Management of advanced and/or metastatic GIST

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Historically, gastro-intestinal stromal tumors (GISTs) have been treated by the three traditional cancer therapeutic modalities: surgery, chemotherapy and radiotherapy. Surgery is effective for patients with localized resectable disease, but disease may recur in as many as 50% of individuals. Chemotherapy and radiotherapy have shown little efficacy [1-2]. Identification of KIT mutations led to the development of specific targeted therapies with tyrosine kinase inhibitors (TKIs). Therapy with the TKIs imatinib mesylate (STI571, Glivec; Novartis Pharmaceuticals, Basel, Switzerland) and sunitinib malate (SU11248, Sutent; Pfizer, Inc., New York, USA) is effective for unresectable, metastatic, and recurrent disease [3-4].

Patients with advanced and metastatic disease are therefore now treated with targeted TKIs. Application of the novel oral TKI imatinib mesylate for the treatment of GIST represented a major advance in therapy. Imatinib selectively inhibits several tyrosine kinases including KIT, PDGFRA, and ABL [5]. Its clinical potential was first illustrated in a Finnish patient with metastatic GIST who was treated with a daily dose of 400mg and demonstrated a rapid and sustained partial response (PR) [6]. A multicenter, phase II trial randomized 147 patients with advanced or metastatic KIT-positive GIST to receive 400 or 600 mg of imatinib daily [7]. PR or stable disease (SD) was noted in nearly 85% of patients. There were no significant differences in response rate or duration of response between the two dose levels. The 1-year OS for all patients was 88%, higher than any OS rate reported prior to imatinib with a median survival, which has now been reached, of 5 years. Concordant results were noted in a multicenter European trial [8]. These results were further confirmed by 2 larger trial, carried out in Europe [9] and US, addressing the issue of dosing. Optimal dose has been fixed at 400 mg daily, but specific mutations seem to benefit from a higher dose [10], though these results need to be confirmed in larger sample size.

The success of imatinib in the treatment of metastatic GIST has also changed the paradigm for the approach to locally advanced primary tumors. When, due to the size and location of the tumor, resection would require the risk of severe organ dysfunction or where negative margins would be difficult to achieve, it may be advisable to treat with imatinib first to downsize the tumor so as to make complete resection easier and safer to achieve (figure 1). Patients can be treated with imatinib until the optimal time for sur-
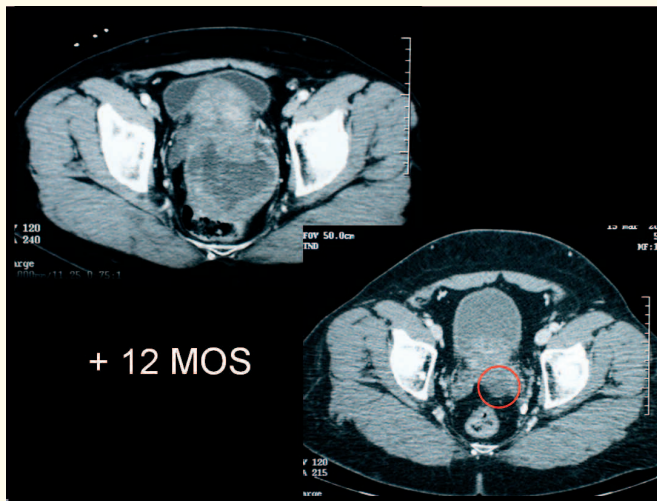
Figure 1 – **Initial rectal GIST and the remnant after 12 months of Imatinib**

Figure 2 – **Initial gastric GIST involving the whole stomach and dislodging the spleen and its remnant after 12 months of Imatinib, with a limited gastric involvement and uninvolved spleen**

gery (when the GIST becomes resectable and the chance of morbidity is acceptable), which can take as long as 6 to 12 months [11]. Maximal response could be defined as no further improvement between 2 successive CT scans. However, it is not always necessary to wait for a maximal response to perform surgery. Each new cross-sectional imaging of the patient should prompt multidisciplinary re-appraisal of the timing of surgery.

