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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.

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 *PDGFR*A 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 *PDGFR*A. 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

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