

## GIST AND OTHER RARE SMALL BOWEL TUMORS – RETROSPECTIVE CLINICAL, IMAGISTIC AND IMUNOHISTOCHEMICAL STUDY

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*The rarity of the small-bowel tumors is well-known, representing 3-6% of all gastrointestinal tumors. In general the diagnosis is late, due to a hemoragic complication or, most-likely, intestinal occlusion. In most cases patients have a background of asthenia, anemic syndrome, diarrhea, Koenig's syndrome which lead to explorations such as endoscopy, ultrasound, radiology, CT scan, MRI scan or pill-cam endoscopy. Malignant tumors of the small bowel (approx. 60%) are represented by: lymphoma (42%), adenocarcinoma (32%), carcinoid tumors (10%) and sarcoma with fusiform-like cell (10%), among the few last being leiomyosarcoma, malignant schwannoma, liposarcoma or GIST (Gastrointestinal Stromal Tumors) represent 2–5% of the small-bowel tumors. Our study was a clinical, imagistic and immunohistochemical one and counts 12 malignant small bowel tumors, represented by: carcinoid, GIST, malignant lymphoma, mesenteric fibrosarcoma, entero-mesenteric metastases and adenocarcinomas. Most of the cases have been documented with advanced histological and immunohistochemical studies which confirmed, especially in the case of metastatic tumors, the origin and parentship with the initial malignant tumor. The clinical evolution was in close connection with the stage of the diagnosis, lymphatic extension and local tumor spread degree, the presence of metastasis, the surgical method performed and adjuvant therapy involved. The aim of this paper was to show to the surgical community some extremely rare tumors, placed at an extremely rare level of the small bowel for which surgical resection is the primary treatment, especially in the case of duodenal carcinoids, leiomyosarcoma and enteric metastasis and currently is the only therapy that offers a chance of cure.*

**Keywords:** GIST, malignant tumors, small bowel, imagistic, immunohistochemistry

### INTRODUCTION

Primary tumors of the small intestine are very rare, comprising approximately 3-6% of all tumors of the gastrointestinal tract. Malignant tumors of the small bowel (approx. 60%) are represented by: lymphoma (42%), adenocarcinoma (32%), carcinoid tumors (10%) and sarcoma with fusiform-like cell (10%), among the few last being leiomyosarcoma, malignant schwannoma, liposarcoma or GIST (Gastrointestinal Stromal Tumors) represent 2–5% of the small-bowel tumors.

Most small intestine tumors are clinically silent for long periods; nearly half of all benign small intestine tumors are found only incidentally either during an operation or an investigation to visualize the intestine for other reasons. Symptoms can be chronic and/or intermittent and include abdominal pain, nausea, weight loss and bleeding. The larger the tumor, the more likely the patient will experience symptoms of bowel obstruction. Tumors can also become ulcerated and bleed<sup>1</sup>.

Gastro-intestinal stromal tumors (GIST) are the most common mesenchymal tumors of the gastro-intestinal tract (GI). Usually, GISTs present in middle age people with a peak age of presentation at 58 years, affecting males and females equally. Frequently, they are solitary, well circumscribed tumors with a pseudocapsule. A GIST can be located anywhere in the gastrointestinal tract, about 40-70% occur in the stomach, 20-40% in the small intestine, and 5-15% elsewhere in the GI tract (oesophagus, rectum, omentum or peritoneum).

They arise from embryological mesoderm of the GI tract and were initially thought to be smooth muscle tumours. These tumors are originated in interstitial cells of Cajal (intestinal pacemaker cells) and were first described by Mazur MT and Clark HB in 1983<sup>1</sup>. Histologically, they are mesenchymal spindle cells and immunohistochemically positive for tyrosine kinase receptor CD 117 (c-KIT), related tyrosine kinase receptor PDGFR (platelet-derived growth factor receptor  $\alpha$ , a KIT), and CD34 expression<sup>2</sup>. KIT has been demonstrated as a very

specific and sensitive marker to mesenchymal tumors in the GI tract and around 95% of GISTs express KIT.

