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4

Surgical Treatment of Gastrointestinal Stromal Tumors (GISTs)

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1. Introduction

Gastrointestinal stromal tumors (GISTs) are the most common gastrointestinal tract (GI) mesenchymal tumors (Mazur and Clark 1983; Howe, Karnell et al. 2001), accounting for ~1-3% of all malignant neoplasms in this location. Most GISTs are sporadic, but there are hereditary forms, including some families with germline *KIT* and *PDGFRA* gene mutations. GIST diagnosis must be confirmed by immunohistochemistry of tumors, and integrated with other clinical and morphological features. GISTs usually express CD117 (95%) and CD34 (70%). Biological behavior is uncertain and classification (including largest size, mitotic rate and GI site) in risk categories is useful for predicting clinical behavior of GISTs. Other parameters have been described as prognostic of GISTs, including RKIP expression (Martinho, Gouveia et al. 2009). These tumors are characterized by oncogene mutations in *KIT* (up to ~85%) or *PDGFRA* (5-8%) receptor tyrosine kinases (RTKs) genes (Heinrich, Corless et al. 2003; Corless and Heinrich 2008; Gomes, Gouveia et al. 2008; Hoeben, Schoffski et al. 2008; Gajiwala, Wu et al. 2009; Liegl-Atzwanger, Fletcher et al. 2010), and rarely BRAF (Agaram, Wong et al. 2008; Agaimy, Terracciano et al. 2009; Martinho, Gouveia et al. 2009; Hostein, Faur et al. 2010); 10-15% does not harbor any of the aforementioned gene mutations: so called wild-type GISTs. *KIT/ PDGFR* mutations in GISTs are biodiversity markers, tyrosine kinase inhibitor (TKI) targets, predictive markers of TKI response, prognostic markers of tumor recurrence/progression, and frequent cause of TKI resistance. Thus, good clinical practice in bio-therapeutic decision of GIST patients should include mutational analysis status of the tumors.
Most importantly, complete surgical resection, without lymph node dissection, is considered standard treatment for primary localized GISTs (without peritoneal dissemination or metastatic disease), and is the only potential curative treatment for patients harboring these tumors.

2. Localized primary disease

There is a general consensus that the definitive treatment of primary GISTs with dimensions ≥ 2 cm and without evidence of peritoneal dissemination or distant metastases is complete

macroscopic surgical resection (Casali and Blay 2010; Demetri, von Mehren et al. 2010). However, when esophagogastric or duodenal subepithelial nodules with < 2 cm diameter are detected, the standard procedure consists in endoscopic ultrasound (EUS) assessment and active surveillance of the individual patient, because many of these small nodules, when they correspond to GISTs, are tumors of low biological risk (Fletcher, Berman et al. 2002; Miettinen and Lasota 2006) or whose clinical behavior remains to be clarified. Surgery is reserved for patients whose tumor increases in dimension or is symptomatic. The results of a recent retrospective analysis (Lok, Lai et al. 2009) indicate that only some (3 out of 23; 13.0%) of the small tumors without high-risk EUS characteristics (large dimension, irregular extraluminal limits, heterogeneous echo pattern, presence of cystic areas, and hyperechoic foci) progressed during the long-term follow-up with EUS. As an alternative, the decision can be shared in an individual base with the patient, either to opt for an initial histological evaluation (needle biopsy) or for the tumor excision, when the morbidity is not substantial. On the other hand, when facing intra-abdominal nodules without endoscopic evaluation, the laparoscopy/laparotomy resection is the standard approach. Also for rectal nodules (or in the recto-vaginal space), the best management must be the accomplishment of biopsy/resection, after EUS evaluation, regardless of the tumor dimension, because GISTs in this location display high biological risk, and the local implications of a surgical intervention in this region is more critical, mostly in tumors of great dimensions.

The guidelines of the ESMO and the NCCN coincide in the recommendation that tumors with dimension > 2 cm must be resected (Casali and Blay 2010; Demetri, von Mehren et al. 2010), because being GISTs, they imply a higher risk of aggressive behavior.

