuous therapy regimen is an effective and safe alternative (4,32,51). Another randomised, double-blinded, placebo-controlled trial by *Demetri et al.* was published 2012. Design was similar to the other one published in 2006. 361 patients were randomised 2:1 to either sunitinib (n=243) or placebo (n=118). As expected by the authors due the crossover design, Conventional statistical analysis showed that overall survival converged in the sunitinib and placebo arms (median 72,7 versus 64,9 weeks; hazard ratio 0,876; P = 0,306). Estimated median overall survival for placebo was 39,0 weeks (hazard ratio 0.505, 95% CI, 0.262–1.134; P = 0.306). They concluded that the crossover design provided evidence of sunitinib clinical benefit based on prolonged time to progression during the double-blind phase of the trial. Furthermore, Long-term sunitinib treatment was tolerated without new adverse events occurring (59). In regard to adverse events, sunitinib shows a wider range of adverse events due to their wider spectrum of inhibition (32,42).

Notably, the genotype of GIST has a significant influence on the sunitinib response. *Heinrich et al.* published a phase I/II trial of sunitinib of patients with either metastatic, imatinib resistant GIST or intolerable toxicities. Tumour responses were assessed radiologically. KIT/PDGFRA mutational analysis was performed for 78 patients by using tumour specimens obtained before and after imatinib therapy. Clinical benefit (partial response or stable disease for more or at least 6 months) with sunitinib was observed for the three most common primary

GIST genotypes: KIT exon 9 (58%), KIT exon 11 (34%), and wild-type KIT/PDGFRA (56%). They found progression-free survival to be significantly longer for patients with primary KIT exon 9 mutations (P = 0,0005) or with a wild-type genotype (P = 0, 0356) than for those with KIT exon 11 mutations. The same pattern was observed for overall survival, and progression free survival and overall survival were longer for patients with secondary KIT exon 13 or 14 mutations (which involve the KIT-ATP binding pocket) than for those with secondary exon 17 or 18 mutations (which involve the KIT activation loop). Accordingly, they concluded that clinical activity of sunitinib after imatinib failure is significantly influenced by both primary and secondary mutations in the predominant pathogenic kinases (60).

**Third line therapy**

If both imatinib and sunitinib fail or are intolerable, regorafenib is the standard third line therapy, based on the findings of the GRID trial (32,42). This randomised, placebo-controlled phase 3 trial, published by *Demetri et al.* in 2013, aimed at evaluating the safety and efficacy of regorafenib after failure of imatinib and sunitinib in metastasised or unresectable GISTs. Patients were randomised in a 2:1 ratio to receive oral regorafenib 160 mg daily or placebo, plus best supportive care in both groups, for the first 3 weeks of each 4 week cycle. The trials primary endpoint was progression-free survival. At disease progression, patients assigned to the placebo arm were allowed to crossover to open-label regorafenib. From January 4$^{th}$ to August 18$^{th}$ 2011 199 patients were randomised to receive regorafenib (n=133) or matching placebo (n=66). Cut-off date was January 26$^{th}$ 2012. Median progression free survival was 4,8 months (inter-quartile range 1,4 to 9,2) in the regorafenib arm and 0,9 months (inter-quartile range 0,9 to 1,8) in the placebo arm (hazard ratio 0,27, 95% CI 0,19 to 0,39; p<0·0001). After progression, 56 patients (85%) randomised to the placebo arm crossed over to the regorafenib arm. Adverse events were reported in 98% (n=130) of patients assigned to the regorafenib arm and 68% (n=45) of patients assigned to the placebo arm. The most common regorafenib-related adverse events of grade 3 or higher were hypertension (31 of 132 patients; 23%), hand-foot skin reaction (26 of 132 patients; 20%), and diarrhoea (7 of 132 patients; 5%). The authors concluded that the results of the trial show that oral regorafenib can provide a significant benefit in

progression free survival compared with placebo in patients with metastatic GIST after progression on standard treatments (61).
For patients with unresectable, metastatic GIST regorafenib is the only treatment that is evidently beneficial. Otherwise, treatment options are limited (42).

