Gastrointestinal stromal tumors – a clinical-morphological study on 15 cases

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Abstract
Aim: The authors present their experience in addressing the gastrointestinal stromal tumors (GIST). Materials and Methods: 15 GiSTs operated in the last five years (2008–2013) were analyzed. Results: The preoperative diagnosis was difficult: established by clinical examination and CT in two cases; imagistic accidental discovery in four cases and revealed by evolving complications in nine cases (gastrointestinal bleeding in four cases and bowel obstruction in five cases). CT may be useful in the preliminary estimation of the tumor extent. Tumor location was: stomach four, duodenum one, small bowel seven, and colon three. Pathological examination set the main criteria for assessing the risk of recurrence and indication for adjuvant therapy: the tumor size, the histological type (spindle cell nine, epithelioid four, and mixed two) and the mitosis rate, while the immunohistochemistry examination established the correct diagnosis (positivity for CD117 and CD34) and highlights the markers of aggressiveness (elevated Ki67 labeling index). Conclusions: GiST has been imposed over the last decade as the main type of non-epithelial tumor of the digestive tract. The preoperative imagistic investigations can be very useful for setting the surgical strategy. The improvement of the mitotic index and/or Ki67 labeling index (LI) determination could render more accurate the scales for prognostic assessment. The two steps algorithm – surgery + adjuvant therapy – still remains the only option to make this dangerous condition a curable one.

Keywords: gastrointestinal stromal tumors, immunohistochemistry, assessment.

Introduction
The term “gastrointestinal stromal tumor (GIST)”, introduced by Mazur and Clark in 1983 [1] was originally used to refer to all non-epithelial tumors of the digestive tract. Since the 90s, with the identification of the molecular basis of GIST and particularly with c-kit protein [2], the term is used to assign a well-defined anatomo-clinical entity among non-epithelial tumors of the digestive tract – the mesenchymal tumors that originate from a precursor of interstitial Cajal cells (ICC), belonging to normal myenteric plexus.

Rare tumors but the most common mesenchymal neoplasms of the gastrointestinal tract [3, 4], with an incidence estimated between 0.1% and 3.0% of the whole malignant digestive tumors (11–14 cases/1 000 000 inhabitants, 3300 to 6000 new cases/year in U.S.A.) [5–7] they affect both male and female in almost equal proportions, predominantly in the 6th and 7th decades of life [8]. Having a patchy distribution along the digestive tract, the stomach being the most common involved, all should be considered potentially malignant, but the risk of recurrence and metastasis are different, depending on the location of the primary lesion, the size, histological type, degree of differentiation and mitosis rate.

Their extramural growth in a very permissive space, favoring a prolonged asymptomatic evolution together with a vague and non-specific clinical picture make the preoperative diagnosis extremely difficult, set accidentally by imaging tests (CT, MRI) and/or endoscopy performed for suffering most commonly attributed to other diseases or revealed intraoperatively during an emergency surgery, imposed by evolutionary complications such as bowel obstruction or bleeding (gastrointestinal or peritoneal).

The diagnosis of certainty belongs to the morphological examination: macroscopic, histological and immunohistochemical.

Histological assessment determines the histological type, the degree of cell differentiation and the mitosis rate, which, along with the topography and size of the tumor are the main criteria for the primary lesion staging, the recurrence risk assessment and implicitly for the adjuvant therapy opportunity, while the immunohistochemistry (IHC) provide the diagnosis of certainty (positivity for CD117 and CD34) and highlights the markers of aggressiveness (elevated Ki67 labeling index).

Surgery based on oncological principles (resection with free-tumor margins histological confirmed) is the main therapeutic option and the adjuvant therapy with
Imatinib, indicated in cases with medium and high recurrence risk, completes the therapeutic algorithm.

**Materials and Methods**

The study was carried out on 15 patients operated in the 1st Surgical Department of Emergency County Hospital of Craiova, Romania, between 2008 and 2013, whose pathologic diagnostic established in the Pathology Department of the same hospital was of GIST.

The study was based on a protocol, following elements of clinical, imaging and morphological diagnosis (macroscopic, histological and IHC), on which was established the indication for surgery and adjuvant therapy.