For patients with localized primary GIST, the surgical resection continues to be the only possibility of cure of their illness. In our experience we obtained complete macroscopic resection (R0 or R1) in 92.3% of GISTs and microscopic negative margins (R0) in 75% of cases. 5-year disease-specific survival (DSS) and recurrence-free survival (RFS) was 87.7% and 89.8%, respectively, after surgical resection of patient's primary GIST. The recurrence rate was significantly ($p=0.045$) lower in R0 cases. In the multivariate analysis, only the presence of macroscopic residual tumor (R2) was significantly associated ($p=0.013$) with shorter DSS (Gouveia, Pimenta et al. 2008). The DSS and RFS values in our patients fit with results published in other studies (DeMatteo, Lewis et al. 2000; Crosby, Catton et al. 2001; Fujimoto, Nakanishi et al. 2003; Langer, Gunawan et al. 2003; Lin, Huang et al. 2003; Wong, Young et al. 2003; Bucher, Taylor et al. 2004; Bucher, Egger et al. 2006; Bumming, Ahlman et al. 2006). The recurrence rate was significantly lower in R0 cases, but in multivariate analysis only R2 resection was significantly associated with shorter survival of patients. According to the actual consensus recommendations (Casali and Blay 2010; Demetri, von Mehren et al. 2010), our results underline the prognostic importance of complete macroscopic surgical tumor resection, with the aim of achieving negative microscopic margins, and avoiding tumor rupture.

The surgery of GISTs should allow a complete margin of normal tissue around the primary tumor. The revision of most important published series shows that several authors refer to complete macroscopic resection (Ng, Pollock et al. 1992; Crosby, Catton et al. 2001; Pierie, Choudry et al. 2001; Eisenberg and Judson 2004; Boni, Benevento et al. 2005; Wu, Lee et al. 2006) of the tumors, whereas others specify R0 resection (Connolly, Gaffney et al. 2003; Langer, Gunawan et al. 2003; Wu, Langerman et al. 2003; Aparicio, Boige et al. 2004; Heinrich and Corless 2005; Bucher, Egger et al. 2006; Wardelmann, Buttner et al. 2007) as the standard procedure for the surgical treatment of GISTs. Some authors sustain that the

microscopic status of the surgical margins (positive or negative), in contrast to the results obtained with other malignant solid tumors, does not influences the survival of patients, or even the recurrence of GISTs (DeMatteo, Lewis et al. 2000; Pierie, Choudry et al. 2001; Demetri, Baker et al. 2007). In a study of 200 patients with GIST, DeMatteo *et al*. (DeMatteo, Lewis et al. 2000) report that the microscopic margins do not significantly influence the evolution of the tumors and that recurrence occur most probably due to the intrinsic characteristics of the tumors. However, in the reported series, the relative small number of cases with positive microscopic margins after macroscopically complete resection is an important limitation to the clarification of the aforementioned author's suggestion. Additionally, this series included a substantial number of large dimension GISTs with high biological risk, in which complete macroscopic resection may not prevent the occurrence of recurrence (e.g., metastases) of the tumor or the shorter survival of these patients. In fact, the analysis of the results reported by DeMatteo *et al.* confirms that most resections were performed in patients with large GISTs with high biological risk (Lin, Huang et al. 2003; Bucher, Egger et al. 2006). The value of negative surgical margin, for instance in GISTs > 10 cm, is highly controversial, since it is possible to argue that those tumors may release to the peritoneal cavity cells not detectable clinically (DeMatteo, Lewis et al. 2000; Crosby, Catton et al. 2001). In addition, some of these reported results may be biased by the effect of adjuvant treatment performed in advanced or incompletely removed GISTs (He, Wang et al. 1988; DeMatteo, Lewis et al. 2000).

