SAS Journal of Surgery
Abbreviated Key Title: SAS J Surg
ISSN 2454-5104
Journal homepage: https://www.saspublishers.com

OPEN ACCESS

A Rare Case of a Giant Locally Advanced Stromal Tumor of the Stomach Made Resectable by Imatinib

Alae Eddine El Aissaoui[1*], Abderrahim Ait Abderrahim[1], Tarik Souiki[1], Ahmed Zerhouni[1], Imane Toughrai[1], Khalid Mazaz[1], Karim Ibn Majdoub[1]

[1]Visceral Surgery Service, Hassan II University Hospital, Faculty of Medicine and Pharmacy of Fez, Sidi Mohammed Ben Abdallah University, Fez, Morocco

DOI: 10.36347/sasjs.2021.v07i08.005 | **Received:** 06.07.2021 | **Accepted:** 11.08.2021 | **Published:** 12.08.2021

***Corresponding author:** Alae Eddine El Aissaoui

Abstract | **Case Report**

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the digestive tract. Most gastrointestinal soft tissue neoplasms, previously classified as leiomyomas, leiomyoblastomas, schwannomas or leiomyosarcomas, are now classified as GISTs on the basisof histology, molecular study and immunohistochemistry. They originate from the stem cells which differentiate toward the pacemaker cell (Interstitial cell of Cajal). Prognostic factors have been identified for GISTs,they include the tumor size and the mitotic rate. Surgery is the standard treatment for resectable GISTs. Metastatic and inoperable GISTs should consider medication with tyrosine kinase inhibitor (imatinib mesylate), which inhibits the c-kit receptor. We present the case of a locally advanced giant stromal tumor that became resectable after neoadjuvant chemotherapy with Imatinib; our work shows the importance of this molecule which can modify tumor status and surgical prognosis in locally advanced or metastatic GISTs.

Keywords: GIST, stromal tumors,stomach, Imatinib.

INTRODUCTION

GISTs are mesenchymal tumors arising mainly from the stomach and small bowel, less often from the rectum, colon, mesentery, or esophagus. GISTs, larger than 10cm in diameter, are referred to as giant GISTs and have been rarely reported in the literature [1].

We report the case of a 67-year-old patient operated for a locally advanced giant stromal tumor of the stomach, whose surgical resection was made possible after a 6-months treatment with Imatinib.

CASE REPORT

This is a recent case of an exophytic GIST of gastric origin. A 67-year-old patient presented with abdominal pain for 6 months associated with post prandial vomiting and progressive abdominal swelling, there were no other associated general symptoms.

The clinical examination found a patient ranked WHO 1 with a slightly distended abdomen and a palpable epigastric mass, the lymph nodes were free.

The Abdominal CT scan (Figure 1A) showed a large epigastric tumor mass extending to the left hypochondrium and the left flank, presenting intimate contact with the left colon and stomach, sparing the left kidney and pancreas and infiltrating the lower surface of the left liver, associated with 2 hepatic hilar and retro portal nodes suggesting a digestive tumor with exophytic development (GIST).

An ultrasound-guided biopsywas performed and immuno-histochemical results were in favor of a digestive stromal tumor with low proliferation and low mitotic activity.

The case was discussed at the multidisciplinary consultation meeting (MCM): the decision was to use a neo-adjuvant treatment: Imatinib.

A scan was performed after 6 months of treatment(Figure 1B), showed a significant decrease in the size of the epigastric tumor, currently measuring 17 cm long axis versus 21 cm and 9 cm short axis versus 14 cm. The tumor being avascular: not enhanced after injection of iodinated contrast agent.