**Imatinib rechallenge**

*Kang et al.* conducted a prospective, randomised, double-blind trial to assess the efficacy of imatinib rechallenge in patients with metastatic and/or unresectable GISTs following objective progression of prior approved tyrosine kinase inhibitor therapy. The primary endpoint was progression-free survival. Between July 2010 and January 2013, 81 patients with prior benefit from first-line imatinib (initial response or stable disease for ≥6 months) and subsequent progression on at least imatinib and sunitinib were randomised 1:1 to either imatinib 400 mg/day (n=41) or placebo (n=40), both treatment arms received best supportive care. If disease was progressive, crossover to open-label imatinib was allowed. The median PFS was 1,8 months (95% CI, 1,7 to 3·6) with imatinib, compared with 0,9 months (95% CI, 0,9 to 1,7) with placebo (hazard ratio for progression or death 0,46; 95% CI, 0,27 to 0,76; p=0,005) In the placebo arm, 93% of patients (n=37) crossed over to open-label imatinib after progression. The most common grade 3 or higher adverse events of imatinib re-challenge was anaemia (12 of 41 patients, 29%), fatigue (4 of 41 patients, 10%), and hyperbilirubinemia (t3 of 41 patients, 7%). In conclusion, the authors found imatinib rechallenge to significantly improve progressive free survival in GIST patients after disease progression on at least imatinib and sunitinib, showing that a certain population of tumour cell clones is still sensitive to imatinib (62).

**Other targeted therapies**

Even if the therapies above were proven to be effective, almost all metastasised GISTs become resistant to them at some point. Several other tyrosine kinase inhibitors have been tested for their efficacy. Unfortunately, data is either limited or the respective agents have been found to only have limited activity (42). Agents that have been tested include sorafenib, nilotinib, and mastinib, among others (32,42).

**Surgical treatment of advanced and metastasised GISTs**

A smaller tumour diameter is associated with better progression free survivals on imatinib therapy (63). Therefore, it might be assumed that reduction of tumour mass may prolong survival. However, no prospective, randomised trials have been published to assess surgical treatment of metastatic GIST.

A series published by *Raut et al.* in 2006 analysed 69 consecutive patients who underwent surgery for advanced GISTs while receiving kinase inhibitors. Patients were categorised in stable disease, limited disease progression, and generalised disease progression based on the extent of disease before surgery. Following surgical treatment, patients were categorised by surgical result in no evidence of disease, minimal residual disease, and bulky residual disease. It was shown that disease status before surgery was associated with surgical result (p<0;0001; median follow-up 14,6 months). After surgery, there was no evidence of disease in 78% of patients with stable disease, in 25% of patients with limited progression, and in 7% of patients and generalised progression, respectively. Bulky residual disease after surgery was present in 4% of the patients with stable disease, in 16% of patients with limited progression, and in 43% of patients with generalised progression. Twelve-month progression-free survival rate was 80% for patients with stable disease, 33% for patients with limited progression, and 0% for patients with generalised progression (p<0001). Twelve-month overall survival was 95%, 86%, and 0% for patients with stable disease, limited progression, and generalized progression (p<0,0001). Authors concluded, that patients with advanced GISTs categorised as stable disease or limited progression on kinase inhibitor therapy benefit from debulking surgery, while those with general progressive disease do not (64).

*DeMatteo et al.* published a series 40 patients with metastatic GIST who received tyrosine kinase inhibitors therapy, followed by surgical resection. Surgery was performed after a median of 15 months. Based on tumour growth, assessed by serial radiologic imaging, patients were categorized at the time of surgery in responsive disease (n=20), focal resistance (1 tumour growing; n=13), or multifocal resistance (more than 1 tumour growing; n=7). Median follow up was 15 months (range 6 to 46 months) after surgery. Thereafter, the patients with responsive disease had a 2-year progression-free survival of 61% and 2-year overall survival of 100%. In comparison, the patients with focal resistance had a

median time to progression of 12 months after surgery, with a 2-year overall survival of 36%. Patients with multifocal resistance progressed postoperatively at a median of 3 months, with a 1-year overall survival of 36%. This data given, the authors argue that selected patients with metastatic GIST who have responsive disease or focal resistance to tyrosine kinase inhibitor therapy may benefit from elective surgical resection. For patients suffering from multifocal resistance, they do not see a benefit.