Depending on the size, location and the presence of mucosal ulceration, the clinical presentation of GIST varies significantly including bleeding, abdominal pain, dyspepsia, intestinal obstruction. Approximately half of individuals with GIST present with anemia or anemia-associated symptoms due to mucosal ulceration of a tumor<sup>3</sup>. GISTs may also be discovered as an incidental finding during radiologic imaging, endoscopy, or abdominal surgery performed for other reasons. Patients with clinically malignant GISTs may also be discovered as an incidental finding during radiologic imaging, endoscopy, or abdominal surgery performed for other reasons. Patients with clinically malignant GISTs may present with disseminated disease. Metastases occur primarily in the liver and abdominal cavity. Metastases to the lung, bone, lymph nodes, skin, or soft tissues are rare and generally only seen in the setting of very late-stage disease. Overall 5-year survival is about 35%<sup>4</sup>.

The aim of this paper was to showcase the rarity of such cases, their evolutive particularities, the survival rate, the histopathological or immunohistochemistry aspects and last but not least, that the therapeutical plan must be customized.

## MATERIAL AND METHODS

Our report is a retrospective study at "Witing" Clinical Hospital and takes into account all cases diagnosed and treated for small bowel tumors during a period of 4 years, from 2010 to 2014. Data obtained for all relevant cases included demographics (sex, age), clinical and para-clinical features (presenting symptoms, diagnostic methods, tumor location, loco-regional and distant extension), surgical treatment, pathological diagnostic (histology and immunohistochemistry) and prognosis.

## RESULTS AND DISCUSSIONS

Despite the rarity of these tumors, 12 cases were identified (Table 1).

Type of small bowel tumors	Number of patients	%
Carcinoid	3	25
GIST	2	16,66
Malignant Limfoma	1	8,33
Mesenteric Fibrosarcoma	1	8,33
Adenocarcinomas	2	16,66
Eentero-mesenteric Metastases	3	25

**Table 1.** Histological type of small bowel tumors

Patients presented with a variety of symptoms. Six patients suffered from vague abdominal pain, anorexia and weight loss, one patient was operated urgently due to severe upper GI bleeding, two patients presented with melena and anemia (Table 2).

Symptoms	Number of patients	%
Vague abdominal pain	7	58,33
Anorexia	5	41,66
Weight loss	7	58,66
Nausea and vomiting	3	25
Melenas and anemia	3	25
Severe GI bleeding	1	8,33

**Table 2 –** Symptomatology in small bowel tumors

Computer tomography (CT) was performed preoperatively in 6 patients, which demonstrated accurately the location and extent of the tumors. Gastroendoscopy was performed in 6 patients, but it was irrelevant for the final diagnosis. Two tumors were located in the duodenum – in the Treitz angle, 2 in the jejunum and 5 in ileonum and others in multiple locations. The metastatic lesions appeared after breast, colon and ovary cancer. The first case that this paper is depicting is a case of a male patient whom the objective exam revealed:

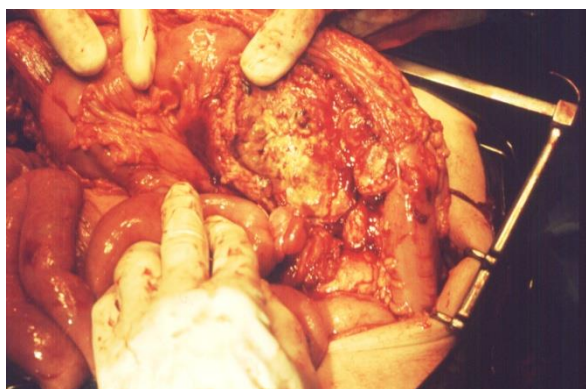
Objective exam highlights a voluminous tumor, painless, consistent, with smooth contour, which occupies the entire epigastric area, without being accompanied by signs of intestinal obstruction low or high, which at first impression could be attributed to a possible gastric neoplasm, pancreatic tumor, hepatic lobe tumor or the transverse colon tumor. The carcinoid syndrome was absent and humoral and urinary determinations showed negative readings.

Ultrasound examination revealed a mass of about 11 cm in diameter near the tail of the pancreas in contact with intestinal loops in the area of Treitz ligament. No peritoneal or hepatic metastases. Contrast radiography revealed a filling defect with ulceration and pancreatic invasion of the distal duodenum tumor, without signs of obstruction (Figure 1).

At laparotomy we found a mass of about 11 cm diameter of the angle of Treitz, ulcerated and invasive in the pancreas, an area of about 8 cm. No macroscopic involvement of regional lymph nodes or hepatic metastases (Figure 2).