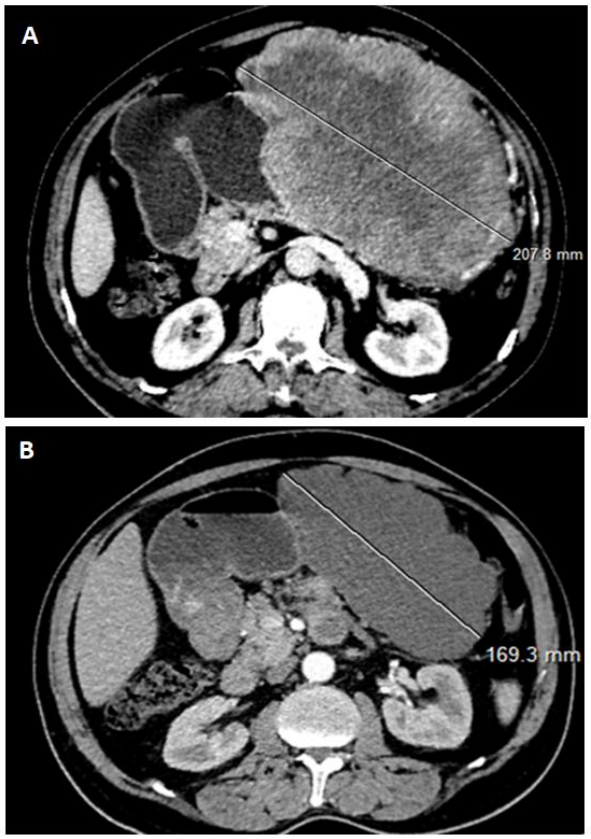

Figure 1: Abdominal CT scan in axial slices after injection of contrast product, in the portal phase, before (A) and 6 months after Imatinib (B), shows: in the image (A) a voluminous tumor mass with exophytic development from the greater curvature of the stomach, with twocomponents: peripheral fleshy and central necrotic. Image (B) shows a regression in size of the tumor mass, which has become completely necrotic

The case was rediscussed in the multidisciplinary consultation meeting and the decision of surgery has been made**.**

Surgical exploration revealed a huge tumor with a 6cm implantation base on the great gastric curvature invading the transverse mesocolon (Figure 2). The procedure consisted on the resection of the invaded transverse mesocolon with transverse resection followed by a mechanical side to side colo-colonic anastomosis and then realization of an atypical gastrectomy with safety margins, all being extracted in a mono-block (Figure 3).

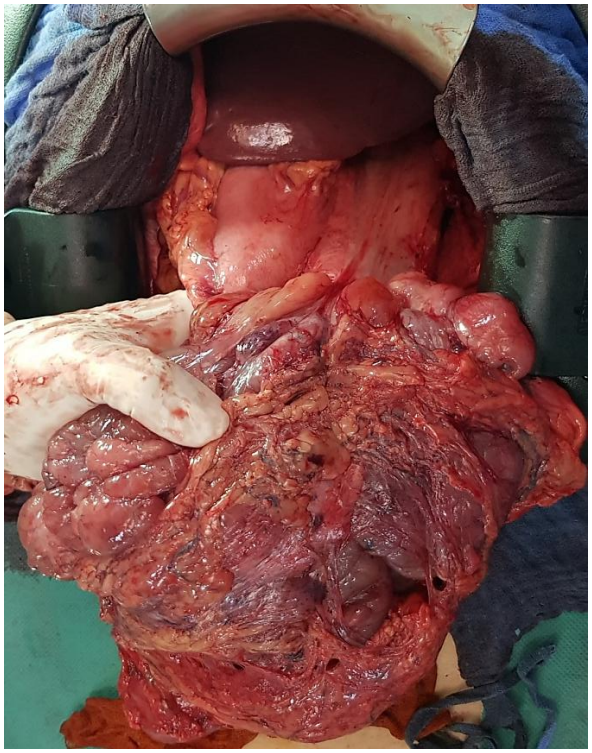

Figure 2: Intraoperative picture showing huge tumor with a 6cm implantation base on the great gastric curvature invading the transverse mesocolon

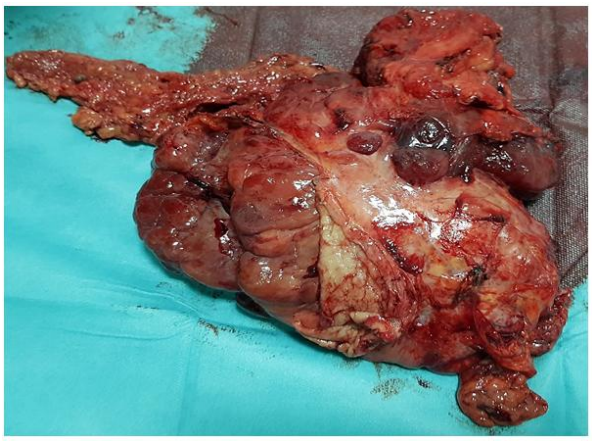

Figure 3: Image of the operative part (the monoblock resection)

The histological study results revealed a high-risk GIST classified as pT4N0, the resected margins were reported clear of the tumor, and the decision of theMCM was an adjuvant treatment with Imatinib.

The postoperative course was simple. As of a year after surgery, no signs of recurrence have been observed and the CT scans didn't show any abnormalities. Our patient is still on Imatinib.