Other authors suggest that R0 resections may influence the prognosis of patients (Lehnert 1998; Pidhorecky, Cheney et al. 2000; Langer, Gunawan et al. 2003; Lin, Huang et al. 2003; Wu, Langerman et al. 2003; Yan, Marchettini et al. 2003; Bucher, Egger et al. 2006; Bumming, Ahlman et al. 2006; Hinz, Pauser et al. 2006; Ahmed, Welch et al. 2008); however, these results can also be influenced by the number of incomplete resections in GISTs of high biological risk (Lin, Huang et al. 2003).

Similar to the reports of DeMatteo *et al*. e Pierie *et al*. (Pierie, Choudry et al. 2001), our own results reinforce that complete macroscopic resection of GISTs has a positive impact in the prognosis, being significantly shorter the specific survival of patients with R2 tumor margin status.

Despite the remaining controversy, R1 margins resection may expose patients to a higher risk of tumoral locoregional recurrence of GISTs.

ESMO and NCCN recommend that in cases with R1 resections one should consider widening of resection, whenever the exact location of the lesion is possible to identify and the risk of surgical morbidity is low.

The surgical management recommended for small intestinal GISTs is segmental resection with 2-3 cm, and for gastric GISTs 1-2 cm free macroscopically margins (Dematteo, Heinrich et al. 2002; Matthews, Walsh et al. 2002; Wardelmann, Buttner et al. 2007; Hohenberger and Eisenberg 2010). An intraoperative histological frozen examination of peri-tumoral tissues must be compulsory whenever there is a possibility of not avoiding positive tumor surgical margins.

Usually, the resection causes low morbidity in tumors <10 cm, localized to stomach or small intestine. In contrast to more common gastrointestinal (GI) carcinomas, GIST does not originate from the epithelial layers of GI tract and, therefore, they present different biology and behavior implications. These facts are important for the surgical margins status procedures and locoregional lymph node management. The surgical procedures can differ, depending on the organ where GIST originates, on its precise localization, and the

dimensions of the tumor. The treatment goal is complete resection of GIST, with negative microscopic margins (R0) and preservation of an intact pseudocapsule (i.e. preventing the tumoral rupture) (Casali and Blay 2010; Demetri, von Mehren et al. 2010).

As GIST does not have generally intraparietal infiltrative features, the attainment of wide surgical margins rarely associates with a prognostic benefit for the patients. The present recommendations for surgical margins are based on expert experience, consensus meeting reports, and application of the pathobiology concepts on GIST (Casali and Blay 2010; Demetri, von Mehren et al. 2010). In fact, there is no prospective conclusive evidence that allows predicting the relation between the extension of resection margins and the risk of local or distant recurrence of GISTs.

The wedge resection is the most frequent option for GISTs located in the stomach and the segmental resection is the procedure of choice for small bowel tumors. For GISTs of large dimensions in gastric lesser curvature and/or with pyloric involvement, wedge resection may not be possible, and a distal gastrectomy might be a more adequate procedure. Total gastrectomy is not usually necessary, but it has to be considered depending on the localization (esophagogastric junction) and/or extension of the tumor.

The rectal GISTs are uncommon and their definitive diagnosis is frequently obtained after the anatomopathological study of the surgical specimen. The rectal GIST of small dimensions, located in lower third, can be removed with complete parietal resection, through a transanal or transsphincteric procedure. However, these type of procedures must be performed with due care, because there are lower R0 resections (32% *versus* 82%) and higher rates of local recurrence (77% *versus* 31%), when compared with the previous lower anterior rectal resections, that is the procedure recommended for GISTs of the upper and middle thirds of the rectum (Changchien, Wu et al. 2004; Dong, Jun-Hui et al. 2007).

The surgical technique used to resect GISTs has implications in the occurrence of tumoral recurrence. The rupture of the tumor must be strictly prevented in all the GIST cases, especially in those which have great cystic or necrotic areas. The enucleation of the GISTs is considered an insufficient option, because it can easily not remove part of the pseudo-capsule, with persistence of viable tumor cells; on the other hand, it also associates with more frequent tumoral rupture. For these reasons, the enucleation is not recommended, even when the objective is to preserve a vital structure (Nishimura, Nakajima et al. 2007).