**Figure 1.** Radiological aspects of the tumor.

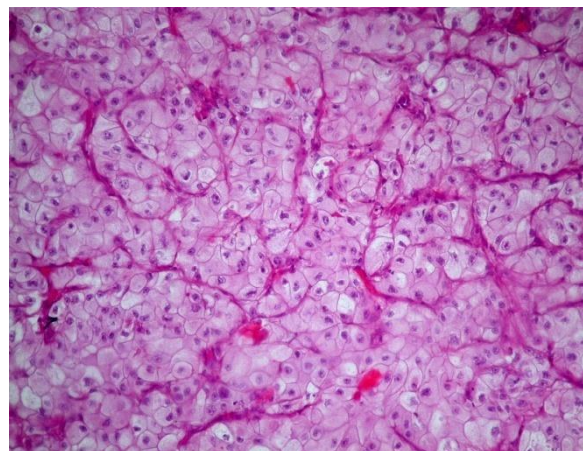


**Figure 2.** Intraoperative aspects.

The histology studies revealed a a carcinoid tumor of duodenum, developing from the submucosal area in the entire duodenal wall (H&E staining, Optical magnification of 200x), with a well-differentiated duodenal clear cells carcinoma (atypical carcinoid) and with nuclear atypical development and mitosis (Figure 3).

Imunohistochemistry shows negative staining for CD30, excluding exocrine pancreas histochemistry. The full range of tests revealed that the tumor stained positive for chromogranin, somatostatin, synaptophysin, cytokeratin, gastrin, carcinoembryonic antigen and neuronal specific enolase and was negative for all other stains, including

serotonin, glucagon, alfa-fetoprotein, vimentin and CD30, exocrine pancreas antibody (Table 3).



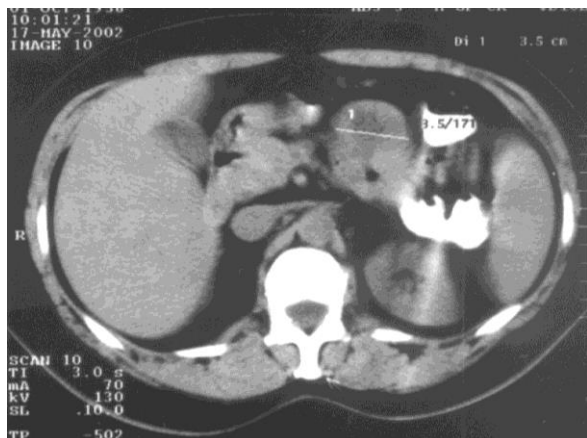
**Figure 3.** Histological aspect. H&E staining, optical magnification of 200x.

Staining	Result
EMA (epithelial membrane antigen)	positive
NSE (neuron specific enolase)	positive (focal)
EP4 (epithelial antigen)	positive
Somatostatin	positive (focal)
CEA (carcinoembryonic antigen)	positive
CK (cytokeratin)	positive (diffuse)
K1 Antitripsin	positive (focal)
Gastrin	positive (focal)
Chromogranin	positive (diffuse)
Synaptophysin	positive (focal)
Alfa-fetoprotein	negative
Vimentin	negative
VIP (vasointestinal polypeptide)	negative
HK1 (TB1)	negative
CD 30 (exocrine pancreas)	negative
PCNA (nuclear factor of cellular proliferation)	staining intensity, 15%

**Table 3.** The whole range of tests performed.

Postoperative evolution is marked by the appearance of a peritonitis due to a postoperative anastomotic fistulae installed at the seventh day after surgery with an initial low flow rate (100 ml/24 hours), but with an extremely serious and major sistemic impact, marked by a septicaemic phenomenon followed by hepatic and renal disfunction and therefore exitus after 24 hours, by sepsis. On the other hand we had an interesting case of leiomyosarcoma, namely a female patient, age 46, that shows postprandial pain at the level of the epigastric area, accompanied by biliary and mixed food regurgitations, with a recent background of weight loss.

The radiological study revealed a filling defect of the fourth portion of the duodenum without bowel obstruction or dilated bowel proximal to the site of this level. CT scan identified a pedunculated mass of about 6 cm, in contact with the distal duodenum wall of the angle of Treitz. (Figure 4).