The rationale for neoadjuvant treatment of GIST is similar to that for many other tumors. Most GISTs will respond to imatinib. Resection of responsive tumors may be accomplished with less morbidity and sacrifice of adjacent organs (figure 2). Some tumors that are deemed unresectable may become resectable. Manipulation of smaller, treated tumors may result in less intraoperative dislodgement of viable tumor cells. Early treatment of distant micrometastatic disease may improve oncologic outcome. Last but not least, progression, particularly distant progression, of patients on neoadjuvant treatment may indicate the futility of surgery in these patients.

Furthermore there are tools, not available in other solid tumors, to predict the response to treatment, and allow to identify very early those patients who will benefit from the preoperative treatment and those who
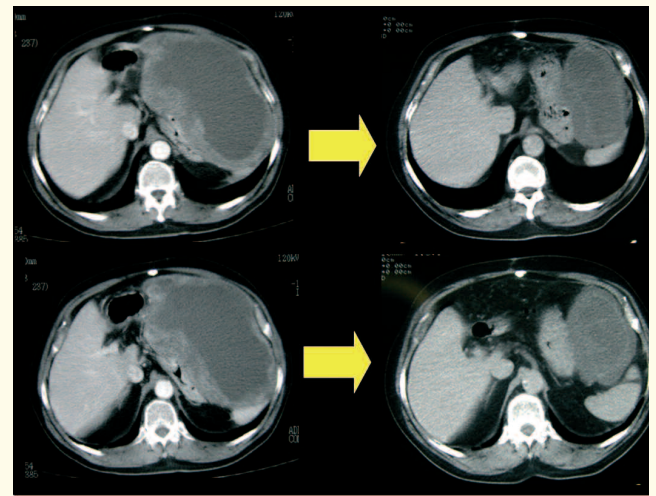
will not. These tools are molecular analysis and PET scan. Molecular testing can be performed even on small biopsies and allow the identification of the genetic profile of the tumor. This may help both in choosing the preoperative optimal dose of Imatinib and in excluding resistant mutations on kit receptor or PDGFRA and wild type GIST, which very unlikely will respond to the preoperative treatment. PET scan is also able to provide a reliable functional information on response. It's important to have a baseline PET, because 5% of GIST are PET negative and should be excluded by this approach. Once a baseline PET has been obtained and the preoperative treatment has been started, it's possible to know whether the treatment will be effective or not just by repeating the PET scan even 1-2 weeks later [12].

It's now therefore reasonable to consider the preoperative treatment with Imatinib in all bulky presentations and in all difficult sites, where a downsize of the tumor will allow a more conservative approach. Nevertheless we shall have to wait for the results of the 2 ongoing trials on preoperative Imatinib, one from the Radiation Therapy Oncology Group (S-0132), which has recently completed accrual, and one from Germany (CSTI571 BDE 43, the Apollon study), the accrual of which is still ongoing, in order to shed more

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light on the real impact of the preoperative treatment on surgical morbidity and local outcome.

In contrast, it should not be forgotten that the standard of care for resectable primary GIST is surgery alone. Whether any patient should receive adjuvant or neoadjuvant TKI therapy after resection of a localized primary GIST is being addressed by several ongoing randomized trials in Europe, United States and Scandinavia.

In recurrent or metastatic GIST surgery alone had limited efficacy, with reported median survival not exceeding one year in the era before TKIs [13].

Imatinib is therefore the standard treatment of metastatic disease.

The utility of surgery in patients with metastatic GIST treated with TKIs has not been clearly defined. Because the median time to recurrence on imatinib therapy is 2 years, surgery has been added to TKI therapy for selected patients with metastatic GIST in an effort to delay or prevent recurrence. However, it must be emphasized that the true benefit of the addition of surgery to TKI therapy in metastatic GIST has not yet been proven in a randomized clinical trial. Hypothetically, patients whose disease is rendered resectable on TKI treatment may achieve longer PFS by gross tumor resection before secondary resistance develops. Even in the setting of partial response or stable disease on TKIs, the residual tumors typically harbor viable cells; complete pathologic responses are rare (< 5%) [14]. Moreover the tumor burden has shown to have an impact on the time to progression on Imatinib therapy [15]. These observations support the rationale to operate on advanced disease that is responding to TKI therapy and is completely resectable. Imatinib can be given to patients up until the time of surgery; imatinib can be restarted when the patient can start oral intake.