When the GIST develops and presents great dimensions, it can be submitted to a pre-surgical (neoadjuvant) treatment with imatinib, aiming to get better conditions of resectability of a tumor that is, many times, necrotic and friable (Eisenberg, Harris et al. 2009). This option can facilitate the complete surgical resection associated to tumor response to the treatment (Fig. 1), and/or the preservation of the function or the organ, particularly in GISTs of the esophagogastric junction, the second portion of the duodenum and the lower rectum (Casali and Blay 2010; Demetri, von Mehren et al. 2010). When there is invasion of adjacent organs, *en bloc* resection can be an alternative (Fig. 2). However, it is generally accepted that an incomplete resection of the tumor must be only performed as a palliative therapeutic option, in cases of hemorrhage, pain or symptoms secondary to the mass effect of the tumor.

When the R0 surgical resection is predicted to result in functional complications or important co-morbidities, and the neoadjuvant medical treatment was not efficient or cannot be given, the decision to carry a R1 resection must be discussed with the patient. The R1 resection can be acceptable in GISTs of low risk. There are no studies that clearly

demonstrate the association between R1 surgery and shorter survival of the patients (Hohenberger and Eisenberg 2010).

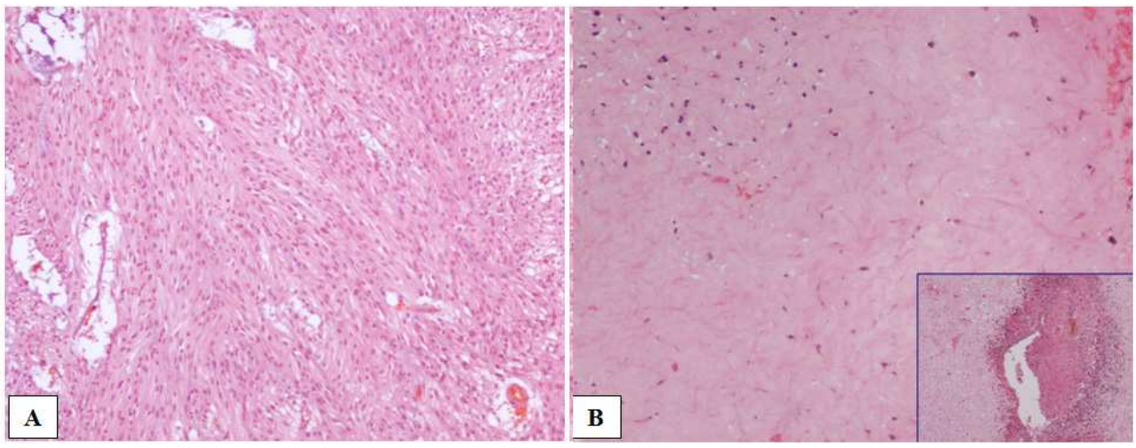

Fig. 1. GIST: biopsy microscopic features of an unresectable tumor (A); the tumor was submitted to a R0 resection after neoadjuvant imatinib (B). Note the substantial decreasing of the tumor cells density (B) with abundant sclero-hyaline stroma and hemorrhagic areas (inset) compared to pre-imatinib features (A).