*Mussi et al.* analysed 80 patients who were treated with surgery for metastatic GIST after imatinib therapy. Primary end points were progression-free survival (PFS) and disease-specific survival (DSS). Two groups were formed. Group A were those with surgery at best clinical response (n=49), group b those with surgery at focal progression (n = 31). Progressive free survival 2 years after surgery was 64,4% in group A, and 9.7% in group B ($p < 0.01$). For group A, median progression free survival was not reached; for group B it was 8 months. Median disease specific survival, measured from the time of imatinib onset, was not reached in either group. 5 year DSS was 82.9% in group A and 67.6% in group B ($p < 0,01$). For group B, multivariate analysis confirmed a significantly shorter PFS and DSS. Thus, the authors deem surgery for focal progressive lesions as a possible part of second-line and/or third line treatment in selected cases. Furthermore, they argue that surgery of residual disease upon best clinical response seems to be associated with a survival benefit, compared with historical controls in similar series treated with imatinib alone. Though, they point out that prospective randomized trials are needed to make definite recommendations (66).

Considering the findings above, the NCCN guidelines see a possible indication for surgery in metastatic GISTs if disease progression is limited and refractory to imatinib, or if a locally advanced or previously unresectable GIST shows a favourable response to imatinib, making resection feasible (51). Both ESMO and NCCN guidelines name imatinib as first line treatment in advanced and metastatic GIST (8,51).

**Non-surgical treatment of metastases**

Other interventional, non-surgical procedures may be considered when dealing with metastases, including radiofrequency ablation, embolisation, or chemoembolisation. Radiofrequency ablation is especially useful for liver metastases, if performed with curative intent, and may be even preferred to surgery due to reduced morbidity (4).

## 1.6 Follow-up care

Main objective of follow-up is to detect recurrences as early as possible. The most commonly used method is abdominal and pelvic computed tomography. Magnetic resonance imaging is called a valuable alternative, but is deemed limited in use due to higher costs and limited access. Of course, a substantial advantage of MRI is the lacking exposure to radiation (see below) (13).

As pointed out by *Joensuu et al.*, studies on follow-up for GISTs are few, and therefore the optimal schedule is not known (13). Additionally, guidelines diverge on their recommendations on follow-up. The ESMO guidelines acknowledge that the optimal schedule for follow up is unknown. For selection of a follow-up policy, established risk factors may be used. They give an example for a schedule for a high risk patient: Abdominal CT or MRI every 3 to 6 months for 3 years during adjuvant imatinib therapy, every 3 months after discontinuation of adjuvant therapy, followed by annual scans for further 5 years. Low-risk patients may be followed-up with an abdominal CT or MRI every 6 to 12 months for 5 years. Follow up for low risk tumours is not recommended (8).

The NCCN guidelines recommend, that every patient with completely resected, incompletely resected and metastatic GIST should be thoroughly physically examined and that the recent medical history should be discussed every 3 to 6 months. An abdominal/pelvic CT scan with contrast should be performed every 3 to 6 months for 3 to 5 years. Less frequent follow-up may be acceptable for very small tumours (<2cm) (51).

*Joensuu et al.* recommend that follow-up schedules should be strongly dependent on the risk of GIST recurrence. To estimate the risk of recurrence, they argue that

the commonly used risk assessment tools (modified NIH classification, AFIP classification; see 1.3.5) are better suited than tumour size alone. Thus, they strongly recommend using these. Furthermore, they point out that adjuvant imatinib changes the patterns of recurrence and decreases the risk of recurrence, and therefore should be taken into consideration upon planning the follow-up (13).

They provide an example for recommended follow- up protocols, which are based on the author's personal experience (table 7.1, table 7.2) (13).

