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Gastrointestinal Stromal Tumors: From Diagnosis to Adjuvant Therapy

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Abstract **Original Research Article**

Gastrointestinal stromal tumors (GISTs) represent a very rare form of digestive tract cancer belonging to the sarcoma family. The aim of this study is to establish the epidemiological profile, diagnostic challenges, and therapeutic difficulties of this malignant tumor in a developing country. A retrospective study, spanning 4 years from 2020 to 2023, was conducted in the Gastroenterology Department I at HMIMV in Rabat, identifying 37 cases of stromal tumors. The average age of our patients was 58 years. The average duration of disease progression was 4 months. Biopsy confirmed the diagnosis in 19 cases and surgery in 18 cases. The main histological form was spindle-shaped (67.6%). The GISTs in our series had an average tumor size of 8.4 cm, with C-Kit positivity in 36 cases. The risk of recurrence was established for all patients, with 17 being at high risk. In the staging evaluation, the tumor was localized in 83.8% of cases, locally advanced in 8.1%, and metastatic in 8.1%. Surgery was the primary treatment for the patients in our study. Drug treatment with imatinib was prescribed for 24 out of 37 patients in the series, accounting for 62.2% of cases. With an average follow-up of five years, the mean survival rate was over 70% at five years, with complete remission in 62.2% of cases, partial remission in 6.3%, tumor recurrence in 9.4%, and death in 15.6% of cases.

Keywords: Stromal tumors - Prognosis - Imatinib – histology Recurrence Complete resection.

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the digestive tract, accounting for 1 to 3% of all digestive cancers [1, 2]. They are characterized by the overexpression of a tyrosine kinase called c-KIT. This c-KIT mutation is identified in 95% of cases and plays a crucial role in the pathogenesis and tumor progression of these tumors. The majority of GISTs, approximately 65% of cases, develop in the stomach, followed by the small intestine, which accounts for about 25% of these tumors [3, 4]. Locations in the colon and rectum are much rarer, involving only 5 to 10% of cases. Other development sites are extremely rare, such as the esophagus, pancreas, mesentery, or omentum. Surgical excision remains the only curative treatment for GISTs. However, in cases of unresectable or locally advanced GISTs, treatments with tyrosine kinase inhibitors, such as imatinib, have shown great efficacy. GISTs are characterized by significant heterogeneity in terms of malignancy. Indeed, there are low-grade GISTs, which have an excellent prognosis, and high-grade GISTs, which are associated with a very poor prognosis. The aim of our study is to describe the clinical and paraclinical characteristics of these tumors, assess the prognosis based on the degree of malignancy, and determine the appropriate therapeutic choices for each GIST profile.

METHODS

This is a retrospective 4-year study conducted in the Hepato-Gastroenterology Department of the Mohamed V Military Teaching Hospital in Rabat. A consecutive series of 37 cases of stromal tumors from 2020 to 2023 was studied. We collected the following data: epidemiological, clinical, morphological, endoscopic, pathological, immunohistochemical, prognostic, therapeutic, and follow-up information.

RESULTS

During the study period, we identified 37 cases of GIST. The median age at diagnosis was 58 years, with ages ranging from 29 to 72 years. A clear male predominance was noted with a sex ratio of 2.08. The most frequent location was gastric in 29 cases (78.4%), followed by the small intestine (ileum) in 4 cases (10.8%). Our series also included 2 cases located in the colon and 2 cases in the mesentery (5.4%). The duration of symptoms before the first consultation varied from 1 month to 13 months, with an average of 4 months; the majority of our patients (78.37%) consulted within 6

months. The tumor was discovered incidentally in only 2 patients, while the other patients presented with a rich and complex clinical symptomatology, with pain being the main symptom in 67.6% of cases. Clinical examination revealed an abdominal mass upon palpation in 7 patients (18.9%), abdominal tenderness in 14 patients (37.8%), and abdominal distension in only one patient. However, almost half of the patients had a normal clinical examination.