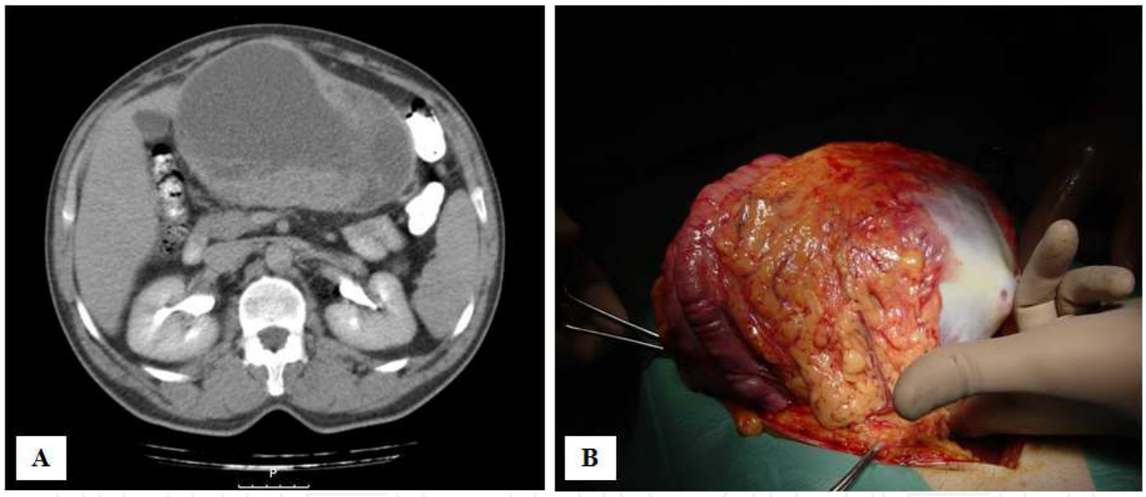

Fig. 2. GIST: CT scan of a large dimension GIST invading adjacent transverse colon (A); macroscopic aspect of the surgical specimen with R0 resection (B).

Many authors described that GISTs metastasize rarely for the lymph nodes, even in high risk cases. Bucher *et al.* (Bucher, Egger et al. 2006) described that 5 out of 80 patients (6%) with localized GIST developed hematogenous metastases, with or without lymph node involvement. In the series of Rutkowski *et al.* (Rutkowski, Nowecki et al. 2007), that include 335 patients, only four cases (1.2%) disclosed metastatic lymph nodes. The published studies indicate that there is no evidence of benefit for routine lymphadenectomy in the surgical treatment of GISTs, except when there is macroscopic lymph node involvement by the tumor (DeMatteo, Lewis et al. 2000; van der Zwan and DeMatteo 2005; Bucher, Egger et al. 2006; Otani, Furukawa et al. 2006; Casali and Blay 2010; Demetri, von Mehren et al. 2010).

3. Laparoscopic surgery

The laparoscopic surgery in GISTs is gradually expanding and being more used in recent years. The endoscopic diagnosis improved the capacity to identify gastric GISTs of small dimensions that are associated with a low risk of aggressiveness (Fletcher, Berman et al. 2002; Miettinen and Lasota 2006). The minimally invasive approach has become generally used in these tumors, due to the potential benefits of preventing the laparotomy of the patients. One should follow the strict oncologic principles of the open surgery: complete resection of the tumor with free margins (R0), preventing the dissemination of tumor cells into the peritoneal cavity (Otani and Kitajima 2005; Casali and Blay 2010; Demetri, von Mehren et al. 2010). In the GISTs of large dimensions, R1 resection can be complicated by rupture due to manipulation of the tumor and peritoneal dissemination. Therefore, laparoscopic resection has been discouraged in patients with GISTs of great dimensions (Blay, Bonvalot et al. 2005; Hohenberger and Eisenberg 2010). However, Novitsky *et al.* (Novitsky, Kercher et al. 2006) suggested that these recommendations should be reviewed, because they were not based on evidence but only translated precaution for the inexperienced surgeons with this procedure, aiming over all to prevent the increase of the incidence of tumor rupture. Several authors proposed the adoption of widened indications for the laparoscopic surgery in GISTs (Mochizuki, Kodera et al. 2004; Mochizuki, Kodera et al. 2006). Several studies described the accomplishment of laparoscopic resection of tumors with dimensions between 0.3 and 12.5 cm (Catena, Di Battista et al. 2008; Hohenberger and Eisenberg 2010), supplying evidence for the application of this procedure mainly in gastric GISTs. However, there are no controlled randomized studies in prospective clinical trials concluded to date to validate these options.

In the NCCN 2007 update, it is considered acceptable the laparoscopic resection of tumors > 5 cm, depending on the localization and the morphology, using laparoscopic or hand-assisted techniques (Novitsky, Kercher et al. 2006; Demetri, Benjamin et al. 2007; Catena, Di Battista et al. 2008; Demetri, von Mehren et al. 2010).