**Table 7.1: Follow-up of GIST patients treated with surgery alone as recommended by *Joensuu et al.*** (13)

| **Risk assessment method** | | | **Follow-up recommendation** |
|---|---|---|---|
| **Modified NIH** (9) | **AFIP** (1,31) | **Prognostic heat maps** (38) | |
| very low risk | ≤2cm; ≤5 mitoses/50HPFs; any site mentioned | 0-10% | likely cured by surgery; No regular follow up |
| low risk | >2cm ≤5cm; ≤5 mitoses/50HPFs; any site mentioned | 0-10% | No follow-up; or abdominal/pelvic CT or MRI annually for 5 years |
| intermediate risk | >5cm ≤10cm; ≤5 mitoses/50HPFs; gastric and jejunal/ileal | 10-20% | Abdominal/pelvic CT or MRI annually for 5 years; first scan 6-8 months after surgery |
| high risk | all other | 30-100% | Abdominal/pelvic CT or MRI every 6 months for 5 years, then annually for further 5 years |

**Table 7.2: Follow-up of GIST patients treated with surgery and adjuvant imatinib as recommended by *Joensuu et al.*** (13)

| **Risk group** | **During adjuvant imatinib (3 years)** | **After discontinuation of adjuvant imatinib (2 years)** | **Remainder of follow-up (approximately 10 years from imatinib initiation)** |
|---|---|---|---|
| High risk | Abdominal/pelvic CT or MRI every 6 months | Abdominal/pelvic CT or MRI every 3-4 months | Abdominal/pelvic CT every 6-12 months |

The authors mention that high risk patients should be treated with adjuvant imatinib, and that the high risk group in table 7.1 refers to patients whose GIST is insensitive to imatinib ( see 1.5.1 for further reference) (13).

It has to be considered, that if all performed follow-up imaging procedures would be computed topographies', total radiation exposure would be substantial, taken into account that one abdominal CT's average radiation dose is approximately 8mSv (=Sievert, the SI unit of equivalent absorbed radiation dose) (67). In comparison, for Austria the annual dose of radiation is 4,3mSv, of which 1,3mSv are due to medical radiation exposure (68). ). Thus, a single abdominal CT imposes almost the same radiation dose as approximately 3 years of non-medical-related radiation. Consequently, the risk of radiation exposure should be weighed against the risk of progression of disease. Of course, as pointed out by *Joensuu et al.* risk of radiation exposure seems acceptable if compared to metastatic GIST (13).

# 2 Retrospective analysis of 66 upper gastrointestinal GIST cases

## 2.1. Background and aims

Generally spoken, diagnosis, therapy, and prognosis of GISTs have improved substantially since the beginning of the 2000s. However, as seen in the literature review before, there are subjects that need further investigation. In particular these are the neoadjuvant use of imatinib, the surgical treatment of advanced and metastasised GISTs, and the follow-up care. Thus, we retrospectively analysed upper gastrointestinal GIST cases at our department. We compared our results to results, recommendations, and guidelines given in the literature above. In particular, we tried to make conclusions with regard to follow-up care.

## 2.2. Methods

We retrospectively analysed 66 patients who were treated for upper gastrointestinal GIST at the department of surgery, division of general surgery, Medical University of Graz between 1997 and 2016. Inclusion criteria were operable GIST of the upper GI-tract.

## 2.3. Results

**Patient characteristics**

38 (57,6%) of the 66 analysed patients were male and 28 (42,4%) female, with a median age of 63 years (range 11 to 74) at the time of surgery. 1 patient in our cohort suffers from Carney's triad, and 2 from Carney-Stratakis syndrome.

39 patients (59,1%) showed no symptoms. Table 8 provides an overview of the recorded symptoms.

60 GISTs (90,9%) were located in the stomach, 3 (4,5%) in the oesophagus, and 3 (4,5%) in the duodenum. 53 (80,3%) patients had a gastroscopy shortly before they underwent surgery. Of those, 21 GISTs (31,8%) were correctly diagnosed with the pre-operative gastroscopy. 37 (56,1%) were diagnosed intraoperatively, and 8 (12,2%) were diagnosed by other means preoperatively.

