

# The role of the surgeon in the management of GIST

## *O papel atual do cirurgião no tratamento do GIST*

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### INTRODUCTION

The recent advances in the treatment of gastrointestinal stromal tumors (GIST) promoted a change in the natural history of the disease. The enhanced knowledge on the molecular mechanisms<sup>1,2</sup> was paramount to the development of a molecular-targeted drug capable of achieving results that had never been attained before<sup>3,4</sup> in any solid tumor treatment. The introduction of imatinib in clinical practice<sup>5</sup> changed not only the survival of metastatic GIST patients, but also meant breaking through well-established paradigms. Nevertheless, despite the advances and the encouraging outcomes with the use of imatinib, the surgeon still has a key role in the management of GIST<sup>6</sup>, as much in the approach to the primary lesion as in the metastatic disease.

#### Treatment of the non-metastatic disease

##### *Approach to the Primary Lesion*

Total surgical resection still constitutes the standard treatment for non-metastatic GISTs, since it is the only modality of treatment capable of being curative. The complete R0 resection (absence of residual disease) represents one of the most important determinant factors in the treatment outcome (disease-free interval and survival); R0 resection is achieved in approximately 40% to 60% of all cases of GIST and in over 70% of the non-metastatic cases<sup>7,8</sup>. The primary goal of surgery is the total resection of the tumor. The type of resection to be performed is dependent on tumor location and size. Lesions suspected of having invaded adjacent organs must be treated by radical surgery through an *en bloc* resection of the organs involved. It is mandatory that the resection achieves negative margins verified by intraoperative frozen section examination, since the presence of residual disease negatively influences survival<sup>9</sup>. The ideal extension of the surgical margin has not been established, but a consensus exists that a wide margin is not necessary for total resection of the lesion. Thus, depending on the location and size of the tumor, the segmental resection of the organ of origin of the lesion can be performed (usually feasible in the treatment of lesions of gastric origin), as long as the premise of negative margins is respected (Figure 1). Meticulous surgical technique is required so as to prevent tumor rupture during the operation, since the tumor capsule ruptures easily,

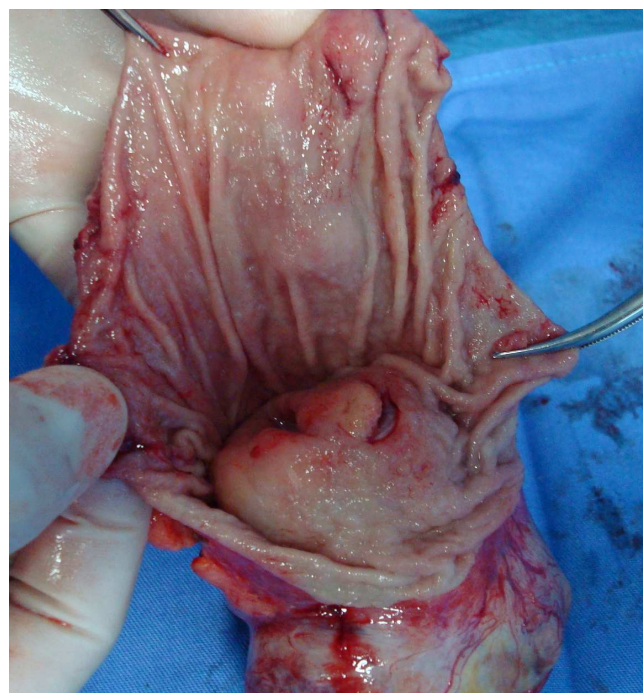
which could result in neoplastic spread and, consequently, an increase in the likelihood of relapse and reduction in survival<sup>10</sup>.

#### Lymphadenectomy

Lymph node metastasis is an infrequent occurrence: an incidence between 4% and 10% has been reported<sup>7</sup>. Regardless of the restrictions found in this respect (underreporting of lymph node metastasis due to a failure in performing routine lymphadenectomy; studies with a small number of cases), the presence of lymph node metastasis has not been recognized as a prognostic factor<sup>11</sup>; in fact, no data can be found in the literature to support routine lymphadenectomy. Therefore, lymphadenectomy should be performed when gross examination suggests lymph node involvement.