DISCUSSION

Prior to 1970, stromal tumors were divided into two main categories: potentially malignant smooth muscle tumors and benign schwannomas. The year 1980 was marked by the generalization of immunohistochemical techniques, which madepossible to identify and classify more precisely digestive mesenchymal tumors on the basis of the specific expression of cell differentiation markers. Two main markers were then identified on tumor cells: CD34 and KIT protein (also called CD117). The expression of KIT protein is specifically restricted and specific to Cajal's interstitial cells. These phenotypic similarities suggest that GISTs are derived from interstitial cells of Cajal [2]. The discovery of this marker solved many diagnostic problems but also opened up new therapeutic avenues with the introduction, in 2000, of a targeted chemotherapy based on Imatinib Mesylate, which revolutionized the management of GIST [3].

GISTs representabout 0.1 to 3% of all gastrointestinal tumors [4], but they are the most common mesenchymal tumors of the digestive tract [5]. The stomach beingthe most frequently affected site (60%) [6]. Their exact incidence is difficult to determine and has long been underestimated because on the one hand these tumors were not clearly identified as a nosological entity and on the other hand the asymptomatic forms are frequent [7]. GISTs are generally sporadic; the genetic component has been evoked due to the familial forms that have been reported by studies [2].

The median age at diagnosis is around 50.6 years [9] and there is no sex predominance [10]. Pediatric cases are exceptional [11].

The etiology and mechanism of GISTs are still poorly understood [12], however, thanks to the development of molecular biology techniques, GISTs are defined as anarchic proliferations of interstitial cells of Cajal expressing specific surface proteins: KIT and CD34.

Stromal tumors are silent tumors that remain asymptomatic for a long time, making their incidental discovery frequent [7]. In about 20% of cases, the diagnosis is made after endoscopy or an imaging for another indication. In 15% to 25% of cases, the disease is discovered at metastatic stage [13]. The symptoms of stromal tumors are variable and heterogeneous depending on their location and size; these symptoms are consecutive to the complications of these tumors. They are represented by atypical abdominal pain due to the size of the tumor, by externalized or occult digestive bleeding when the tumor is ulcerated, which can go as far as hemoperitoneum and by the risk of occlusive syndrome for tumors of the small intestine [14]. The other possible symptoms are varied, directly related to the location of the tumor, for example dysphagia or rectal syndrome [13], which shows the diagnosis difficulty which comes from the fact that these symptoms have no specific characteristics and can therefore evolve over several years before the diagnosis is made [15]. This was the case for our patient; the symptoms reported were atypical intermittent abdominal pain associated with an increase in abdominal volume especially in the epigastric region and the patient dragged a long time with these symptoms before consulting.

Imaging plays an important role not only in the diagnosis and localization of GIST, but also in the assessment of extension, the choice of treatment, the evaluation of prognosis and finally in the follow-up of the patients. The choice of which examinations to perform first depends on the size and location of the tumor, but also on the circumstances of discovery [16]. In the case of large abdominal tumors, the combination of several means of imaging exploration is sometimes necessary in order to better define the tumor extension.

Abdominal CT is the examination of choice for the diagnosis of these tumors, for the initial assessment of extension and for follow-up after treatment. It usually allows the diagnosis of GIST and to guide an appropriate course of action [17]. Typically, they appear as masses with exoluminal development and clear contours, of variable size. The density may be spontaneously heterogeneous, due to areas of hypodense necrosis or hyperdense hemorrhagic changes.Multiplanar reconstructions (MPR mode) as well as maximum intensity mode (MIP) reconstructions are useful for analyzing the lesion and its vascular pedicles. After injection of contrast agent, the enhancement is most often heterogeneous, especially for larger tumors. Generally, no lymphadenopathy or calcifications are found. Peritoneal effusion is rare as is vascular invasion. More rarely, some tumors may have a predominantly intramural or intraluminal component or may be homogeneously enhanced [17].

MRI is not routinely used in the evaluation of GIST but remains superior to CT in pelvic locations and in the research and characterization of hepatic metastases. GISTs appear in the form of well-limited masses hypointense in T1 and hyperintense in T2 with heterogeneous enhancement after injection of gadolinium and signs of necrosis in the hemorrhagic or pseudo cavitary aspect. [16]

PET scan is mainly used to monitor tumor regression under medical treatment with Imatinib Mesylate, because it is assessed much earlier and more accurately than CT scans. It is therefore useful in the assessment of GISTs before the start of Imatinib treatment and in evaluating the effectiveness of the latter at an early stage (1 month), but also in the case of equivocal images suggestive of metastases.However, routine PET scanning in patients with localized GIST

before and after complete resection is not recommended [18].