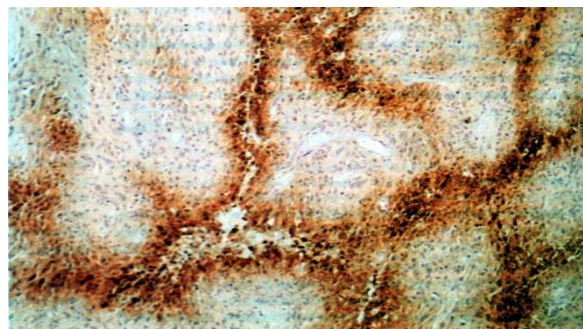
**Figure 4.** Preoperative CT Scan.

At laparotomy, we found a pedunculated mass, of about 6 cm diameter, without involvement of the lymph nodes or hepatic metastases, and without invasion of the pancreas or the left kidney (Figure 5). Gross examination of the specimen revealed a tumor that protruded both intra and extraluminally, with wide ulceration of the duodenal mucosa.



**Figure 5.** Intraoperative aspect.

A diagnosis of low-grade leiomyosarcoma was made on basis of the large sizes of the tumor, wide ulceration and microscopic features of increased cellularity with scattered mitotic figures. Immunostaining for neuronal-specific enolase showing strong, characteristically zonal (brown) positivity (Figure 6).



**Figure 6.** Immunohistochemistry study.

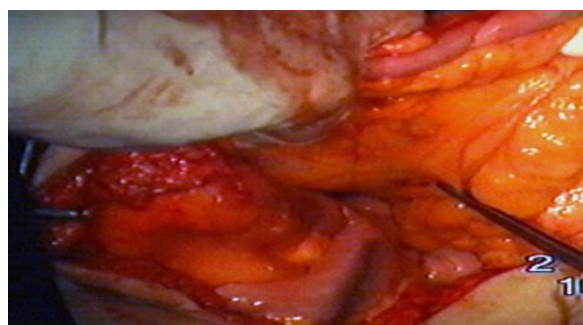
Even more interesting is the next case, depicting a mesenteric metastasis of a female patient, age 67, that was admitted in our clinic for signs of piloric stenosis with GI transit disruption of constipation periods alternating with accelerated intestinal flow. In this case, the obstruction of the Treitz angle was made by an invasive colonic adenocarcinoma mesenteric metastasis, extended from a right colon tumor.

The radiological barium study revealed dilated stomach and duodenum with filling defect at the angle of Treitz. This was a diagnosis trap. Abdominal ultrasound revealed a polypoid mass of about 11 cm diameter, including the superior mesenteric vessels, with retroperitoneal extension and invasion of the distal duodenum (Figure 7).



**Figure 7.** Ultrasound aspect of the tumor.

At laparotomy we found an unresectable, duodenal obstructing mesenteric metastasis in contact with the superior mesenteric artery and vein, extended from a right colon adenocarcinoma. In this situation, after the right hemicolectomy we performed also a gastrojejunostomy. (Figure 8).



**Figure 8.** Intraoperative aspect of the tumor.

Regarding the GIST tumors, we had quite an interesting case of GI bleeding with some difficulties in establishing the correct diagnosis. It is the case of a male patient, E.I., 67 years of age, that was admitted in our clinic (4749/12.06.2012) for rectal bleeding, asthenia and pallor of skin, symptoms debuted in the last 3 months. The patient was a heavy drinker and smoker and he was in treatment for arterial hypertension.

On examination the patient is found under weight, fatigue, pale; the belly is mobile with respiratory movements, sensitive to deep touch, bowel preserved. Rectal examination does not reveal pathological lesions, but point out blood clots and fresh blood. The patient is hemodynamically balanced - TA = 120/70 mmHg, AV = 90 / min. Blood tests revealed a severe anemia (Hb=6,2 g/dl, Hct = 17,9% and MCV, MCH, MCHC in normal range), leukocytosis (WBC=15.60x10<sup>3</sup>/mm<sup>3</sup> with neutrophils 78%), slightly altered kidney function (BUN = 60 mg/dl, Creatinine=1,34 mg/dl), other blood tests were within normal limits. The abdominal ultrasound exam does not describe pathological changes. An upper gastrointestinal (UGI) endoscopy revealed esophagus, stomach and duodenum without bleeding sources. Colonoscopy procedure is possible up to 40 cm. because colon is filled with clotted blood residues and fresh blood. Due to the severe anemia and the impossibility of determining the precise etiology of gastro-intestinal bleeding, we decided to delay the surgical intervention in order to rectify the hemodinamics and haemathological status of the patient. During the admission day and the following one, the patient received 4 units of selected and compatible blood, but the general status is getting worse, the stools are filled with blood and so the surgical approach clearly becomes the only available option for hemostasis. In the preoperative stage the Hb had a value of 7.5g/dl with a Ht of 22%. On the third day of admission, an exploratory laparotomy was performed, which revealed an irregular, firm mass, 4/5 cm., in jejunal location (Figure 9), with a mass protruding from the antimesenteric wall (Figure 10). The lesion was resected with primary end-to-end anastomosis.

