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## Review

# Follow-up strategies for patients with gastrointestinal stromal tumour treated with or without adjuvant imatinib after surgery



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**Abstract Background:** Patients with gastrointestinal stromal tumour (GIST) are often followed up after surgery with longitudinally repeated imaging examinations to detect recurrence early. Studies on follow-up of GIST patients are few, the optimal follow-up methods are unknown and the recommendations for follow-up vary in guidelines.

**Methods:** We reviewed the current evidence for follow-up of patients treated with surgery alone and of patients who were treated with adjuvant or neoadjuvant imatinib.

**Results:** Imaging of the abdomen and the pelvis with computerised tomography (CT) or magnetic resonance imaging (MRI) usually suffices, since metastases are uncommon at other sites. The frequency of imaging may be adjusted with the risk of recurrence with time.

Very low risk GISTs are very frequently cured with surgery and usually require no regular follow-up after complete surgery, and annual CT of the abdomen and the pelvis for 5 years suffices for most patients with a low to intermediate risk for recurrence. Most high-risk patients are treated with imatinib for at least 3 years after surgery. CT or MRI may be carried out 6-monthly during adjuvant imatinib, 3 to 4-monthly during the 2 years that follow

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discontinuation of imatinib when the risk of recurrence is high, and then at 6–12 month intervals to complete 10 years of follow-up. Recurrence after the first 10 years of follow-up is infrequent.

**Conclusions:** The follow-up schedules are best tailored with the risk of recurrence. The risk of recurrence should be estimated with the prognostic tools that consider the most relevant prognostic factors.

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## 1. Introduction

Gastrointestinal stromal tumour (GIST) is by some estimates the most common single type of sarcoma [1]. GISTs arise at any site of the gastrointestinal tract, most frequently in the stomach [2]. Oesophageal GISTs are rare (<1% of all GISTs), and therefore almost all GISTs arise from a site located below the diaphragm [2]. Most GISTs (80–85%) are localised when detected [2,3], but they frequently give rise to metastases. Metastases usually arise in the liver and within the abdominal cavity, whereas pulmonary, bone, lymph node and brain metastases are uncommon. Mutations in *KIT* and *PDGFRA* are considered the driving molecular aberrations, but in 10–15% of GISTs both *KIT* and *PDGFRA* are wild type in gene sequencing ('wild type GISTs'). Mutations are often found in other genes than *KIT* and *PDGFRA* in these GISTs [4].

The standard treatment of localised GIST is its macroscopically complete removal whenever feasible. Preoperative imatinib may be given to shrink a large GIST to improve its operability and to spare normal tissues, in particular when GIST is located at a site where extensive resections of normal tissues would otherwise be required. Patients with a high risk for recurrence are treated after surgery with adjuvant imatinib. Imatinib reduces the risk of recurrence [5–7] and may improve survival [6] provided that GIST harbours an imatinib-sensitive mutation in *KIT* or *PDGFRA*. The standard duration of adjuvant imatinib is currently 3 years [6].

Approximately 60% of patients with operable GIST survive 10 or more years after surgery [8], and most GIST patients are subjected to clinical follow-up after surgery. Yet, the optimal procedures of follow-up are poorly defined, as prospective studies have not been conducted to investigate different follow-up schedules and methods, likely due to the rarity of GIST and the cost of such studies. In this article we review the key evidence concerning planning of follow-up strategies for GIST patients who have undergone surgery for GIST. To our knowledge, articles focusing on the follow-up strategies and their rationale in a patient population with operable GIST are not available in the literature.

## 2. Objectives of follow-up

An important question is whether patients who have undergone macroscopically complete surgery benefit from regular follow-up, or might repeat imaging examinations even be harmful due to the radiation hazard and other hazards involved, such as those associated with contrast agent administration. In the absence of randomised trials the answer remains unknown, but the trade-off between the benefits and the harms likely depends on the risk of recurrence, the frequency and the type of imaging examinations performed, and the potential benefits associated with early detection and treatment of recurrence.