**Surgery and tumour parameters**

The surgical procedures performed are shown in table 9. Resection was R0 in 57 cases (86,5%), R1 in 2 cases (3%), and R2 in 5 cases (7,5%), respectively. Intraoperative tumour rupture occurred in one case (1,5%), and in one case resection margin was not recorded (1,5%). All patients that were resected R2 had metastases at diagnosis. In only 2 cases lymph nodes with tumour invasion were found. Median tumour diameter was 4,1cm (range 0,8cm to 21,0cm) and arithmetic mean was 6,0cm (standard deviation 4,8). 38 tumours (57,6%) had a tumour diameter below 5cm. Mitotic count was <5 in 46 cases (69,7%) and >5 in 19 cases (28,8%). Of the latter, median mitotic count was 10 (range 6-25/50HPFs). Tumours were KIT positive in 89,4%. The histological subtype of the tumours showed a spindle cell pattern in 48 cases (72,7%), an epithelioid one in 12 cases (18,2%), and a mixed one in 4 cases (6,1%).

Two patients had a PDGFRA D842V mutation, one of which was a high risk tumour. Otherwise, mutational analysis was not recorded.

**Risk assessment**

For risk assessment the AFIP classification was used. Table 10 provides an overview of the relative and absolute frequency of our cohort. Table 11 shows risk groups in relation to respective tumour location.

**Imatinib therapy**

9 patients (13,6%) received adjuvant imatinib. Of those, 7 had a high risk tumour, one had a moderate risk tumour and one had a very low risk tumour (who was diagnosed with Carney's triad).

3 patients (4,5%) received neoadjuvant imatinib for 2, 6, and 22 months, respectively. All 3 had low risk tumours. One of those patients received imatinib after surgery for one year. 5 patients (7,5%) received imatinib after surgery because of disease progression.

**Metastases, recurrences, and follow-up**

5 patients (7,6%) had metastases at the time of diagnosis, but where deemed resectable and thus where included in our analysis. All those patients had liver metastases, one had additional peritoneal metastases. Of those, one patient who was diagnosed with Carney-Stratakis syndrome was administered neoadjuvant imatinib. Two other patients with metastatic disease received imatinib after surgery.

Patients were followed for a median of 61 months (inter-quartile range 30 to 101 months). 35 patients (53%) were followed up for more than 5 years. Follow-up was not standardised and planned individually for each patient. CT and MRI scans of the abdomen were performed, as well as gastroscopies.

A total of 10 patients (15,2%) showed disease progression after surgery. 4 (6,1%) of those had local recurrences and 7 (10,6%) metastatic recurrences. One of those patients was diagnosed with both local and metastatic recurrence. The median time to recurrence was 38,5 months (2 to 69 months). The 5 year recurrence free survival rate was 86,4%. A total of 13 patients (19,7%) died during follow-up.

Of the patients who suffered from a disease recurrence 3 had a moderate risk (n=9) (one of these was diagnosed with Carney-Stratakis syndrome), 6 had high

risk (n=14), and one had very low risk GIST (n=27), respectively. The latter was a local recurrence in a patient who was diagnosed with Carney's triad.

**Table 8: Recorded symptoms**

| Symptoms | Absolute frequency | Percentage |
|---|---|---|
| Unspecified abdominal discomfort | 1 | 1,5% |
| Feeling of fullness | 5 | 7,6% |
| Dysphagia | 6 | 9,1% |
| GI-Bleeding | 7 | 10,6% |
| Melaena | 3 | 4,5% |
| Anaemia | 5 | 7,6% |
| Total symptomatic | 27 | 40,9% |
| No symptoms | 39 | 59,1% |

**Table 9: Surgical procedures performed**

| Surgical procedures | Absolute frequency | Percentage |
|---|---|---|
| Wedge resection | 27 | 40,9% |
| Laparoscopic wedge resection | 8 | 12,1% |
| Billroth I | 1 | 1,5% |
| Laparoscopic Billroth I | 1 | 1,5% |
| Billroth II | 13 | 19,7% |
| Gastrectomy | 9 | 13,6% |
| Whipple's operation | 1 | 1,5% |
| Distal pancreatectomy + sleeve gastrectomy | 1 | 1,5% |
| Enucleation | 1 | 1,5% |
| Oesophagectomy | 1 | 1,5% |
| Resection of duodenal wall | 2 | 3,0% |
| Not recorded | 1 | 1,5% |

**Table 10: Risk assessment according to *Miettinen et al.***

| Risk group | Absolute frequency | Percentage |
|---|---|---|
| no risk | 5 | 7,6% |
| very low risk | 27 | 40,9% |
| low risk | 11 | 16,7% |
| moderate risk | 9 | 13,6% |
| high risk | 14 | 21,2% |

