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Review Article

Surgical Approach for Metastatic Gastro-Intestinal Stromal Tumors (GIST)

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INTRODUCTION

GISTs are the most common mesenchymal tumors of the digestive tract. They usually originate in the stomach (60%), the small intestine, jejunum and ileum (30%), the duodenum (5%), the rectum (2 to 3%), the colon (1 to 2%) and the esophagus (less than 1%). They may also rarely present as disseminated tumors in extra visceral locations such as the omentum, the mesentery, the pelvis and the retroperitoneum, with no identified primary lesion[1,2].

GISTs are generally positive for CD 117 (c-kit), a tyrosine kinase receptor type III (TKR) encoded by activating mutations in KIT and PDGFRA genes[3]. KIT mutations are found in 60 to 85% of GISTs while PDGFRA mutations are found in 5 to 10%. However, in 10 to 15% of the cases, we do not detect any mutation in any of these two genes. These "wild type GISTs" suggest the involvement of other molecular routes in the pathogenesis of the tumor[4,5].

The mutations of PDGFRA exon 18 as well as KIT exon 11 substitutions are more likely to be seen in patients with localized GISTs, while KIT exon 9 and KIT exon 11 deletions are more frequent in metastatic GISTs[6].

At the time of diagnosis, GISTs could present as localized, locally advanced or metastatic disease. Each presentation has its own therapeutic indications. While surgery remains the gold standard in the first two, its place is not entirely clear in metastatic disease despite some of its benefits discussed in the following.

Surgery in localized and locally advanced GISTs

Complete surgical resection is the only curative mean for localized GISTs. It is recommended that all patients with GISTs bigger than 2 cm should have surgical resection. With a local recurrence rate of around 40%, Imatinib based adjuvant therapy is indicated for high-risk patients for at least three years to prevent any recurrence[7].

Locally advanced GISTs are considered borderline resectable due to their proximity of a vital structure, or to the fact that their surgical management requires multi-visceral resection or involves severe post-surgical morbidity. The aim of the treatment is to achieve R0 resection and to avoid tumor rupture, while preserving vital organs with a less invasive procedure. Imatinib based neoadjuvant therapy is recommended to obtain preoperative cytoreduction[7] Without surgery, locally advanced GIST prognosis is similar to the metastatic disease one.

Surgery in Metastatic GISTs

A multimodal approach

GISTs could present as low-risk lesions remaining stable for years or could progress rapidly to wide spread metastatic disease. They are frequently metastatic at the time of diagnosis. The metastases typically involve the liver and/or the peritoneum[8].

Before the era of Imatinib, there was no effective treatment for metastatic GISTs. In the absence of any alternative, surgeons usually attempted surgical resection especially as an emergency procedure for obstructive or hemorrhagic lesions. The outcomes were not satisfactory as the overall survival (OS) was 41% at 2 years and 25% at 5 years[9]. Advances in the understanding of GIST pathogenesis lead to the development of Imatinib, that changed the therapeutic approach to this pathology, including the metastatic disease. Verweij et al. showed that 50% of the patients with metastatic lesions had a measurable response to Imatinib, and that 75% will have at least a stable disease. Although the OS of these patients has increased due to the use of Imatinib, 50% will evolve to a progressive disease by 24 months, and less than 5% will experience complete remission[10].

Some authors stated the benefit of the combination of Imatinib and surgery as a multimodal approach in metastatic GISTs, as they noted improved progression-free survival (PFS) and OS compared to Imatinib alone. In fact, Park et al. compared the clinical outcomes of surgical resection of residual lesions after Imatinib treatment with Imatinib treatment alone in patients with

metastatic GISTs. PFS was significantly longer in the patients who underwent surgery (87.7 vs. 42.8 months)[11]. Another study conducted by Gao et al. gathered 318 patients with metastatic GISTs that were divided into 4 groups: 14% had surgery alone, 34% were treated with Imatinib alone, 44% had a combination of Imatinib and surgery, and 8% had other treatment options. PFS was the longest in both Imatinib alone (44 months) and combination of Imatinib and surgery (35 months), with no significant difference between the two of them (p=0.251). However, the group of patients who had the combination therapy showed a significantly longer OS (92 months), compared to the group who had Imatinib alone (69 months), the group who had surgery alone (24 months) and the group who had the other treatment options (12 months)[12].

In all, the multimodal approach that combines Imatinib and surgery in patients with metastatic GISTs could improve outcomes of the treatment by extending PFS and OS.

Surgery as an adjuvant to Imatinib

Systemic treatment with Imatinib is the mainstay of metastatic GIST. However, the development of secondary resistant clones may limit the response duration to this drug, leading to the introduction of second and third-line agents such as Sunitinib and Regoratinib.

It is well known that the larger the number of tumor cells exposed to Imatinib, the higher the chance of developing secondary resistant clones. Therefore, in order to increase the longevity of response to Imatinib and to delay the introduction of second line therapies, some authors suggested cytoreductive surgery as an adjuvant to Imatinib[13,14].

Surgery for metastatic GIST that have been downsized by Imatinib therapy has been reported with good results if the resection is done while the tumors are still under control, before drug resistance, and the therapy is maintained post-operatively. Several GIST surgeons advocate resection of metastatic GIST within one year of starting Imatinib therapy, for optimal outcomes[15].

Surgery and disease progression

There are three described possible evolutions of metastatic GISTs: Stable disease responsive to TKI therapy, progressive growth in isolated lesions within a generally responsive tumor and rapidly multifocal progressive disease. The last group is found in a minority of patients and has a relatively poor prognosis[16].

Raut et al. studied a group of patients with metastatic GISTs under Imatinib. They all had surgery. 33% had previous stable disease, 46% had limited progression and 21% had generalized progression. The group with a previously stable disease showed a PFS at 12 months post-surgery at 80%, while the other two groups showed no satisfactory outcomes (33%, and 0% respectively). After surgery, there was no evidence of disease in 78%, 25%, and 7% of patients with stable disease, limited progression, and generalized progression, respectively. Residual disease remained in 4%, 16%, and 43% of the patients in the respective groups. The authors concluded that surgery presents some benefits in patients with stable disease who respond to Imatinib especially when total macroscopic clearance can be achieved, which subsequently extends the efficacy of the drug[17]. A study conducted by Bauer et al. confirmed that a stable non-progressive disease associated with complete macroscopic resection (R0/R1) has a positive prognostic value, compared to R2 resections. It also shows that patients who underwent complete macroscopic resection are more likely to have a lower tumor load and consequently a better response to Imatinib[18].

When to operate

Bauer et al. have noticed poorer outcomes of the surgery in patients with prolonged Imatinib therapy prior to surgery, and concluded that the optimal timing to operate would be from 6 to 12 months following the introduction of the drug []. Furthermore, upfront surgery for metastatic GIST has shown no benefit compared with initial Imatinib treatment, and authors prefer avoiding it. In fact, initial Imatinib therapy helps select responsive patients and prevent unresponsive ones from unnecessary surgery[13,14].

Conclusion

While systemic treatment with Imatinib is still the gold standard for metastatic GISTs, additional surgery could add benefits in terms of OS and PFS and may even potentiate the TKI and increase the duration of its activity. It has been demonstrated that surgery should be considered only when macroscopic clearance can be achieved in patients with stable disease. Surgery could also be discussed in patients with limited progression but should not be offered in patients with generalized progression. Finally, for better outcomes, patients should be operated 6 to 12 months after the onset of Imatinib therapy, when possible, with a limited interruption of the Imatinib to avoid rapid rebound in tumor progression.

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