Biopsy confirmed the diagnosis in 19 patients: endoscopically in 16 cases and via ultrasound or CT-guided percutaneous methods in 3 cases. Additionally, 18 of our patients (48.7%) had their diagnosis confirmed only during surgery. Histological study showed a predominance of the spindle cell type (67.6%), the epithelioid type was found in 24.3% of cases, while the mixed type was observed in only 3 patients. The average tumor size was 8.4 cm (ranging from 2 to 30 cm). The mitotic count was five or fewer mitoses per 50 high-power fields in 19 cases (51.3%) and more than ten mitoses in 5 cases (13.5%). Ten patients had low-risk GISTs, ten patients had intermediate-risk GISTs, and 17 patients had high-risk GISTs. No patient had GIST with a very low risk of malignancy. The C-kit test, performed on all patients in our series, was positive in 36 cases, representing 97.3% of the cases. Molecular biology to search for mutations in the c-KIT and PDGFR genes was performed in only one patient.

At the end of the radiological and histological assessment, the diagnosis was localized GIST in 31 cases, locally advanced in 3 cases, and metastatic in 3 cases. The treatment consisted of surgical resection in 35 cases (R0). In addition to surgery, Imatinib was indicated in 21 cases as an adjuvant therapy decided in the multidisciplinary tumor board, and as neoadjuvant therapy in three cases. Among the 24 patients treated with Imatinib, 16 of them, or 66.6% of the cases, suffered from adverse effects described in the table below according to the severity grade:

Table 1: Side effects of Imatinib retained in our series

Side Effects	Number of Cases
Headache	37.5 % (6 cases)
Lower limb edema	18.75 % (3 cases)
Asthenia, myalgia	12.5% (2 cases)
Diarrhea	25 % (4 cases)
Glossitis	6.25 % (1case)

Depending on the degree and tolerance of side effects, the therapeutic prescription consisted of adding symptomatic treatment in 5 cases, reducing the doses in one case, or permanently discontinuing Imatinib in one case.

After a follow-up of 4 years, five patients in our series were lost to follow-up. Among our evaluable patients (n=32), we observed complete remission in 68.7% of cases (n=22), partial remission and stabilization in 6.3% of cases (n=2), and recurrence and progression in 9.4% (3 cases). Additionally, follow-up revealed five deaths (13.5%), including two patients who died due to progression and tumor recurrence, one patient who died from advanced pancreatic neoplasia associated with GIST, one patient who died on day 14 post-surgery, and one patient who died on day 3 due to postoperative multivisceral failure.

DISCUSSION

GISTs are rare tumors that account for only 1% of all gastrointestinal tract tumors and belong to the sarcoma family, most often developing from Cajal cells or their precursors. However, they remain the most common mesenchymal tumors of the gastrointestinal tract. They have an estimated incidence of about 15 cases per million inhabitants per year. They occur mainly in adults with a median age at diagnosis of around 60 years. Generally, there is no marked preference for one sex over the other; however, some series indicate a slight male predominance. Some authors, both internationally and in Morocco, have observed an equal sex distribution in the incidence of the disease, while others have noted a male predominance, as also observed in our series. In our series, the average age was 58 years (29–72 years), which is consistent with the literature.

Table 2: Comparison of the average age and sex ratio between the series

Series	Average ages (Years)	Sex ratio M/F
O. Hellara *et al*., [6]	60,5	Close to 1
CHU Ibn Rochd [7]	55,2	1.16
CHU Avicenne [8]	60	3
Nasir Ud Din *et al*., [9]	51	1,4
K. Søreide *et al*., [10]	60	Close to 1
Our series	58	2.08

GISTs can develop at any level of the digestive tract, from the esophagus to the rectum. However, their frequency varies significantly depending on the location. The stomach is the predominant site, accounting for 60 to 70% of cases, and the small intestine is the second most common site, representing 20 to 30% of GISTs. Conversely, colonic and rectal locations are much rarer, accounting for only 5 to 10% of cases, and exceptionally

found in the esophagus (1% of cases) or in the mesentery and omentum. In our series, the stomach accounted for 78.4% of the locations, the small intestine 10.8%, and the colon 5.4%. Notably, we found an exceptionally high frequency of mesenteric locations (5.4% of cases) compared to the literature data.

Gastrointestinal stromal tumors (GISTs) most commonly present with symptoms related to their tumor growth. The most frequent modes of presentation include gastrointestinal bleeding, non-specific abdominal pain [13, 14], and the palpation of an abdominal mass once the tumor has grown large enough to be detected during clinical examination [3, 15]. They can remain asymptomatic for a long time in 30 to 50% of cases until they become large or cause complications [13, 15]. In our series, abdominal pain was the presenting symptom in over half of the cases (67.6%), followed by gastrointestinal bleeding in 19 cases (51.4%), 7 patients presented with an abdominal mass (18.9%), and one case presented with a pseudo-obstruction syndrome (2.7%). Only two patients were incidentally discovered.