GIST recurrence may be associated with abdominal pain, sudden or insidious bleeding leading to anaemia and fatigue, and changes in the bowel function. In the authors' experience, most recurrences detected during a scheduled follow-up programme consisting of longitudinally repeated computerised tomography (CT) examinations are either asymptomatic or minimally symptomatic, suggesting that follow-up schedules may spare the patient from symptoms related to bulky GIST metastases.

The most important consideration that favours regular follow-up is the potential for early detection of recurrence at a time when the tumour bulk is still small. Emergence of secondary *KIT* mutations leading to acquired drug resistance is very frequent in the treatment of advanced GIST, and drug resistance is the most important cause for treatment failure in the advanced disease setting [9]. Patients with a large tumour bulk at the time of imatinib initiation for advanced GIST have the shortest time to imatinib failure [10], suggesting that the risk of secondary mutations that confer drug resistance is a function of tumour mass, although the lead time bias is a confounding factor. Therefore, detection of recurrence early might prolong the time to drug resistance, which in turn might lead to achieving longer survival. However, there are few research data available to support this hypothesis.

## 3. Evaluation of the risk of recurrence after surgery

GIST patients have a widely variable risk for recurrence after surgery ranging from virtually no risk in

the patient population with GIST that is only a few millimetres in diameter to close to 100% in patients with ruptured GIST or large non-gastric GISTs with a high mitotic rate [8]. As the main purpose of follow-up is to detect recurrence early, the efficacy of follow-up schedules is likely the higher the better they are adjusted to the risk of GIST recurrence over time.

The most important prognostic factor for recurrence is tumour proliferation rate, which is often assessed by counting of the number of mitotic figures per 50 high power fields (HPFs) of the microscope, or by providing the number of mitotic figures per 1 mm<sup>2</sup> of tumour [8,11–13]. Although mitosis counting is subject to confounders, such as lack of reliable identification of mitoses, variations in the size of the field-of-view of the microscope, and the quality of tissue fixation, high mitotic counts are consistently associated with poor outcome in different studies [14]. Other factors that are frequently independently associated with a high risk of recurrence include non-gastric location of GIST, large size and tumour rupture [14,15].

Outcome of GIST patients is usually estimated with one of the prognosis stratification tools. Of these, the Armed Forces Institute of Pathology (AFIP) risk stratification [16], the modified National Institutes of Health scheme [2,14], and the prognostic heat maps [8] may be the most frequently used methods. All of these schemes consider tumour mitotic count, site and size and the modified National Institutes of Health (NIH) scheme and the prognostic heat maps consider also tumour rupture. All three tools are validated [8].

Whether GIST mutational data should be included in risk stratification is controversial. *KIT* exon 9 mutation or the mutations involving *KIT* exon 11 codons 557 and/or 558 are associated with a high risk of recurrence, and, on the other hand, *PDGFRA* mutation D842V with favourable outcome [17–21]. However, patients with an identical *KIT* or *PDGFRA* mutation may have widely different outcomes depending on the tumour mitotic rate suggesting that further genetic aberrations may influence the risk of recurrence more than the *KIT* or *PDGFRA* mutation [21]. Multigene panels based on gene expression or tumour DNA aberrations are promising prognostic tools [22]. In general, the standard prognostic factors are more important in the estimation of prognosis than the *KIT* or *PDGFRA* mutation type.

In sum, risk stratification tools should be consulted when the risk of recurrence after surgery is being evaluated. These schemes are better prognosis estimators than their single components, such as tumour size. Tools where the mitotic count and size are treated as continuous variables [8] are recommended when tumour mitotic count or size is equal or close to the cut-off value of a categorised prognostication tool, e.g. 5 mitotic counts/50 HPFs or 5.0 cm, since the estimated risk for recurrence often differs substantially between GISTs

that have mitotic count or size just above or below the cut-off value [14,16].

#### 4. Estimation of the risk of recurrence after adjuvant imatinib

The most reliable data for estimation of the risk of recurrence in a patient population treated with adjuvant imatinib comes from the analyses of the randomised trials that evaluated adjuvant imatinib in the treatment of operable GIST. The most important factors that predict recurrence after surgery and adjuvant therapy turned out to be largely the same factors that predict GIST recurrence after surgery only.