#### Laparoscopy

Laparoscopic resection has been used in the treatment of GIST. Short series of cases are described



**Figure 1 -** Segmental gastric resection (GIST of the greater curvature).

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concerning the laparoscopic management of small lesions (up to 5 cm), offering advantages such as minimal manipulation of tumors and efficacy in the diagnosis and treatment of incidental lesions, as well as those presenting gastrointestinal hemorrhage without an identified focus<sup>12,13</sup>. Although oncologic success has been reported with laparoscopic resections<sup>14,15</sup>, studies with a larger number of cases and long-term follow-up are required in order to define the actual role of laparoscopy in the treatment of this neoplasm. Current recommendation<sup>16</sup> is that laparoscopy should be restricted to the treatment of small lesions (up to 5 cm) (Figure 2) due to the possibility of tumor rupture as a result of the manipulation of larger lesions.

### Approach to gastric tumors smaller than 2 cm

The diagnosis of submucosal gastric tumors is increasingly more frequent by virtue of the greater availability of endoscopy (Figures 3 and 4). The management of those lesions is a dilemma in clinical practice, as they comprise a range of diverse diagnoses (GIST, ectopic pancreas, neuroendocrine tumors). Because no epidemiological studies exist on the matter, and the actual frequency of each one of those conditions is unknown, the diagnosis of a GIST must always be investigated, since every GIST is potentially malignant. Although there are prognostic factors that stratify GISTs according to their biological behavior<sup>17,18,19</sup>, reports exist on the development of metastases even in low-risk lesions (lesions between 2 and 5 cm with fewer than 5 mitoses/50 high-power fields)<sup>7,20</sup>. That fact demonstrates that no fully reliable prognostic factors are available to date.

Endoscopic biopsy of the lesion may be of help, yet it is not always possible to achieve a diagnosis because there may be a reduced number of samples. Iwashashi *et al.*<sup>21</sup> demonstrated that endoscopic ultrasonography was capable of enhancing the diagnostic accuracy in GISTs and the prediction of its biological behavior by means of fine needle biopsy, in addition to parameters such as size, presence of ulceration and heterogeneity of the

lesion. However, that prediction was not satisfactory for lesions smaller than 3 cm. The explanation is that the correct assessment of the mitotic index requires that the whole lesion be examined, given the low number of mitoses in GISTs; the analysis of 50 high-power fields is necessary. This means that, if a GIST is suspected, the lesion must be resected completely so as to allow risk stratification and reduce the likelihood of metastasis or tumor growth, even when it comes to small lesions. The type of resection (endoscopic or laparoscopic) will depend not only on the size and location of the lesion, but also on the endoscopist's experience and technological resources available. The two therapeutic modalities are equivalent, provided that the premises adopted in the treatment of GISTs are observed (total resection of the lesion with negative margins, preventing the rupture of the lesion during manipulation).

### Treatment of the metastatic disease

Until 2001, surgical resection was the only effective treatment for GISTs, achieving a 5-year survival

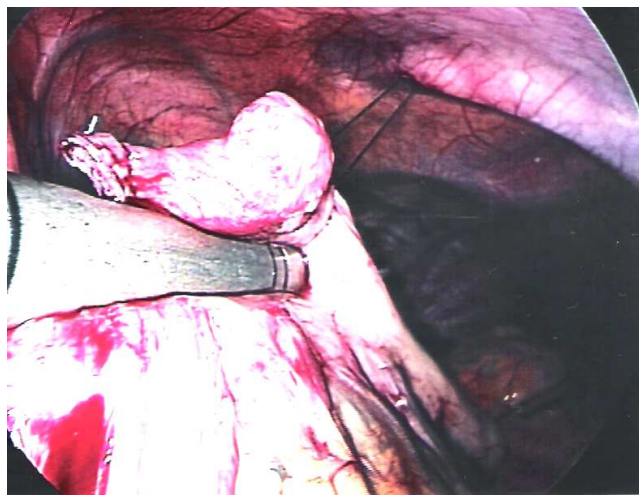


Figure 2 - Laparoscopic resection of a 2-cm gastric GIST.



Figures 3 and 4 - Endoscopic aspect of a gastric GIST.



rate around 50%<sup>7,10</sup>. However, 50% of the patients who underwent surgical treatment developed metastatic disease<sup>7</sup> with a median survival of 15 months<sup>7</sup>. There was little to be offered, since conventional chemotherapy and radiotherapy were ineffective<sup>22</sup>. The introduction of imatinib in clinical practice in 2002 brought about a change in the natural history of GISTs, and quite encouraging outcomes have been achieved (81% of clinical benefit with the use of imatinib in the metastatic disease, as well as a considerable gain in terms of survival<sup>4,23</sup>). Such outcomes relegated surgery to a secondary role in the treatment of the metastatic disease, thus being restricted to palliation. Even though imatinib is effective for most patients with a metastatic GIST, the development of resistance to the drug is a problem that has been increasing<sup>24</sup>. Clinical trials in phase II/III have shown that two-thirds of the patients with metastatic disease in use of imatinib will have progression; median progression-free survival is around 20 to 24 months<sup>3,4,23,25</sup>. Some molecular mechanisms seem to be implicated in the development of secondary resistance, especially the

occurrence of secondary mutations and the growth of resistant clones<sup>24</sup>.