Table 3: Comparison of mode of discovery and symptomatology between series

Series	Incidentally Discovered	Functional signs according to their frequency
O. Hellara *et al*., [6]	8%	Digestive hemorrhage 48% Abdominal pain 48% Abdominal mass in 24%.
K. Søreide *et al*., [10]	18,7%	Abdominal pain, gastrointestinal bleeding and obstruction
Jiehua Li *et al*., [16]	21,4%	Abdominal pain 31.3% Digestive hemorrhages 31.3% Intestinal obstruction 8.9% Weight loss 8.9%
Our series	5.4 %	Abdominal pain 67.6% Digestive hemorrhage 51.4% Abdominal distension 2.7% Abdominal mass 18.9% Deterioration of general condition 13.5%

GISTs are generally sporadic, and so far, no genetic or environmental risk factors have been identified [17, 18]. However, in very rare cases, they may be associated with certain hereditary syndromes. These syndromes include Carney triad, which typically involves pulmonary chondroma, malignant gastric GISTs, and extra-adrenal paraganglioma, or sometimes two of these tumors, affecting adolescents and young women. In the case of neurofibromatosis, about 5% of patients develop symptomatic digestive stromal tumors, which are often multiple. Finally, cases of familial forms of multiple stromal tumors have also been reported [19-22]. Our study does not rule out such mutations, as no germline mutation testing has been conducted.

The necessary examinations to diagnose a GIST depend on its size and location. The median diameter of a symptomatic GIST is 6 cm, compared to 1.5 cm for incidentally discovered tumors [23]. For tumors smaller than 5 cm in diameter, the diagnosis of gastric, duodenal, or colorectal GIST is typically considered during endoscopy. Small intestinal tumors are detected using enteroscopy and/or capsule endoscopy (which is contraindicated in cases of stenosis), with these examinations subsequently guiding enteroscopy with biopsies.

GISTs typically appear on endoscopy as rounded submucosal tumors protruding into the digestive lumen. The mucosa covering them is usually normal, occasionally with ulceration or central depression. However, endoscopy alone does not definitively distinguish GISTs from other submucosal lesions, especially when the tumor exhibits exophytic growth [24]. In our series, esophagogastroduodenoscopy was performed in 32 of our patients, representing 86.5% of cases. It revealed gastric submucosal tumors in 15 cases, ulcerative protruding gastric lesions in eight cases, and extrinsic compression appearance in seven cases. Rectosigmoidoscopy identified ulcerative processes in 2 patients.