**Table 11: Risk in relation to tumour location**

| | Tumour location | | | |
|---|---|---|---|---|
| **Risk** | Oesophagus | Stomach | Duodenum | Total |
| no risk | 0 | 5 | 0 | 5 |
| very low risk | 1 | 26 | 0 | 27 |
| low risk | 1 | 8 | 2 | 11 |
| moderate risk | 0 | 9 | 0 | 9 |
| high risk | 1 | 12 | 1 | 14 |
| Total | 3 | 60 | 3 | 66 |

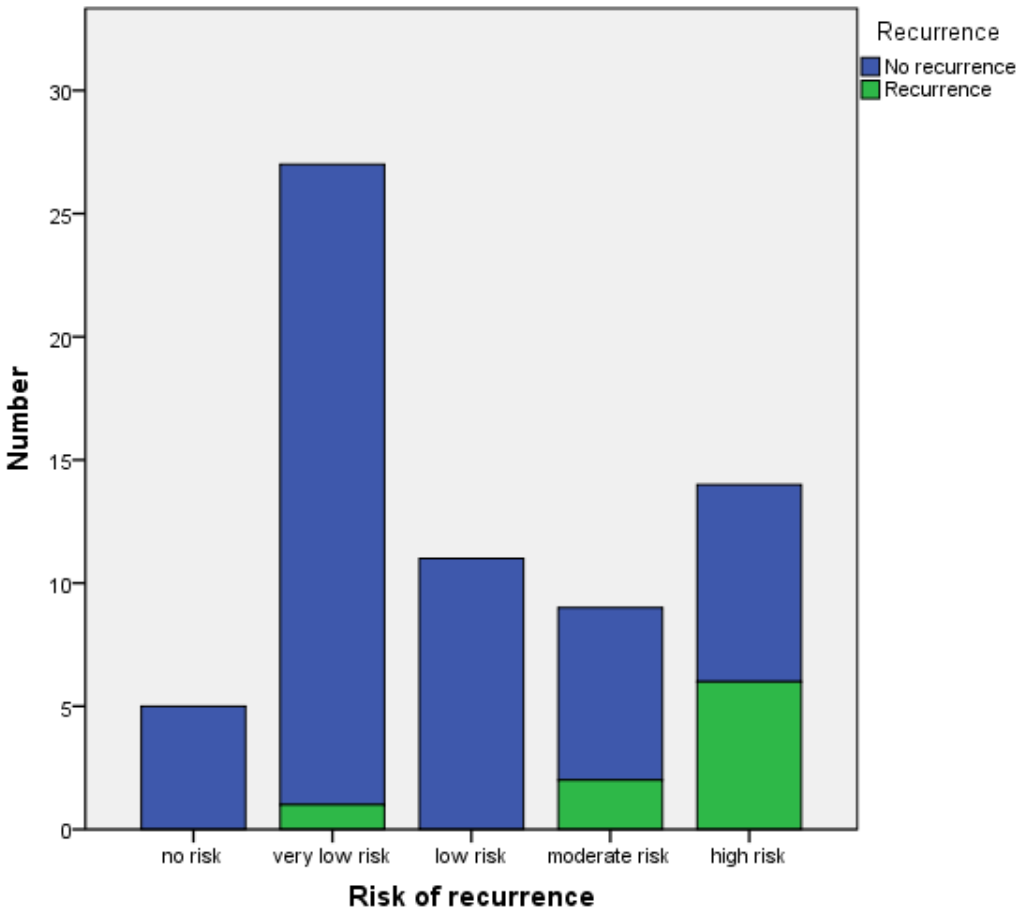


**Figure 6**: Number of Patients in respective risk groups with number of recurrences (percentage of recurrences: very low risk 3,70%; moderate risk 33,33%; high risk 42,85%)