The first large study to report survival rates after resection of advanced GIST following TKI therapy came from Dana-Farber and detailed the results of surgery in patients with advanced GIST on TKI therapy [16]. Outcomes of surgery and survival rates correlated with response to TKIs. Three clinical categories of disease response to TKIs were defined. *Stable* disease was defined as disease that was radiographically stable or responding to drug therapy and all sites of disease progression could be resected. *Limited (localized)* disease progression was defined as progression on drug therapy at one or a few sites (but not all sites) of disease; in such patients, all sites of progressing disease could be resected, and other sites of stable disease were resected if the associated morbidity was relatively low. *Generalized* disease progression was defined as disease progressing in multiple sites in patients on drug therapy and in whom complete resection of all progressing disease sites was not possible. A macroscopically complete resection was achieved in 78%, 25%, and 7% of patients with stable disease, limited disease progression, and generalized disease progression, respectively (*P* < .0001). The 12-month PFS rates for patients with stable disease, limited disease progression, and generalized disease progression were 80%, 33%, and 0%, respectively (*P* < .0001). The 12-month overall survival rates were 95%, 86%, and 0%, respectively (*P* < .0001). Thus, patients with stable disease who underwent surgery achieved substantial rates of PFS and overall survival. In those with limited disease progression preoperatively, cytoreductive surgery did not prevent disease recurrence (reflecting the evolution of more aggressive tumor biology), but overall survival was prolonged. In patients with generalized disease progression, surgery offered no survival benefit, with median PFS of 2.9 months and the median time to death of 5.6 months. Data from the other studies are remarkably consistent [11,17-20]. More follow up is necessary to determine the long-term survival of the patients in these retrospective series. A randomized trial of surgery in imatinib-stable metastatic GIST is being opened in Europe and one is being planned in the United States.

Thus, until those trial will be able to give precise data concerning this issue, surgery in recurrent or metastatic GIST can be proposed to patients having disease that is stable or shrinking on TKI therapy when complete gross resection is possible (stable disease).

For patients having isolated clones progressing on TKI therapy after initial response (indicative of sec-
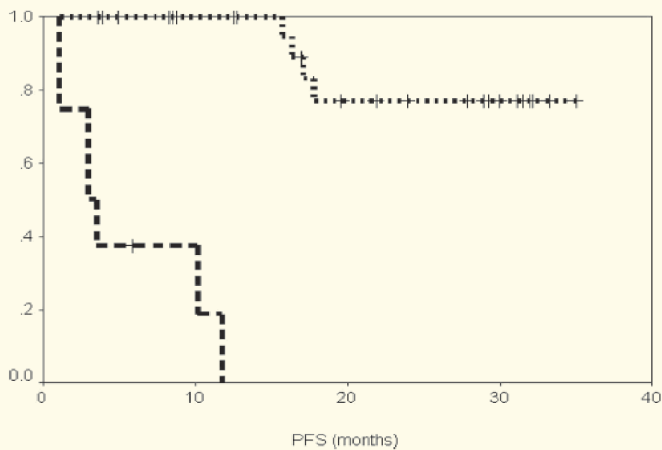
Figure 3 – **Progression-free survival from date of surgery: dotted line = patients operated in response; dashed line = patients operated in progression [19].**

ondary drug resistance), while other sites of disease remaining stable (limited disease progression), surgery may be an option, among other medical treatments, able to add roughly 6 months to the natural history of the disease (figure 3).

In contrast, patients with widespread or diffuse disease progression on imatinib therapy (generalized disease progression) should have their imatinib dose increased as tolerated, should be treated with a second-line agent like sunitinib, or should be enrolled in clinical trials.