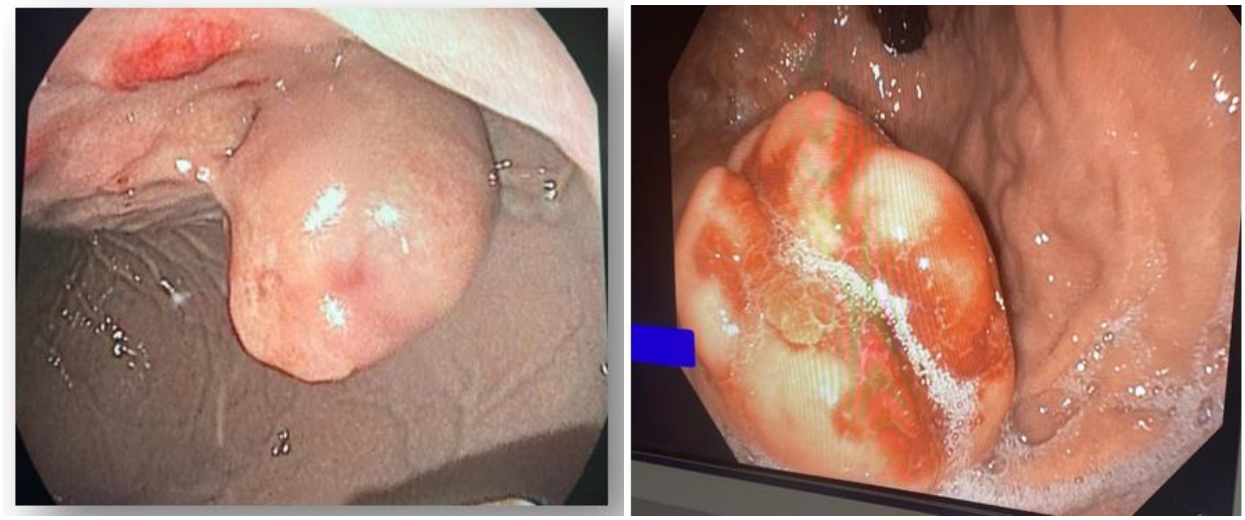

Figure 1: Endoscopic images of the different gastric GISTs

Imaging techniques play a crucial role in the management of GISTs, enabling local and locoregional assessment to determine the feasibility of curative surgical resection, guide percutaneous biopsies for histological diagnosis, and monitor and detect early signs of recurrence or tumor progression. These techniques include ultrasound, CT scan, MRI, and endoscopic ultrasound (EUS). CT scan is generally the preferred initial diagnostic tool for assessing extension and therapeutic follow-up of GISTs. Suspicious criteria for malignancy on CT scan include [25] dimensions exceeding 5 cm, lobulated contours, mesenteric infiltration, heterogeneous enhancement, exophytic growth, presence of ulcerations, areas of necrosis, and hemorrhage. MRI is specifically used for local evaluation of pelvic lesions prior to surgery, offering more detailed tissue analysis than CT scan [26, 27]. EUS is indicated for rectal and esophagogastroduodenal locations, helping to differentiate GISTs from extrinsic compression while assessing predictive criteria of malignancy [28, 29]. Analysis of EUS characteristics supports the presumed diagnosis of GISTs, typically presenting as oval, hypoechoic, homogeneous lesions with well-defined and regular borders, developing from the fourth hypoechoic layer corresponding to the muscularis propria of the digestive wall [30, 31]. While other submucosal lesions may exhibit similar features, they are much rarer. These include gastric Schwannomas, leiomyomas—benign tumors originating from smooth muscle cells more common in the esophagus and rectum—and very rarely, digestive metastases or leiomyosarcomas. In our series, CT scan was performed in 100% of cases for diagnosis, MRI in only two patients, while EUS was conducted in 13 patients (35.1%), allowing for guided aspiration biopsy and leading to diagnosis. Imaging revealed a localized tumor in 31 cases, locally advanced disease in three cases, and metastatic disease in three cases.