The histology exam revealed a high-grade ulcerated GIST with classic spindle cells, clear resection margins, and no lymph node invasion (Figure 11). Immunohistochemistry was positive for c-kit (CD117) and CD34 immunomarkers (Figure 14). Ki67 proliferation marker labels 10% of the nuclei (Figure 12). Mitotic activity was 12/50 on high-power fields.

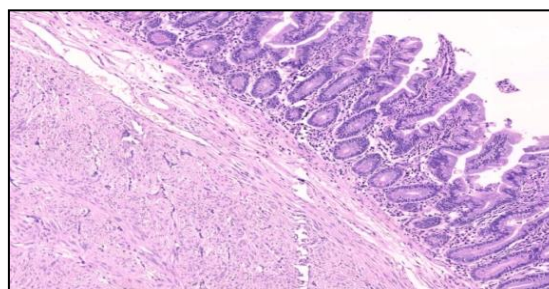
The patient recovered postoperatively without incidences and is clinically stable at 3 years postresection, without evidence of recurrent disease on follow-up CT scans. Malignant neoplasms of the small intestine represent a heterogen group, extremely variable as histologically types, with a malignant potential, being the possible association with other systemic manifestations of carcinoid syndrome, like the PEUTZ-JEGHERS syndrome, the RECKLINGHAUSEN disease, many of which are discovered incidentally during surgery or autopsy<sup>11</sup>.



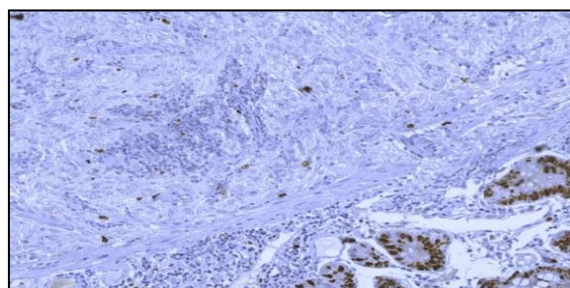
**Figure 9.** Intraoperative aspect of the tumor.



**Figure 10.** A cross-section on the tumor, endoluminal view.



**Figure 11.** Microscopic finding: histological examination showing bundles of spindle cells with elongated nuclei and significant mitotic figures (H&E staining; magnification of 100x).



**Figure 12.** Microscopic finding: immunohistochemistry exhibiting a positive for Ki 67 (Ki67 staining; Magnification of 40x).

Their proportion is obviously higher than benign tumors of the small intestine that do not exceed 0.2-0.3 % from the total digestive tumors.

Malignant lesions of the small intestine is often diagnosed in advanced stages when already become unresectable,

the difference that only 27% no remote metastases at the time of surgery.

Their incidence is rated at less than 2% of the digestive tract neoplasms, although surface absorption of small intestine represents approximately 90% of its detinind, stretching about 70-80% of its length. The most common malignant neoplasms of the small intestine, in descending order are the carcinoid tumors, adenocarcinomas, lymphomas and sarcomas.

Leiomyosarcoma fits in the range of 11-12% of intestinal malignant lesions, with greater incidence in the distal third segment of the duodenum. Direct extension through the invasion of neighbourhood areas is the most common form of dissemination and metastasis at distance follows the hematogenic path. Survival rates at 5 years, in the best statistics, do not go above 50% of the cases, and are published 15 years after the resection for non-invasive leiomyosarcoma<sup>7</sup>.