At laparotomy for metastatic GIST that has been treated with TKIs, multivisceral resections (including liver resections) are often necessary because of the extent of disease. Unfortunately, CT often underestimates the extent of peritoneal disease, and it is not uncommon to identify numerous other nodules at laparotomy. Omentectomy and/or peritoneal stripping and liver resection are frequently necessary. Liver metastases are commonly distributed in both lobes, often precluding standard hepatectomies for complete resection. To fully treat or eradicate liver parenchymal disease, radiofrequency ablation or cryoablation in conjunction with liver resection may be required [17,19]. Percutaneous ablation of liver lesions less than
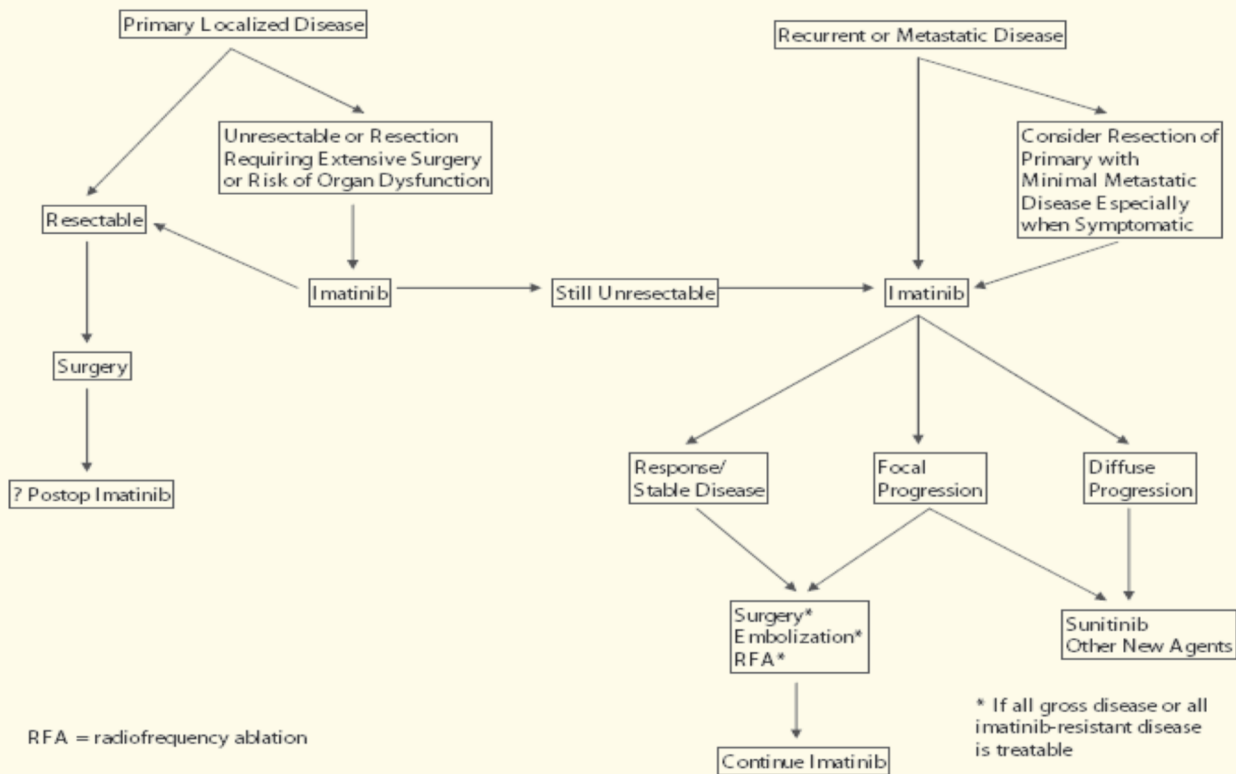

Figure 4 – **Algorithm for the treatment of GIST [24]**

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5 cm in size may also be considered. For bulkier disease, hepatic artery embolization should be considered [21-22].

An unresolved issue is how long to keep patients on imatinib/sunitinib therapy before surgery if the tumors are still responding to therapy. Data from the EORTC trial indicated that the median time to development of secondary resistance was approximately 2 years [9]. Thus, surgery (if planned) should be done before 2 years, and most would recommend surgery after demonstration of 6 to 12 months of disease stability or response.

All patients who undergo surgery, no matter whether achieve a complete surgical cytoreduction or not, must undergo post-operative Imatinib therapy, as clearly shown by the French randomized studies on Imatinib interruption [23].

In conclusion patients affected by advanced and metastatic GIST can now be successfully treated by TKIs, such as Imatinib in first line and Sunitinib in second line. Surgery, which is the standard treatment in primary localized disease, may play a role to improve the duration of TKIs activity and possibly the cure of the subset of patients who have tumors responsive to the medical treatment, though a definitive answer will only be given by a randomized trial (figure 4) [24]. Patients experiencing secondary progression, after response to medical treatment, should be considered for new agents. Surgery might be an option for very limited progression, with an expected benefit of some months [24].

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