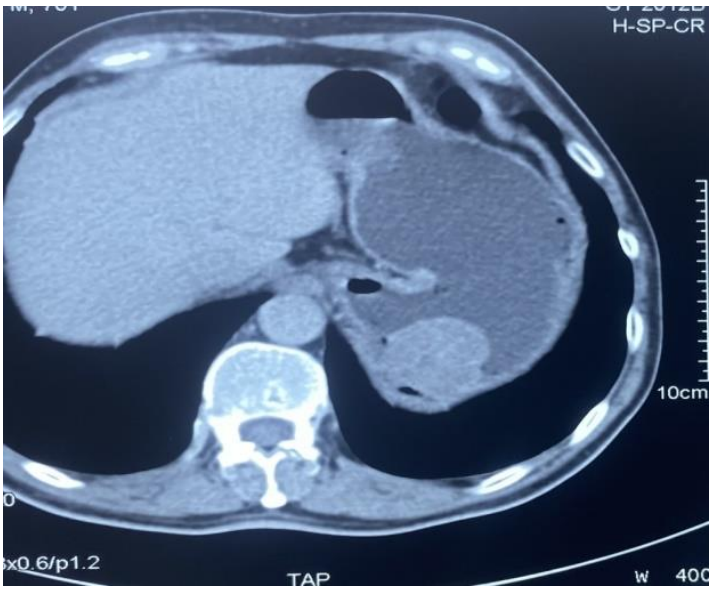

Figure 2: CT image of a gastric GIST

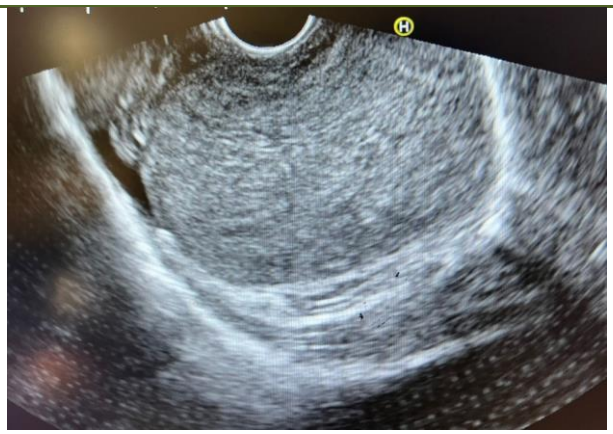

Figure 3: Echoendoscopy of a gastric tumor

A positron emission tomography (PET) with FDG may be recommended during pre-therapeutic assessment if rapid evaluation of Imatinib medical treatment efficacy is desired, as it allows detection of response as early as the eighth day of treatment [25]. It's worth noting that PET has a sensitivity of 86 to 100% for detecting GISTs [32]. In our series, none of the patients underwent this examination.

The diagnosis of GIST can be suspected based on clinical or radiological criteria, but only histological analysis, through pathological examination of a surgical resection specimen or biopsy, can confirm it. In our series, biopsy confirmed the diagnosis in 19 patients, accounting for 51.4%—16 cases through endoscopic biopsy and 3 cases through transcutaneous echo- or scan-guided biopsy, including 2 on hepatic metastases. However, confirmation for 18 of our patients, 48.6% of cases, occurred only at the surgical stage.

Histopathological analysis also allows for the assessment of tumor malignancy potential and guides therapeutic management. Typical GISTs appear as nodules developed within the digestive wall, primarily affecting the muscular layer. These tumors can grow exophytically, projecting into the abdominal cavity, endophytically towards the digestive lumen, or exhibit a mixed growth pattern, forming a "hourglass" shape. They may have an oval or rounded shape, with a sometimes smooth or irregular surface. On sectioning, they are well-defined, non-encapsulated, and typically have a whitish color and very firm consistency. Small lesions are generally homogeneous, whereas larger lesions often show areas of necrosis, hemorrhage, or even pseudo-cystic structures [16]. Their size can vary from a few millimeters to over 40 cm, with exophytic tumors classically being the largest [33, 34]. The average size found in our series upon tumor discovery was 8.4 cm, ranging from 2 cm to 30 cm, closely aligning with observations in the literature where GISTs tend to be of large size [6, 35, 36].

Histologically, gastrointestinal stromal tumors (GISTs) typically consist of spindle cells in 70% of cases, less frequently epithelioid cells in 20% of cases, and a more or less mixed combination of spindle and epithelioid characteristics in 5% of cases, corresponding to the mixed variant [37]. In our study, the predominant form is spindle-shaped, present in 67.6% of cases, followed by the epithelioid form, found in 24.3% of cases, which is consistent with data reported in the literature. Three cases of mixed form were observed [16, 38, 39].

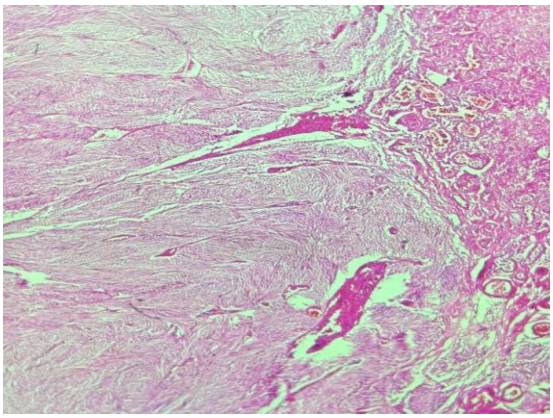

Figure 4: HE staining, magnification × 20: Mesenchymal tumor proliferation composed of interlacing bundles of spindle cells in a loose, edematous exophytic stroma

Immunohistochemistry is essential for the diagnosis of GISTs. The crucial marker is CD117 (KIT), present in 95% of GIST cases. However, KIT expression is not specific to GISTs. In case of negativity, other markers are recommended to support the diagnosis, such as Desmin, H-caldesmon, CD34, and S100 protein [39]. Another sensitive and specific marker for GISTs is DOG-1, expressed in over 99% of cases. This marker is particularly useful in diagnosing GISTs associated with PDGFRA gene mutations, where KIT protein is undetectable in over 60% of cases [41]. In our series, immunohistochemistry was performed on all patients. CD117 and DOG-1 were positive in 36 patients (97.3%). These results closely align with data from the literature [35, 42, 43].