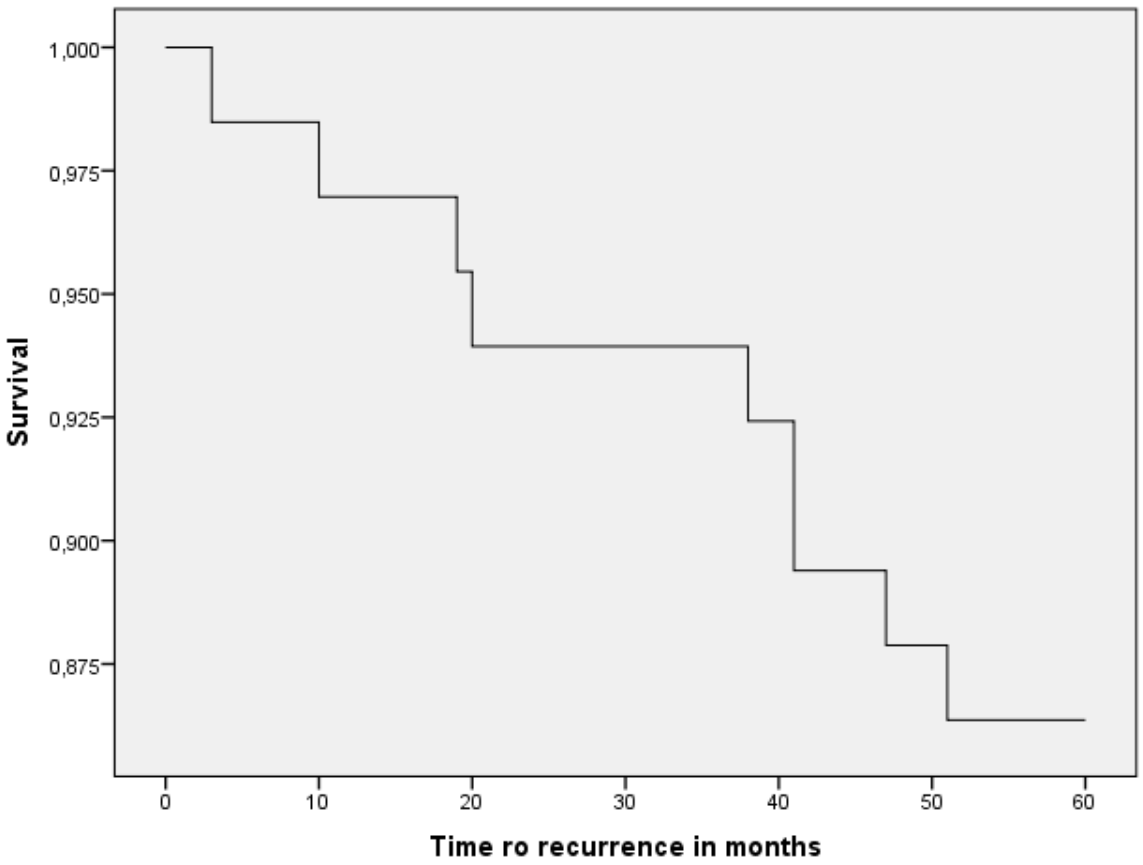


**Figure 7**: 5 year progression free survival

## 2.4. Discussion

Our series shows a light male predominance. As described in 1.3.4, gastric GISTs affect men more frequently than women, and almost all GISTs in our study are of gastric location. The median of 63 years age of affected patients in our series represents the information given in literature very well, being between 60 to 65 years (2,8).

Less than half of the patients who underwent gastroscopy preoperatively were correctly diagnosed. As mentioned in 1.4, this is due to the sub-epithelial growth pattern of most GISTs, which spares the overlaying mucosa of the organ, and as a consequence conventional biopsies often fail to obtain tumour tissue (2,4). Thus, gastroscopies are not the procedure to definitely diagnose GISTs. However, GISTs are often fund incidentally during gastroscopies due to their frequent use.

For only 27 cases (40,9%) symptoms were recorded in our series. In comparison, about two thirds of patients suffer from unspecific symptoms according to literature (see 1.4) (2,4,32). The cause for our lower percentage of symptomatic patients may be exactly this unspecific nature of GIST related symptoms, and were not acknowledged correctly. Another reason may be our relatively low case number or the fact that we only included patients that were deemed operable and thus had less distinct symptoms. Notably, our most frequent was bleeding, followed by dysphagia. These findings diverge from those in literature, where abdominal pain is named as the most common symptom (see 1.4) (2,4,32). Again, this is probably due to the size of our cohort and the unspecific nature of GIST related symptoms.