Before initiating the resection of the tumor, a formal throughout exploration of the abdominal cavity must be carried out to exclude the eventual presence of peritoneal or liver metastases. The use of ultrasound during surgery can be useful in the evaluation of possible liver metastases, and in case of suspected lesions, to guide the accomplishment of their biopsies. The use of intraoperative flexible endoscopy has been also frequently used to assist in more precise localization of small dimension GISTs and in the selection of the most adequate technique for the resection in the individual case. To prevent the risk of tumor rupture occurrence, GISTs should not be directly manipulated with the laparoscopic instruments (Novitsky, Kercher et al. 2006). Although there are no available evidence based data, the use of a bag for the removal of the surgical specimen seems to be essential to prevent the dissemination of tumor cells into the abdominal cavity or in the orifice of the laparoscopic port, and eventually metastases (Novitsky, Kercher et al. 2006; Ronellenfitsch, Staiger et al. 2009; Casali and Blay 2010).

For the treatment of gastric GISTs, different procedures have been used in the diverse published series, depending on several factors (e.g., dimension, localization and macroscopic features of the tumor): wedge or segmental resections using laparoscopy, laparoendoscopy (intragastric) or hand-assisted laparoscopy. The GISTs of the anterior wall and of the lesser and greater curvatures of the stomach are generally submitted to wedge resection, with linear endoscopic GI anastomosis stapler. The tumors of larger dimensions

can be resected with free margins, using the ultrasonic coagulating shears (Novitsky, Kercher et al. 2006). The tumors of the posterior wall are many times removed via the lesser sac, but the transgastric approach, with anterior gastrotomy, constitutes a valid alternative, especially in the GISTs located next to the esophagogastric junction (Matthews, Walsh et al. 2002; Ludwig, Weiner et al. 2003; Li, Hung et al. 2008; Privette, McCahill et al. 2008). This option is, however, technically demanding and there are reports of incomplete resections and postoperative complications, such as stenosis and leakage in the suture line. The combined intragastric endoscopic-laparoscopic resection has been described as an alternative method in the treatment of the esophagogastric junction GISTs (Novitsky, Kercher et al. 2006; Ronellenfitsch, Staiger et al. 2009).

The localization of the tumor does not have to be considered an absolute contraindication for minimally invasive surgery, whenever the experience necessary for the technique and all the indispensable precautions are considered. However, in GISTs with large dimensions and/or with unfavorable localizations, as the gastric lesser curvature or the esophagogastric junction, it may not be possible to perform wedge resection with free tumor margins, being sometimes necessary to opt for subtotal or total gastrectomy. In these cases, the neoadjuvant treatment with imatinib, as suggested in the guidelines of ESMO and NCCN, may be a valid option to reduce the dimension of the tumor, and allow a resection with some preservation of the organ /function. However, the feasibility and the results of this type of procedures need validation from ongoing studies (Eisenberg 2006).

The laparoscopic surgery can be applied in other anatomic sites, such as rectal GISTs of small dimensions. However, the available data relative to the laparoscopic resections of GISTs in other (extra gastric) localizations are limited (Demetri, von Mehren et al. 2010).

The published global results of the laparoscopic surgery describe that the intraoperative and postoperative complications are relatively rare, occurring, respectively, in 6.8% and 7.7% of the patients (Hohenberger and Eisenberg 2010). The resections elapse with minimum losses of blood, satisfying the duration of surgery and short periods of hospital stay (Catena, Di Battista et al. 2008; Ronellenfitsch, Staiger et al. 2009). The morbidity related with the surgical wound of laparotomy is also prevented. The learning curve in the laparoscopic procedures indicates that, with better technical experience, the surgical times will be gradually improved (Shin 2005; Avital, Hermon et al. 2006).