In an analysis of the SSGXVIII/AIO trial data [6] the factors that predicted GIST recurrence independently in a multivariable analysis were a high tumour mitotic count, a non-gastric site of origin, large size, presence of tumour rupture and administration of adjuvant imatinib for 12 months compared to 36 months [23]. A risk score constructed with these factors had a concordance index with GIST recurrence of 78.9% [23]. The score was validated in the ACOSOG Z9001 trial patient population treated with adjuvant imatinib for 12 months [23]. Similarly, in the ACOSOG Z9001 trial imatinib arm tumour size, location and mitotic rate independently predicted GIST recurrence in a multivariable model [24].

Adjuvant imatinib influences greatly the pattern of GIST recurrence in time. While the risk of recurrence after surgery is the highest during the 2 years that follow surgery and decreases gradually thereafter, the patients treated with adjuvant imatinib are at a relatively small risk at the time when they are on imatinib, but have a substantially increased risk during the few years that follow discontinuation of imatinib [6]. These data imply that imatinib often delays the risk of recurrence in patients who have undergone surgery for high-risk GIST.

The different patterns of GIST recurrence in time in patient populations treated with surgery only and those treated with surgery plus adjuvant imatinib argue for distinct follow-up schedules for these two populations to achieve early detection of recurrence while minimising radiation hazards. High-risk patients treated with adjuvant imatinib likely benefit from schedules where imaging is relatively sparse during adjuvant imatinib, but more frequent during the few years that follow imatinib discontinuation when the risk of recurrence is particularly high. An exception to this rule may be the patients who have high tumour mitotic counts (e.g. gastric GISTs with >50 mitoses or non-gastric GISTs with >20 mitoses/50 HPFs), since such tumours frequently recur during adjuvant imatinib [23]. To achieve the most favourable trade-offs between early detection of recurrence and keeping the cumulative radiation dose from

repeat CT scans low, a table for optimal spacing of the follow-up CT scans in time during and after adjuvant imatinib treatment was constructed [25].

## 5. Duration of follow-up

The most reliable information about the long-term outcome of GIST patients treated with surgery alone may be obtained from the population-based series with long follow-up available, although modern imaging and diagnostic improvements may have shortened the time to detection of recurrence. These data show that approximately 70% of all recurrences occur within the first 5 years, 90% within 10 years and about 95% within 15 years from surgery [8], while recurrence after 20 years of follow-up is rare [8,12,13]. Metastases from very low and low-risk GISTs are only rarely detected after the first 10 years of follow-up, although their generally low mitotic rate might suggest a long natural disease history [8].

These findings suggest that the benefits of imaging decreases with time, and may be of only limited value after the first 10 years of follow-up after surgery. The rare patients with syndromic GIST, including patients with SDH deficient GIST, may be exceptions, since these GISTs may progress very slowly and may be associated with other tumours, such as paragangliomas and adrenal adenomas, arguing for a more extended follow-up of such patients [2].

## 6. Follow-up methods

Nearly all GIST recurrences manifest as metastases in the abdominal cavity [26]. Metastasis outside of the abdomen without detectable progression within the abdominal cavity is so infrequent that presence of another malignancy should be suspected in such cases, and a tissue biopsy is recommended. For most GIST patients, longitudinal imaging of the abdomen and pelvis suffices for follow-up [27].

GIST patients are usually followed up with CT, performed with a contrast agent when feasible. Magnetic resonance imaging (MRI) is an alternative to CT especially in young patients to minimise radiation exposure, but MRI is more costly and access to MRI is generally more limited than to CT. The average effective radiation dose associated with one abdominal CT is approximately 8 mSv, which corresponds to the dose received from the natural background radiation over approximately 3 years [28]. Therefore, the radiation hazards from abdominal/pelvic CT scans appear justifiable compared with the life-threatening nature of bulky GIST recurrence.

Ultrasound examination of the abdomen is usually not optimal, since ultrasound waves do not traverse air, and metastases may remain undetectable. Young patients

with wild-type GIST may be an exception due to the high frequency of liver metastases in this patient population, to avoid ionising radiation, and as effective adjuvant therapy is unavailable for this patient population. However, paediatric, paediatric-type and syndromic GISTs not infrequently give rise to metastases in intra-abdominal lymph nodes [29,30] and other intra-abdominal sites that are not readily detected with ultrasound.