In this setting, the impact of surgical salvage on metastatic disease began to be investigated<sup>26-28</sup>. The rationale for this modality of surgery is: reduction of tumor volume, prevention from secondary mutations, an increase in progression-free survival and a larger number of patients with sustained response. Drawing on that rationale, three studies<sup>26-28</sup> demonstrated a gain in progression-free survival and overall survival with surgical salvage in metastatic GIST patients under imatinib. However, the gain only became evident in cases responsive to imatinib (partial response or stabilized disease) (Figures 5,6 and 7 – a patient with hepatic metastasis responsive to imatinib, undergoing surgical salvage). The patients who presented with disease in progression did not benefit from surgical salvage. Blanke *et al.*<sup>29</sup> showed that tumor volume influenced the evolution of patients with metastatic disease using imatinib, that is, there was a positive correlation between tumor volume and survival (both overall survival and progression-free survival). Patients were divided into four quartiles according to tumor volume (1st quartile: <39.1 cm<sup>2</sup>; 2nd quartile: 39.1 cm<sup>2</sup> to 102.15 cm<sup>2</sup>; 3rd quartile: 102.16 cm<sup>2</sup> to 262.5 cm<sup>2</sup>; 4th quartile: >262.5 cm<sup>2</sup>). The rationale is that surgical salvage can reduce tumor volume and afford migration into a smaller quartile, increasing survival. We can take ovarian cancer as an analogy, in which cytoreduction is associated with a better response to the chemotherapeutic drug.

Despite the need for further studies (prospective randomized studies with a larger number of cases), current outcomes suggest clinical benefit (survival gain) with the use of surgical salvage in the treatment of a metastatic GIST, provided that patient selection is judicious.

### Treatment of relapse

Given the similar behavior to metastatic disease, relapse of the tumor must be treated in the

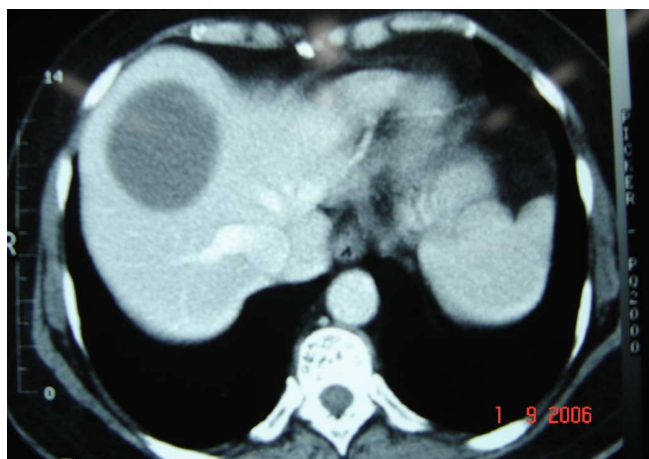


Figure 5 - CT scan showing liver metastasis (pre-imatinib).

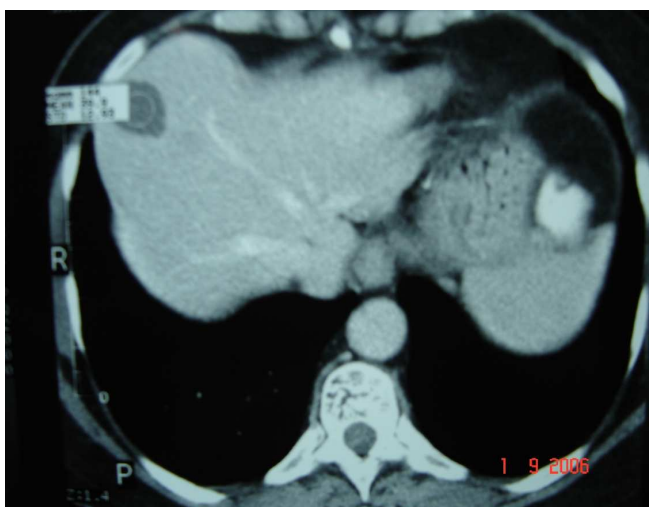


Figure 6 - CT scan after four months under imatinib, exhibiting response criteria (tumor size and density reduction).