Although the follow-up data of the patients are scarce, not exceeding ~ 5 years of duration (Hohenberger and Eisenberg 2010), some series described similar oncologic efficacy in the laparoscopic procedures when compared with those obtained with conventional surgery (Otani, Ohgami et al. 2000; Novitsky, Kercher et al. 2006; Choi, Kim et al. 2007)

The applicability of the laparoscopic approach must, therefore, be based in a variety of factors, including the characteristics of patient, dimension and the macroscopic morphology of the tumor, the pattern of invasion and the localization of the tumor, as well as the experience and qualification in laparoscopic surgery of the surgeon (Novitsky, Kercher et al. 2006).

The data from the literature indicate that laparoscopic resections or assisted by laparoscopy are feasible and associated with reduced rates of recurrence, short periods of internment and low morbidity (Otani, Ohgami et al. 2000; Novitsky, Kercher et al. 2006; Otani, Furukawa et al. 2006; Nishimura, Nakajima et al. 2007; Huguet, Rush et al. 2008; Nakamori, Iwahashi et al. 2008). This procedure must be recommended as the option of choice for the majority of patients with the small and intermediate dimension localized gastric GISTs.

4. Locally advanced primary GIST

In the advanced GISTs, without distant metastases, it can be impracticable the accomplishment of R0 resection. In these cases, it must be considered the tumoral cytoreduction with neoadjuvant imatinib. This option can facilitate the achievement of surgical R0 margins and allow a less extensive surgery, with better functional results, as suggested by the ESMO and the NCCN recommendations in such circumstances. However, these recommendations are based only on publications of retrospective non-randomized data (Shah, Sun et al. 2005; Goh, Chow et al. 2006). The primary treatment with imatinib for tumor cytoreduction can still be considered in GISTs whenever there is a high risk of hemorrhage or tumoral rupture during surgery.

The maximum therapeutic response is usually reached after 6-12 months of treatment. The subsequent surgical intervention can then be safely performed in the majority of the cases (Bumming, Andersson et al. 2003; Eisenberg, Harris et al. 2009; Casali and Blay 2010). However, it is not always necessary to wait for the maximum response to perform the surgery. The mutacional analysis of the tumor can assist to exclude from this therapeutic neoadjuvant option GISTs with lower response rates to imatinib (e.g., with *PDGFRA* D842V mutation), and/or allow to change for a more adequate therapeutic option. A PET or PET/CT, or the evaluation of the tumor density with CT scan, can be particularly useful in the early evaluation of tumor response to the therapeutic option, without delaying the surgical intervention in GISTs that do not respond to the treatment (Townsend, Carney et al. 2004; Goldstein, Tan et al. 2005; Heinicke, Wardelmann et al. 2005; Dimitrakopoulou-Strauss, Hohenberger et al. 2007).

It is essential to establish a multidisciplinary therapeutic decision plan (tumor conference) involving several specialties, including pathologists, oncologists, radiologists, gastroenterologists, and surgeons. The sharing of experiences, available in reference centers for sarcomas, including GISTs, and/or in oncologic networks to assist patients, must be considered as an essential condition for the adequate individual management of patients with GISTs (Casali and Blay 2010).

5. Conclusion

Gastrointestinal stromal tumors (GISTs) are the most common gastrointestinal tract (GI) mesenchymal tumors. GIST diagnosis must be confirmed by immunohistochemistry, rarely by molecular study, and integrated with other clinical and morphological features. Biological behavior is uncertain and classification (including largest size, mitotic rate and GI site) in risk categories is useful for predicting clinical behavior of GISTs.

The definitive treatment of primary GISTs ≥ 2 cm without peritoneal dissemination or distant metastases is complete macroscopic surgical resection. Some authors sustain that the microscopic status (R1 or R0) of the surgical margins does not influences survival, or even recurrence of GISTs, while others suggest that R0 resections may influence the prognosis of patients. In our experience, the recurrence rate is significantly lower in R0 cases, but in the multivariate analysis only R2 is significantly associated with shorter disease specific survival of patients with GIST. R1 resection may expose patients to a higher risk of tumor locoregional recurrence. The gold standard of ESMO and NCCN recommendations for surgery of GIST is complete (R0) resection without tumor rupture.