Other imaging examinations, such as positron-emission tomography (PET), PET-CT, Doppler ultrasound, or isotope scans have limited value in the follow-up, but they may provide further information in patients who have a lesion of an undefined nature in CT or MRI. PET is useful for assessing the metabolic activity of GIST lesions, and may be helpful when surgery is considered.

Most recurrences are detected at imaging, but not all, and, therefore, taking patient history and performing physical examination periodically are recommended especially in the patient population with high-risk GIST. There is no evidence to recommend any blood test for follow-up, although blood haemoglobin and cell counts, and serum liver transaminase and alkaline phosphatase concentrations are often measured.

## 7. Follow-up procedures in guidelines

Clinical practice guidelines provide some advice about GIST patient follow-up, but e.g. the National Comprehensive Cancer Network (NCCN) of the U.S. and the European Society for Clinical Oncology (ESMO) guidelines differ [31,32], and are mostly based on expert consensus opinions.

The NCCN guidelines recommend performing abdominal/pelvic CT with contrast every 3–6 months for 3–5 years after complete surgery for GIST, and then annually with the exception of patients with GIST <2 cm in diameter, who may have less frequent surveillance. The overall duration of surveillance is not defined, and might thus be interpreted to continue for the rest of the patient's life. The guidelines recommend discussing patient history and performing physical examination at 3–6 month intervals. The follow-up recommendations are similar for patients treated with surgery only and for those treated with preoperative and/or adjuvant imatinib [31].

The ESMO guidelines acknowledge that the optimal follow-up policy is unknown [32]. Risk assessment based on tumour mitotic count, size and site may be used for selection of the follow-up policy. The guidelines state that as an example, high-risk patients could be followed up with abdominal CT or MRI every 3–6 months for 3 years during adjuvant therapy, at 3-month intervals after stopping adjuvant therapy, and annually for further 5 years. Patients with low-risk GIST may be followed up with abdominal CT or MRI every 6–

12 months for 5 years. The ESMO guidelines do not recommend follow-up for very low-risk tumours.

## 8. Authors' recommendations

The authors consider follow-up potentially valuable for selected patients to achieve early detection of recurrence, despite the optimal method is unknown.

The follow-up strategy should be adjusted to the risk of GIST recurrence. The risk estimation tools, such as the modified NIH scheme, the AFIP scheme and the prognostic heat maps are likely more accurate than GIST size in the estimation of the risk of recurrence, and, therefore, the follow-up strategy should not be based on size alone. Adjuvant imatinib decreases the risk of recurrence and changes the pattern of recurrence in time, and, therefore, adjuvant imatinib administration and its duration need to be considered in the planning of follow-up. The mainstay of follow-up is abdominal/pelvic imaging, which is usually done with CT.

Examples of recommended follow-up schemes after surgery for localised GIST are shown in Table 1. The patients with the lowest risk are unlikely to benefit from longitudinal imaging, since they are usually cured by surgery.

For the purposes of patient follow-up, the intermediate risk group may be defined as in Table 1. Most intermediate risk patients are cured by surgery with most recurrences detected within the 5 years that follow surgery. The benefit of regular monitoring with CT or MRI may be small in this patient population.

High-risk patients are candidates for adjuvant imatinib with the exception of patients whose GIST

harbours a mutation that confers imatinib resistance (notably *PDGFRA* mutation at the codon D842), or is wild-type for *KIT* and *PDGFRA*. Since the risk of recurrence is relatively low during adjuvant imatinib but high after stopping imatinib, we suggest shorter imaging intervals of about 3–4 months during the time period of approximately 2 years following discontinuation of imatinib (Table 2). Patients with GIST that has a very high mitotic count [23] and those with *KIT* exon 9 mutation when treated with imatinib 400 mg/day have a higher risk for recurrence during adjuvant therapy, and we recommend that such patients have somewhat more frequent abdominal imaging despite being on imatinib.