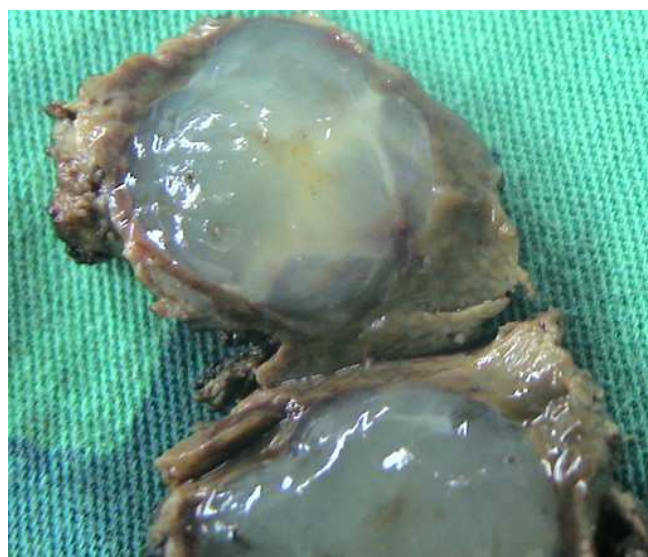
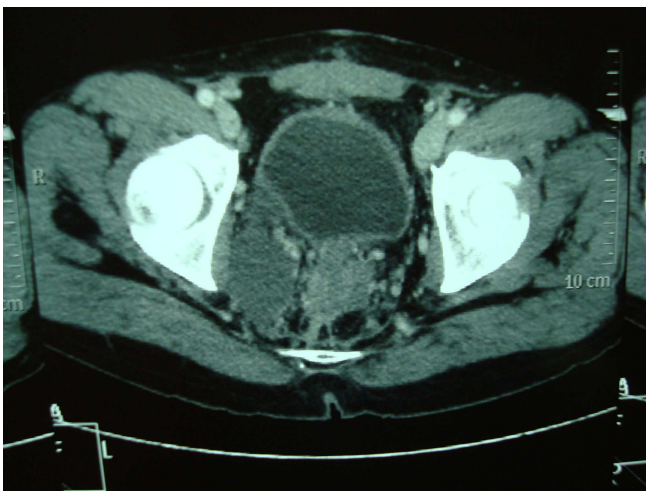


Figure 7 - Surgical salvage (hepatectomy).



**Figure 8 -** Pelvic relapse after two years of a rectal GIST resection.



**Figure 9 -** CT scan three months after the start of imatinib (marked tumor reduction).

same way, that is, the association of imatinib and surgery represent the cornerstones for treatment<sup>30</sup>. Surgery alone is not efficacious in the treatment of relapse, since total resection is only achieved in less than 50% of peritoneal relapses. Moreover, recurrence following a resection of the relapse is considered to be the rule and not an exception<sup>10</sup>. Therefore, the association surgery/imatinib should always be used in this setting (Figures 8, 9 and 10 – patient with post-resection relapse of a rectal GIST. Proposed surgery: cystectomy. Imatinib was initiated in an attempt to reduce tumor size and preserve the bladder. Substantive tumor regression was observed; surgical salvage was possible and the bladder was preserved).



**Figure 10 -** Surgical salvage of the pelvic relapse performed after three months under imatinib.

## A B S T R A C T

Recent progress in the treatment of gastrointestinal stromal tumors (GIST) was responsible for changing the natural history of the disease. Acquiring knowledge on systemic therapies based on molecular mechanisms afforded the development of targeted antineoplastic drugs capable of achieving outcomes that had never been reached before. The introduction of imatinib in clinical practice not only changed GIST patients' survival, but also shifted paradigms. However, despite all these new advances and the improved results with imatinib, the surgeon still plays a pivotal role in the management of the primary GIST tumor and even in the metastatic context.

**Key words:** Gastrointestinal stromal tumors/surgery. Gastrointestinal neoplasms/therapy. Stromal cells. Antineoplastic agents. Protein Kinase Inhibitors /therapeutic use. Treatment outcome.

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Received in 30/05/2008

Accepted for publication in 02/08/2008

Conflict of interest: none

Financial source: none

#### How to cite:

Valadão M, Linhares E. The surgeon's current role in the treatment of GIST. *Rev Col Bras Cir*. [periódico na Internet] 2009; 36(3). Disponível em URL: <http://www.scielo.br/rcbc>

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