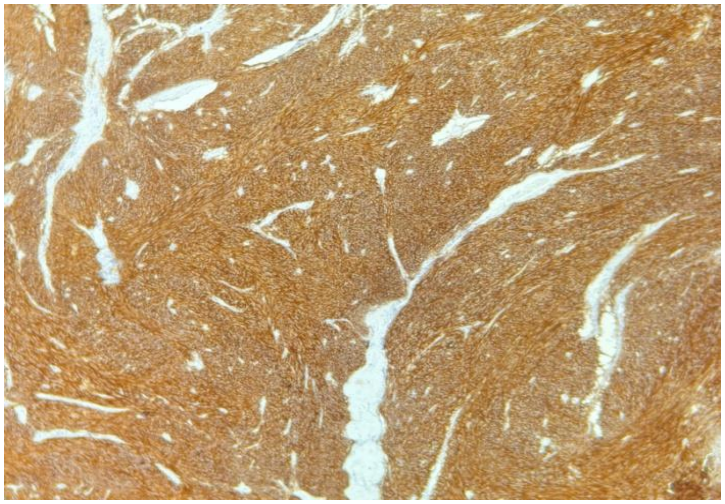

Figure 5: Intense and diffuse cytoplasmic staining with anti-DOG-1 antibody

Mutation testing in PDGFRA and KIT genes through molecular analysis has become standard practice in the management of GISTs. In addition to confirming the diagnosis in challenging cases, this testing identifies the specific type of mutation, which influences prognosis and treatment efficacy, whether in adjuvant or metastatic settings. Genotyping is recommended for all GISTs, except those at very low risk of recurrence [17, 18]. In our series, molecular biology was performed in only one patient.

To assess the risk of recurrence, the National Institutes of Health (NIH) established in 2002 a prognostic classification based on two histological criteria: the mitotic index per 50 high-power fields and the size of the tumor in its largest diameter [43]. In 2006, Miettinen emphasized, based on a large series from the Armed Forces Institute of Pathology (AFIP), that the tumor site, for similar size and mitotic index, is also a prognostic factor. Therefore, small bowel GISTs may present a potentially higher risk of recurrence compared to gastric GISTs [44, 45]. In our series, it is notable that our patients have a high risk of recurrence in 46% of cases. This can largely be attributed to the often significant size of the tumors, which directly impacts the prognostic classification, aligning with findings in the literature [6, 46]. Among our patients, 13.5% had a GIST larger than 10 cm. In 62.1% of cases, the size of the GIST ranged between 5 and 10 cm, while in 24.4% of cases, it measured between 2 and 5 cm. None of our patients had a GIST smaller than 2 cm.

The treatment of GISTs aims to achieve a complete remission. When this is not possible, the objective is to reduce tumor volume and achieve partial remission to prolong survival and alleviate disease symptoms. Surgical resection is the standard initial treatment for localized GISTs that are accessible for complete resection (R0) without capsular rupture, ensuring clear resection margins free of tumor infiltration to prevent intraoperative tumor dissemination, which increases the risk of local recurrence or development of peritoneal metastases. These lesions are often necrotic and fragile, requiring great care during surgery. Some studies have even shown that the survival of patients with intraoperative perforation was similar to that of patients with incomplete tumor resection [47, 48]. Consequently, the conventional open approach is preferred over laparoscopy due to the higher risk of tumor rupture and peritoneal dissemination.

Regarding the optimal resection margin, there is no clear consensus on the necessary safety distance between the tumor edge and the surgical margin. However, a margin of 1 to 2 cm is generally considered sufficient as long as the resection is R0. In our study, treatment involved surgical resection in 94.6% of cases (R0). Surgery for hepatic metastases was performed on one patient during the same operation, involving a metastasectomy, while for the second patient, it was performed after 12 months of medical treatment with Imatinib.