Angiography is not used in the evaluation of GIST but can be used in the assessment of bleeding, prior to embolization or surgery. These tumors are hyper vascularized and often depend on the gastroduodenal or left gastric arteries [19].

The definitive diagnosis of GIST is histological based on expression of the c-KIT marker by tumor cells in immunohistochemistry, GISTs are tumors that develop from precursor cells of the pacemaker cells of the gastrointestinal tract that have the particularity of being c-KIT positive [20]. The c-KIT is a gene responsible for a receptor tyrosine kinase (KIT or CD117), widely involved in the etiogenesis of GISTs [21]. The majority of GISTs (90%) develop as a result of a mutation in the c-KIT gene resulting in activation of the KIT receptor leading to cell proliferation.

Macroscopically, GISTs are pseudo encapsulated tumors, even in the case of malignant GIST, often containing foci of hemorrhage and necrosis. They are often associated with ulcerations of the overlying mucosa, which explains their presentation as digestive hemorrhages.

Microscopically, they are uniform proliferations of mesenchymal cells that are generally strongly positive for c-KIT (CD117) on immunohistochemistry. Other markers can be used such as CD34 [20, 22].

There are rare cases of KIT-negative GIST (about 5% of cases), without mutations in the c-KIT gene, a large proportion of which have mutations in the PDGFR-A (platelet derived growth factor) gene, which is another receptor tyrosine kinase strongly similar to the KIT receptor [23].

The histological diagnosis of GISTs is usually obtained postoperatively by anatomopathological study of the surgical specimen. To date, no pre-therapeutic diagnostic protocol for GIST has been clearly established. This is due to the shortcomings of classical biopsy techniques in the case of GIST. In addition, there is no consensus on the necessity to systematically establish a preoperative diagnosis by micro biopsy.

The systematic extension assessment should include an abdominopelvic CT scan with a thoracic pass, an abdomino-pelvic ultrasound, if possible, with injection and a pelvic MRI in case of pelvic tumor. The CT scan allows a good study of tumor invasion by showing the displacement of the organs and adjacent vessels by the tumor or by visualizing signs of direct invasion [24]. Abdominal lymphadenopathy is never present because these tumors are not lymphophilic. The presence of adenopathy should suggest another diagnosis: lymphoma or adenocarcinoma. It also allows the detection of hepatic metastases, peritoneal invasion, and pulmonary metastases thanks to systematic thoracic sections in the assessment of GIST. Other investigations should be discussed on a case-by-case basis [25].

The treatment of choice for GIST still remains surgery and represents the only potentially curative treatment for these tumors [26-29]. GISTs should be approached surgically with the aim of performing curative surgery with complete resection (R0) of the tumorwith a margin of 1–2 cm being ideal [27, 30]. The overall rate of GIST resectability reported in the literature varies between 50 and 90% [31], it is influenced by the collective recruitment of centers.

Because GISTs are mesenchymal tumors, they should be managed by a specialized team, similarly to sarcomas [32], because: in a hand, GISTs, are encapsulated tumors with little tendency to directly invade surrounding organs [27, 30] And on the other hand, like all sarcomas, they have a hematogenous spread and very rarely a lymphatic spread [27, 30, 32]. These two characteristics influence the surgical management of these tumors for which lymphadenectomy or large mutilating resections of surrounding organs are not recommended [27, 30]. Finally, although encapsulated, these tumors are very friable and their disruption or rupture during excision inevitably leads to intraperitoneal dissemination, as GISTs have a strong affinity for peritoneal dissemination [30, 32].

GISTs have the particularity of showing different degrees of malignancy. Among the most recognized prognostic factors, two seem to play a preponderant role: the size of the tumor and the rate of intra tumoral mitosis.These two criteria are also the basis of the prognostic scale currently used for GIST (Fletcher scale) [26]. The five-year survival rate of patients with low-grade GISTs is greater than 95% after surgical resection and is comparable to that of the normal population. In comparison, that of patients with high degree of malignancy was 20% at five years before the introduction of Glivec [30].

GISTs are highly resistant to radiotherapy and standard chemotherapy [30]. Many protein kinases are overexpressed or abnormally active in cancers and play a major role in their development and progression. They are therefore key targets in the anti-cancer therapeutic arsenal. Imatinib mesylate is a potent and relatively selective inhibitor of tyrosine kinases including: c-KIT, c-ABL, PDGFRA and BCR-ABL [26].