Duodenal carcinoid is ranked differently in the world, on different statistics, between 1950 and 1991 with an incidence of 1.8-2.1% and the rectum localisation with 1.0 and 2.3%, being the most rare tumor localization of this form on the area of the small intestine. The survival rate at 5 years for tumors confined to the duodenal wall is approximately 65% and for cases with advanced metastases, under 36%.

We notice that the location of these malignant tumors at the level of the boundary between the duodenum and jejunum, known as The Angle of Treitz, are extremely rare, this location being the last place of headquarters of neoplasms of small intestine. But not only the location and the incidence is a rarity, but the palette of surgical options for this region is quite reduced and less diversified, being represented by only two possibilities: the more distinctive, angular resection of the duodenojejunal angle and the cephalic duodenopancreatectomy, both with some special features. Of course, for advanced cases we always consider the possibility of a gastro-enteroanastomosis, as a palative means of surgical treatment<sup>6</sup>.

After nearly 40 years, the gastrointestinal stromal tumors (GIST), are considered simple layer smooth muscle cancers of the digestive tract. During the years, the terminology had undergone some modifications, but became a distinct entity from clinically and histopathologically point of views.

The incidence of GISTs has increased in the last few years due to better detection as all mesenchymal tumors are now being tested for CD117. CD117 (Kit protein) is the product of c-kit proto-oncogene, located on chromosome 4q11-21. This protein is a tyrosine kinase growth factor receptor present in 90% of GIST cells. Mutation of kit proto-oncogene results in a CD117 receptor that is constitutively stimulated without the presence of the stem-cell growth factor<sup>8</sup>. Some of the GISTs that lack the kit mutation appear to have a mutation in another Class III protein kinase gene that encodes the platelet-derived growth factor. It is now believed that these tumors arise either from stem cells that

differentiate towards interstitial cells of Cajal (these cells form part of the myenteric plexus in the gastrointestinal tract and regulate peristalsis) or directly from the Cajal's interstitial cells and not from smooth muscle cells<sup>7</sup>.

Benign characteristics are considered a tumor with a small size of under 5 cm, a low mitotic index of under 5/20 mitoses on high power field observations (HPF). Mitotic index is interpreted depending on the type of cellular nuclear atypical readings.

Reaching the diagnostic of small intestine hemorrhage is difficult, and in as many as 5% of patients with obscure GI bleeding, a source cannot be identified despite extensive examination. Hadithi<sup>10</sup> reports that the judicious use of video capsule endoscopy (VCE) and double balloon enteroscopy (DBE) could be useful diagnostic tools with detection rates of 80% and 60% for VCE and DBE, respectively. Other diagnostic methods include contrast-enhanced computed tomography (CT), CT angiograph, and Meckel's scan if Meckel's diverticulum is thought to be involved and diagnostic laparoscopy.

Concerning the hemorrhagic potential of this tumor, some authors have already reported high incidences of presenting with bleeding, 87% of duodenal GISTs and 64% of other small bowel GISTs. Other locations like gastric, rectal or colonic are associated with less than 45% incidence of bleeding<sup>[11]</sup>. In rare cases such as ours, the massive gastrointestinal bleeding requires emergency surgery for hemostasis.

Before the Imatinib<sup>TM</sup> surgical resection was the only option available as GIST are highly resistant to chemotherapy and radiotherapy. The introduction of Imatinib Mesylate<sup>TM</sup>, a tyrosine kinase inhibitor, has dramatically improved the outcomes of treatment.

The histopathological exam, performed with Hematoxylin-Eosine staining may show the following morphological types of GIST :

- a. The spindle-cell type;
- b. The round/polygonal shaped cell type - epitheloid;
- c. The mixed type.

The immunohistochemistry evaluates the expression of the following specific tumor markers :

- c-KIT (CD117), a glycoprotein of about 145 KD, a definitive diagnosis marker for GIST, with a positivity of about 95%;
- CD 34, a mesenchymal cell specific marker; it is positive in about 60-70% of GISTs,
- The smooth muscle specific actine, positive in about 15-60% of GIST,
- The S-100 protein identified in tumors with mesenchymal origin and in the cells derived from the neuronal edge, positive in about 10% of GISTs,
- Desmine, a protein of the intermediate filaments present in the muscular cells,
- Ki67, a nuclear protein, a marker of cellular proliferation, present in the neoplastic cells with a high rate of multiplication.