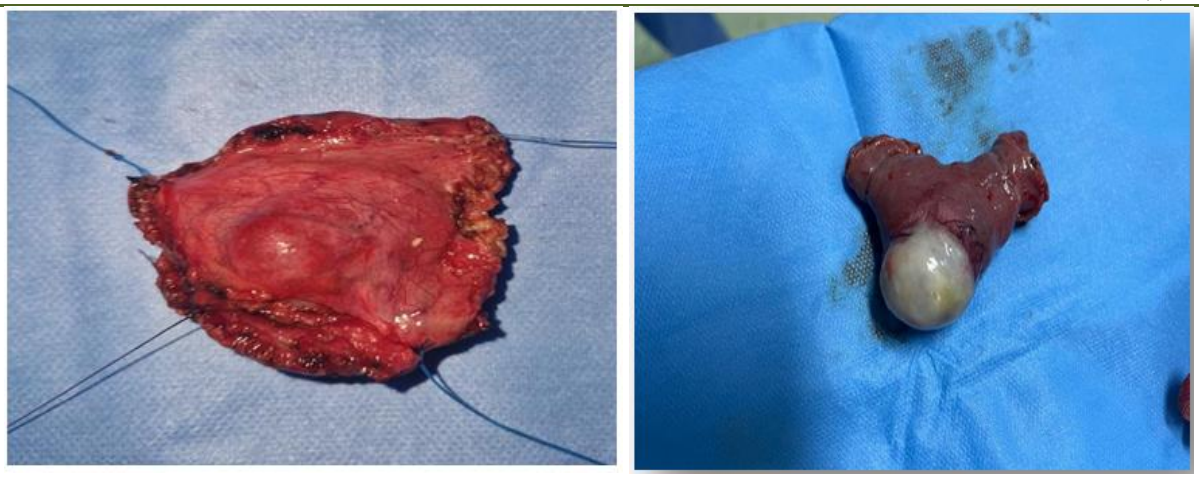

Figure 6: Images of a grelic and gastric stromal tumor

Lymph node dissection is not routinely performed because lymph node metastases are rare, and the risk of nodal recurrence is low, except in pediatric forms.

For aggressive, unresectable, locally advanced, or metastatic tumors, the prognosis has significantly improved since the advent of Imatinib. Its effectiveness is well established, although the optimal administration modalities are not yet definitively determined. The recommended daily dose according to the marketing authorization is 400 mg/day, administered until disease progression, treatment intolerance, or patient refusal [18, 49]. In our series, Imatinib was initiated as adjuvant treatment in 21 cases and as neoadjuvant therapy in three cases.

In the literature, the most commonly reported side effects of Imatinib include fatigue, gastrointestinal disorders, and edema [50, 51].

Among our patients, 66.6% experienced side effects, leading to dose reduction in one case and permanent discontinuation of Imatinib in another. In cases of primary or acquired resistance to standard treatment, as well as in patients with persistent intolerance to Imatinib despite symptomatic treatment, Sunitinib is the recommended therapy.

Sunitinib, acting as an inhibitor of both VEGF and PDGFB receptors, demonstrates strong anti-angiogenic activity in addition to its direct anti-tumor effect. Its efficacy was validated by a multicenter phase III study published in 2006, showing a significant improvement in progression-free survival in the Sunitinib-treated group (6.4 months vs 1.5 months; $p < 0.0001$) [52, 53]. Other targeted therapies such as sorafenib, masitinib, and nilotinib are currently in trial phases [54, 55]. In our study, only one patient was treated with Sunitinib for six weeks, the progress of which could not be clarified he optimal treatment relies on a combination of surgery and targeted therapies such as imatinib, depending on the stage and location of the tumor. Challenges persist, particularly in managing treatment-related side effects and drug resistance, highlighting the need for close and continuous monitoring to enhance long-term outcomes and patient quality of life.

CONCLUSION

Gastrointestinal stromal tumors (GISTs) are rare tumors. Their diagnosis relies on histopathological examination and immunohistochemistry. Complete resection of the tumor is the only potentially curative treatment. Risk assessment for recurrence using the Miettinen classification guides the indication for adjuvant treatment. Imatinib has revolutionized the treatment of GISTs and has become the standard adjuvant therapy following resection of non-metastatic, resectable GISTs with potential for recurrence, as well as first-line therapy for locally advanced and/or metastatic GISTs. Continuous monitoring is essential to minimize treatment toxicities, detect possible recurrences, and limit disease progression. Survival depends on the completeness of surgery and other prognostic factors of the tumor.

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