The response rate in metastatic GIST to imatinib mesylate is 60 to 70% with a median patient survival of more than two years [26, 30]. The response to treatment in patients with GIST is influenced by the

type of c-KIT mutation and for some mutations increasing doses have been shown to improve the response rate [30].

It is important to know that all patients with a tumor response to mesylated imatinib will eventually develop resistance to treatment [30]. For this reason, even in a patient with a complete radiological response, possible surgical treatment should be discussed. Furthermore, once treatment with Glivecis started, if it is effective, it must be continued for life, because the risk of tumor flare-up when treatment is stopped is high [30].

CONCLUSION

The management of gastrointestinal stromal tumors has been revolutionized by an anti-tyrosine kinase: Imatinib, which has transformed the therapeutic indications.

REFERENCES

1. Koyuncuer, A., Gönlüşen, L., & Kutsal, A. V. (2015). A rare case of giant gastrointestinal stromal tumor of the stomach involving the serosal surface. *International journal of surgery case reports*, *12*, 90-94.
2. Rosai, J. (2011). Gastrointestinal Tract. Rosai and Ackerman's Surgical Pathology (10th ed.), Mosby Elsevier, New York, p. 585–816.
3. Miettinen, M., & Lasota, J. (2006). Gastrointestinal stromal tumors: review on morphology, molecular pathology, prognosis, and differential diagnosis. *Arch Pathol Lab Med*, 130 (14), 66-78.
4. Skandalos, I. K., Hotzoglou, N. F., Matsi, K. C., Pitta, X. A., & Kamas, A. I. (2013). Giant extra gastrointestinal stromal tumor of lesser omentum obscuring the diagnosis of a choloperitoneum. *International journal of surgery case reports*, *4*(10), 818-821.
5. Osada, T., Nagahara, A., Kodani, T., Namihisa, A., Kawabe, M., Yoshizawa, T., ... & Watanabe, S. (2007). Gastrointestinal stromal tumor of the stomach with a giant abscess penetrating the gastric lumen. *World journal of gastroenterology: WJG*, *13*(16), 2385-2387.
6. Goldblum, J. R. (2009). Gastrointestinal Stromal Tumors, Odze, R. D., & Goldblum, J. R. (Eds.), Surgical Pathology of the GI Tract, Liver Biliary Tract, and Pancreas (2nd ed.), Saunders, Philadelphia, PA, pp. 681-694.
7. Zhou, L., Liu, C., Bai, J. G., Wei, J. C., Qu, K., Tian, F., ... & Meng, F. D. (2012). A rare giant gastrointestinal stromal tumor of the stomach traversing the upper abdomen: a case report and literature review. *World journal of surgical oncology*, *10*(1), 1-5.
8. Miettinen, M., & Lasota, J. (2001). Gastrointestinal stromal tumors–definition, clinical, histological, immunohistochemical, and molecular genetic features and differential diagnosis. *Virchows archiv*, *438*(1), 1-12.
9. Vij, M., Agrawal, V., Kumar, A., & Pandey, R. (2013). Cytomorphology of gastrointestinal stromal tumors and extra-gastrointestinal stromal tumors: A comprehensive morphologic study. *Journal of Cytology/Indian Academy of Cytologists*, *30*(1), 8-12.
10. Goldblum, J. R., Odze, R. D., & Goldblum, J. R. (Eds.). (2009). Gastrointestinal Stromal Tumors, Surgical Pathology of the GI Tract, Liver Biliary Tract, and Pancreas (2nd ed.), Saunders, Philadelphia, pp. 681-694.
11. Benesch, M., Schneider, D., Brecht, I. B., & Olson, T. A. (Eds.). (2012). Andrea Ferrari. Gastrointestinal Stromal Tumor. Rare Tumors in Children and Adolescents, Springer-Verlag, Berlin, pp. 279-280.
12. Rubin, B. P. (2013). GIST, EGIST Enzinger and Weiss's Soft Tissue Tumors (6th ed.), Saunders, Philadelphia, PA, pp. 569-588.
13. Bellamlih, H., Bouimetarhan, L., Amil, T., Ennouali, H., Chouaib, N., Jidane, S., ... & Belyamani, L. (2017). Tumeurs digestives rares: tumeur gastro-intestinale stromale (GIST): à propos d'un cas de localisation grêlique et revue de littérature. *The Pan African Medical Journal*, *27*, 274
14. Rubin, B. P. (2013). GIST, EGIST. Enzinger and Weiss's Soft Tissue Tumors (6th ed.), Saunders, Philadelphia, PA, pp. 569-588.
15. Scaglia, É., Jazeron, J. F., Diebold, M. D., & Bouché, O. (2010). Tumeurs stromales gastro-intestinales (GIST). EMC. *Elsevier Masson SAS, Paris), Gastro-entérologie*, *9*(27), 1-15.
16. Bassou, D., Darbi, A., Harket, A., Chamssi, M. A., Amezyane, T., El Fenni, J., ... & El Kharras, A. (2008). Tumeur stromale digestive: apport du scanner et corrélations pathologiques. *Feuillets de radiologie*, *48*(1), 39-44.
17. Bensimhon, D., Soyer, P., Boudiaf, M., Fargeaudou, Y., Nemeth, J., Pocard, M., ... & Rymer, R. (2009). Imagerie des tumeurs stromales digestives. *Journal de Radiologie*, *90*(4), 469-480.
18. Alberini, J. L., Al Nakib, M., Wartski, M., Gontier, E., Cvitkovic, F., Rixe, O., ... & Pecking, A. P. (2007). The role of PET scan in gastrointestinal stromal tumors. *Gastroenterologie clinique et biologique*, *31*(6-7), 585-593.
19. Zandrino, F., Tettoni, S. M., Gallesio, I., & Summa, M. (2017). Diagnostic and Interventional Imaging, 98(1), 51-56.
20. Joensuu, H. (2006). Gastrointestinal stromal tumor (GIST). *Ann Oncol*, 17(Suppl. 10), 280-286.
21. Miettinen, M., Sarlomo-Rikala, M., & Lasota, J. (1998, January). Gastrointestinal stromal tumours. In *Annales chirurgiae et gynaecologiae* (Vol. 87, No. 4, pp. 278-281).