The current recommendations in management of GIST are as follows<sup>2</sup>:

- For operable GISTs, perform surgery first followed by adjuvant therapy with Imatinib™ in high risk patients (size > 5 cm, mitotic rate >5 per 50 HPF, incomplete resection, tumour spillage).
- For marginally resectable GIST or in case of inoperable recurrent or metastatic GIST, consider neoadjuvant therapy with Imatinib™ followed by surgical resection.
- For intermediate risk GIST (size < 5 cm and 6-10 mitosis per 50 HPF, or 5-10 cm and, 5 mitosis per 50 HPF), the role of Imatinib™ as an adjuvant therapy is still debatable.

Surgical treatment is one of the most effective forms of treatment for GIST. The opportunity to make a real radiacala, resection is an important prognostic factor. Even if patients with tumors show a direct extension to the organs nearby, they enroll in the same predictable intervals of survival rate just as the localized lesions develop.

The tumoral relapse or metastasis to a distant location is valued at approximately 50% of cases, even in situations where a radical resections of primary tumor was performed. Resection of tumor recurrence allows a survival of about one year after the intervention, and the primary location of most of the tumor recurring frequencies are represented by the liver or peritoneum.

The main objective is the total tumor resection with free margins, with a limit of oncological safety of at least 2 cm away from the wall of the tumor. All GIST being deemed potentially malignant tumors, even those tumors that are smaller than 2 cm with intraparietal localisation must be cut, in this case the laparoscopic technique being admitted. Because not all injuries are intraparietal GIST, especially in the case of the stomach, in order to proceed with resection a preoperative histopathological positive exam is necessary.

Preoperative biopsy requires a selective approach to the cases because of the risk of rupture of the tumor or dissemination, this being made either by means of percutaneous endoscopic or through open approach.

The intraabdominal biopsy can be followed by peritoneal dissemination through efractia of the tumor's capsule. Laparoscopic technique for the same reasons is not a choice, and classical techniques on the path of open surgery should avoid rupture the capsule and its discharge into the peritoneal cavity of the tumor content<sup>12</sup>.

The prognosis of GIST primarily correlates with tumor size, mitotic index, and location. In addition, many other independent predictors of survival have been described<sup>8</sup>, including older age, black race, advanced stage, no surgical intervention or incomplete resection, and high Ki-67 count<sup>13</sup>.

## CONCLUSIONS

1. There are several reasons for which the small bowel tumors are so rare :
  - High speed of the digestive transit;
  - The alkaline pH of the small bowel;
  - Reduced bacteria concentration in the small bowel;
  - The less aggressive liquid content of the small bowel;
  - IgA high concentration;
  - High content of Benzipren-Hidroxylyase with high anticarcinogenetic potential;
2. Surgical resection is the primary treatment for duodenal carcinoids, leiomyosarcoma and enteric metastasis and the only therapy that offers a chance of cure;
3. Duodenal carcinoids appear slow-growing and exhibit a limited propensity for both metastatic and local spread;
4. This favorable biologic characteristics mandate an aggressive surgical approach to this disease aimed at complete tumor excision with negative histologic margins;
5. The location and histology of the tumors permitted a pancreas-preserving segmental duodenectomy, in the first three cases;
6. The operative approach chosen allowed a curative pancreas-preserving resection with a favorable outcome also in the case of leiomyosarcoma;
7. The mesenteric metastases of adenocarcinoma invasive in the angle of Treitz, are unresectable tumors and require a gastrojejunostomy;
8. GIST is an unusual cause of upper gastrointestinal bleeding and sometimes the bleeding can be massive and can require emergency surgery for hemostasis. Early surgical intervention is the primary treatment to prevent rebleedings and cure the disease.
9. All suspected gastrointestinal mesenchymal tumors should be tested for CD117 by an experienced histopathologist. Following surgery, all patients must be referred to centres which have more experience in treating GIST.
10. Imatinib™ has proven to be the first effective systemic therapy in cases of unresectable or metastatic disease. In case of operable GIST, Imatinib™ is indicated as an adjuvant therapy in high risk patients. All GISTs have the potential for aggressive behaviour, the risk being estimated from tumour size and mitotic count<sup>17</sup>.
11. One of the goals of this paper is to show extremely rare tumors placed on extremely rare level of the small bowel.

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