An absolute majority of tumours in our series is below 5cm in diameter, and over two thirds had a mitotic count below 5. Including respective tumour site, these parameters define the risk group (see 1.3.5). As shown in table 10, relative frequency of risk groups in our series was: no risk in 7,6%, very low risk in 40,9%, low risk in 16,7% moderate risk in 13,6%, and high risk in 21,2% of the cases, respectively. In comparison, percentage of risk groups with AFIP criteria is roughly 36% for intermediate-risk tumours and 22% for high-risk tumours (38). The lower percentages for these risk groups in our series is likely due to the fact that we only included GISTs of the upper GI-tract, and 90,9% were gastric GISTs, which have been found to have a less malignant potential than GISTs at other sites (1,2).

The relative frequencies of histological subtypes found in our series are similar to those found in literature. Those were 72,7% spindle cell, 18,2% epithelioid, and 6,1% mixed, compared to 70% spindle cell , 20% epithelioid, and 10% mixed pattern, respectively (4).

Most of the surgical procedures performed in our cohort are associated with rather low morbidity (wedge resection with 40,9% and laparoscopic wedge resection with 12,1%). In literature, laparoscopic resection of gastric GISTs is described as feasible with tumours smaller than 5cm, if performed at specialised centres (4). Despite the high percentage of gastric tumours smaller than 5cm in our cohort (54,6%), the number of laparoscopic wedge resection seems low. This is probably due to the fact that many procedures were performed before laparoscopic procedures were broadly established.

AFIP criteria show excellent correlation with our cohort in regard to risk of recurrence. Only taking the sporadic GISTs (non-syndrome related) into account, only two patients with moderate risk suffered a disease progression during follow-up, all other (6 cases) sporadic GISTs had a high risk for recurrence. Nevertheless, this shows the malignant potential that some intermediate risk GISTs are associated with, and thus justifies a more vigorous follow-up (see 1.6 and below).

Adjuvant imatinib was administered to 8 patients, who had high risk sporadic GIST. Guidelines recommend adjuvant imatinib for all patients with high risk GIST, excluding the occurrence of intolerable toxicities or imatinib resistant tumour (8,51). The latter was the case in one high risk GIST.As adverse events were not included in our analysis, no conclusion in this regard can be made.

Only 3 patients received neoadjuvant imatinib. As the NCCN guidelines recommend (51), neoadjuvant imatinib was given based on an individual decision.

In our series, the 5 year recurrence free survival rate was 86,4%. In comparison, the estimated 5 year recurrence-free survival with surgery-only treatment is 70,5%, according to a study by *Joensuu et al.* (38). Likely, the reason for this difference is because of the high percentage of gastric GISTs in our series.

Due to the limitations of our study, reasonable conclusions with regard to 10 and 15 year progression free and overall survival cannot be made.

As mentioned before, only patients with moderate and high risk sporadic GISTs showed recurrence of disease during our follow-up time (median 61 months).

Similar to the recommendations by *Joensuu et al.* (see 1.6, tables 7.1 and 7.2) (13), we suggest that patients with no risk, very low risk and low risk gastric tumours according to AFIP classification should not be followed-up on regular basis. For patients with intermediate and high risk tumours we suggest to use the follow-up schedule as recommended by *Joensuu et al* (see 1.6, tables 7.1 and 7.2) (13).

In conclusion, it is safe to state that the therapy, and with it the prognosis, of GIST has vastly improved in the past decade. Nevertheless, a great deal of further research is necessary, particularly in the fields of neoadjuvant treatment, surgical treatment of advanced and metastasised GISTs, as well as other targeted therapies, namely tyrosine kinase and multi-kinase inhibitors. Of course, best evidence is provided by prospective, randomised, controlled trials, which are difficult to conduct in these fields . With regard to follow-up, the schedule should be planned individually, and with as little exposure to radiation as reasonable.

Generally, the results of our series correlated well with information found in literature. The retrospective design and the relatively low case number may limit safe conclusions in our study.

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