22. Flethcer, C. D. M. (2002). Diagnosis of gastrointestinal stromal tumors: a consensus approach. *Hum pathol*, *33*, 459-465.
23. Heinrich, M. C., Rubin, B. P., Longley, B. J., & Fletcher, J. A. (2002). Biology and genetic aspects of gastrointestinal stromal tumors: KIT activation and cytogenetic alterations. *Human pathology*, *33*(5), 484-495.
24. Burkill, G. J., Badran, M., Al-Muderis, O., Meirion Thomas, J., Judson, I. R., Fisher, C., & Moskovic, E. C. (2003). Malignant gastrointestinal stromal tumor: distribution, imaging features, and pattern of metastatic spread. *Radiology*, *226*(2), 527-532.
25. Andtbacka, R. H., Ng, C. S., Scaife, C. L., Cormier, J. N., Hunt, K. K., Pisters, P. W., ... & Feig, B. W. (2007). Surgical resection of gastrointestinal stromal tumors after treatment with imatinib. *Annals of surgical oncology*, *14*(1), 14-24.
26. Bucher, P. A. R., Villiger, P., Egger, J. F., Buehler, L. H., & Morel, P. (2004). Management of gastrointestinal stromal tumors: from diagnosis to treatment. *Swiss medical weekly*, *134*(11-12), 145-53.
27. Bucher, P., Egger, J. F., Gervaz, P., Ris, F., Weintraub, D., Villiger, P., ... & Morel, P. (2006). An audit of surgical management of gastrointestinal stromal tumours (GIST). *European Journal of Surgical Oncology (EJSO)*, *32*(3), 310-314.
28. Demetri, G., & Blancke, C. (2004). Optimal management of patients with gastrointestinal stromal tumors (GIST): Expansion and update of NCCN Clinical Guidelines. *J Natl Comp Cancer Network*, 2(Suppl.), 1-26.
29. Connolly, E., Gaffney, E., & Reynolds, J. (2003). Gastrointestinal stromal tumours. *Br J Surg*, 90, 1178-186.
30. Gold, J., & Dematteo, R. (2006). Combined surgical and molecular therapy: The gastrointestinal stromal tumor model. *Ann Surg*, 244, 176-184.
31. Pascal, B., & Philippe, M. Tumeurs stromales gastro-intestinales Service de chirurgie viscérale, Département de chirurgie. HUG, 1211 Genève 14.
32. Woodall, C., & Scoggins, C. (2007). Retroperitoneal and visceral sarcomas: Issues for the general surgeon. *Am Surg*, 73, 631-635.