Surgical procedures can change, depending on the involved organ, its precise site, and the dimension of GIST. Wedge resection is the most frequent option for GISTs in the stomach, and segmental resection for those in the small bowel. For large dimension tumors in the gastric lesser curvature and/or with pyloric involvement, a distal gastrectomy may be better option, and total gastrectomy may be also considered, depending on the site (esophagogastric junction) and/or extension of the GIST. There is no evidence of benefit for routine lymphadenectomy in the surgical treatment of GISTs.

The minimally invasive approach is being commonly used in gastric tumors, avoiding laparotomy of patients. Nevertheless, controlled randomized studies in prospective clinical trials are warranted to validate this option. Worth mentioning, one should follow in this approach the same stringent oncologic standards of open surgery: complete resection (R0) of the tumor, avoiding dissemination into the peritoneal cavity. The NCCN 2007 update considers suitable the laparoscopic resection of tumors > 5 cm, depending on the site and the morphology, using laparoscopic or hand-assisted techniques. Laparoscopic resections or assisted by laparoscopy are feasible with reduced rates of recurrence, short periods of internment, and low morbidity.

In locally advanced GISTs, without distant metastases, tumor cytoreduction with neoadjuvant imatinib can enable R0 margins and less mutilating surgery, with better functional results, as proposed by the retrospective non-randomized based data included in ESMO and NCCN recommendations. The mutational analysis of the tumor can assist to exclude from the neoadjuvant option GISTs with lower response rates to imatinib (e.g., with *PDGFRA* D842V mutation), and/or allow a more adequate available therapeutic option.

Considering the persisting controversies, it is essential to set up a multidisciplinary therapeutic decision plan involving several specialties. The input of experiences, available in reference centers for sarcomas, in addition to the patient involvement and informed consent, must be considered as standard of care conditions for the adequate individual management of GISTs.

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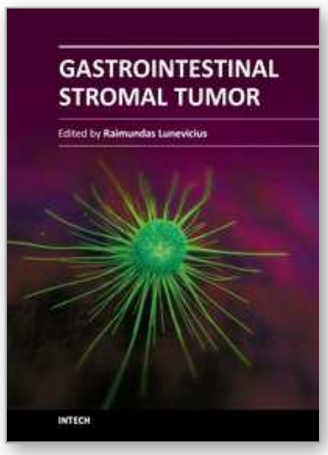

Gastrointestinal Stromal Tumor
Edited by Prof. Raimundas Lunevicius

ISBN 978-953-51-0580-0
Hard cover, 120 pages
Publisher InTech
Published online 27, April, 2012
Published in print edition April, 2012

Almost 30 years have gone by since the postulation that GISTs derive from mesenchymal stem elements, and only 15 years have gone by since the definitive detection of origin of GISTs. Research in the last decade was more focused upon the justification of imatinib mezylate therapy in GISTs and clarification why a secondary resistance that occurred during the kinase inhibitors therapy. The era of therapy for GISTs, targeting the primary activating mutations in the KIT proto-oncogene; is being proclaimed as bringing the message of special importance to the pathologist role in multidisciplinary team that are responsible for treating patients with locally advanced or metastatic GIST. This is the first conclusive message forthcoming from this book. On the other hand, the book provides summarised and case-based knowledge on current management of gastrointestinal and extragastrointestinal stromal tumours. We hope that this book may be considered as a worthwhile timely addition to clinical science dissemination, medical education, further basic and clinical research.

How to reference
In order to correctly reference this scholarly work, feel free to copy and paste the following:

António M. Gouveia and José Manuel Lopes (2012). Surgical Treatment of Gastrointestinal Stromal Tumors (GISTs), Gastrointestinal Stromal Tumor, Prof. Raimundas Lunevicius (Ed.), ISBN: 978-953-51-0580-0, InTech, Available from: http://www.intechopen.com/books/gastrointestinal-stromal-tumor/surgical-treatment-of-gastrointestinal-stromal-tumors-gists

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