Response to neoadjuvant imatinib requires careful monitoring. Tumour mutation analysis is recommended to identify *KIT* exon 9 mutations and imatinib-insensitive mutations. CT or MRI is recommended immediately before starting neoadjuvant treatment and approximately 4 weeks after the date of treatment initiation to assess response early. Comparison of tumour density (Hounsfield units) between the baseline and follow-up CT scans is recommended, since decreased density is usually compatible with response despite lacking shrinking in tumour size. PET or CT-PET may be more sensitive than CT alone in the response assessment. A decrease in the tumour fluorodeoxyglucose (FDG) uptake often occurs sooner (frequently within a few days) than tumour volume change [33]. Imatinib is often administered for approximately 4–6 months prior to surgery provided that the tumour responds, but the optimal durations are undefined. Imaging of the abdomen should be performed during this time period at approximately 2-month

Table 1  
Follow-up of gastrointestinal stromal tumour (GIST) patients treated with surgery alone.

Risk group	Recurrence risk evaluation method			Follow-up recommendation
	Modified National Institutes of Health (NIH) scheme [14]	Armed Forces Institute of Pathology (AFIP) scheme [16]	Prognostic heat maps [8]	
Very low risk	≤2.0 cm, ≤5 mitoses/50 high power fields (HPFs), any tumour site	Group 1	0–10%	Likely cured by surgery. No regular follow-up
Low risk	2.1–5.0 cm, ≤5 mitoses/50 HPFs, any tumour site	Group 2	0–10%	No follow-up; OR abdominal/pelvic computerised tomography (CT)/ magnetic resonance imaging (MRI) annually for approximately 5 years
Intermediate risk	≤2.0 cm, 6–10 mitoses/50 HPFs, gastric tumour OR 5.1–10.0 cm, ≤5 mitoses/50 HPFs, gastric tumour	Group 3a	10–20%	Abdominal/pelvic CT/MRI annually for approximately 5 years, the first scan approximately 6–8 months after surgery
High risk <sup>a</sup>	The rest of the patients; any patient with tumour rupture	Groups 3b, 4, 5, 6a, 6b	30–100%	Abdominal CT/MRI 6-monthly for the first 5 years, then annually for the next 5 years (the total duration of follow-up is 10 years after surgery)

<sup>a</sup> Patients with a high estimated risk for GIST recurrence should be treated with adjuvant imatinib, and they are recommended to be followed up as shown in Table 2. The recommendations shown in Table 1 apply only to high-risk patients whose GIST contains a mutation that confers imatinib resistance (notably *PDGFRA* exon 18 mutation D842V) or is wild-type for *KIT* and *PDGFRA*.

Table 2

Follow-up of gastrointestinal stromal tumour (GIST) patients treated with surgery and adjuvant imatinib.

Risk group	During adjuvant imatinib (currently administered for 3 years)	The 2 years that follow discontinuation of adjuvant imatinib <sup>a</sup>	The rest of the follow-up period (up to approximately 10 years from imatinib initiation)
High risk (30% to 100% risk)	Abdominal/pelvic computerised tomography (CT)/ magnetic resonance imaging (MRI) 6 monthly <sup>b</sup>	Abdominal/pelvic CT/MRI at 3–4 month intervals	Abdominal/pelvic CT at 6–12 month intervals

<sup>a</sup> Patients who discontinue adjuvant imatinib early due to intolerance are followed up as other patients who discontinue adjuvant imatinib.

<sup>b</sup> Patients with a high tumour mitotic count may require more frequent imaging while being treated with adjuvant imatinib (see text).

intervals, keeping the imaging technique the same whenever feasible. Patients treated with neoadjuvant imatinib usually have high-risk GIST and are treated with adjuvant imatinib after surgery, and may then be followed up as other high-risk patients (Table 2).

The clinical value of physical examination and blood tests appears limited. GIST recurrence is only rarely detected at physical examination when abdominal CT is normal, and no blood test has been found helpful in early detection of recurrence. Yet, periodic patient history and physical examination are likely worthwhile to carry out in the patient population with high-risk GIST. Most locoregional recurrences are detected early by CT, but gastroscopy or sigmoidoscopy performed a few months after surgery and potentially serially at later times may be indicated when only an R1 resection of oesophageal, gastric or rectal GIST was achieved at surgery, and in syndromic GIST to detect second primary GISTs or multifocal GIST.

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