The study was a retrospective one and had two components, depending on the assessed parameters:

- a clinical part including: gender, age, clinical picture, imaging tests, the lesion’s location and etiological diagnosis suspicion;
- a histopathological part that focused on the diagnosis assessment on routine stained samples and clearing up of borderline cases using the immunohistochemical techniques.

The materials were obtained from two different data sources:

- clinical, imaging, surgical and histological records;
- histological samples and archived paraffin blocks of each case.

The surgically removed samples were processed using the classical histopathology technique (fixation and paraffin embedding) and then stained with Hematoxylin–Eosin.

In all cases, a panel of antibodies was applied in order to identify the GIST IHC pattern (Table 1).

**Table 1 – Antibodies used to identify and assess the GISTs**

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Clone</th>
<th>Source</th>
<th>Dilution</th>
</tr>
</thead>
<tbody>
<tr>
<td>M pan cytokeratin</td>
<td>AE1/AE3</td>
<td>DAKO</td>
<td>1:50</td>
</tr>
<tr>
<td>M Ab anti-CD117</td>
<td>K1906</td>
<td>DAKO</td>
<td>1:200</td>
</tr>
<tr>
<td>M Ab anti-CD34</td>
<td>QBEnd10</td>
<td>DAKO</td>
<td>1:50</td>
</tr>
<tr>
<td>M Ab anti-smooth muscle actin (SMA)</td>
<td>1A4</td>
<td>DAKO</td>
<td>1:50</td>
</tr>
<tr>
<td>M Ab anti-desmin</td>
<td>D33</td>
<td>DAKO</td>
<td>1:100</td>
</tr>
<tr>
<td>P Ab anti-S100 protein</td>
<td>DAKO</td>
<td>1:100</td>
<td></td>
</tr>
<tr>
<td>M Ab Ki67</td>
<td>MIB-1</td>
<td>DAKO</td>
<td>1:10</td>
</tr>
</tbody>
</table>

Tumor dimensions were accurately determined on post-operative photographs of the gross specimens using the “Measurements” module of the Analysis Pro 5.0 software after preliminary calibration of each image (Figure 1).

For prognostic evaluation of studied GISTS with the aid of Ki67 staining, a scoring system of labeling index (LI) and a corresponding risk category stratification system, both proposed by Hasegawa in 2008 [11] were used (Table 3).

**Table 3 – Hasegawa’s Ki67 Scoring System and Risk Category Scale**

<table>
<thead>
<tr>
<th>Ki67</th>
<th>Risk category for primary GIST</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5%</td>
<td>Low</td>
</tr>
<tr>
<td>5–10%</td>
<td>Intermediate</td>
</tr>
<tr>
<td>&gt;10%</td>
<td>High</td>
</tr>
</tbody>
</table>

The chi-square test was used to analyze the possible relationships between the clinicopathological features, considering p values of <0.05 statistically significant.

**Results**

**Clinical profile**

**Age and gender**

The studied tumors were encountered predominantly in men, with a sex ratio =2 (Figure 2).

Most of the patients included in the study were aged over 50 years, with a mean age of 62.4 years, and the largest number of cases grouped in the sixth decade of life, the trend of age distribution decreasing after this period (Figure 3).
Gastrointestinal stromal tumors – a clinical-morphological study on 15 cases

The preoperative clinical diagnosis was an assumption one in most cases, based on various clinical pictures which only were suggesting a gastrointestinal suffering (Table 4).

Table 4 – Clinical status on admission

<table>
<thead>
<tr>
<th>Type of clinical picture</th>
<th>Presenting clinical picture</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical picture</td>
<td>Non-specific gastrointestinal symptoms</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal bleeding</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Subocclusion syndrome</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>4</td>
</tr>
<tr>
<td>Tumoral acute complication</td>
<td>Hemoperitoneum</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Intestinal obstruction</td>
<td>2</td>
</tr>
</tbody>
</table>

In six of the cases, the intestinal tumor was discovered incidentally, during the investigations performed in order to elucidate the non-specific clinical manifestations.

The tumor existence was taken into consideration when a hemorrhagic syndrome was present, either upper gastrointestinal bleeding or hemoperitoneum or particularly when facing with an intestinal obstruction syndrome.

Imagistic investigation

Computed tomography (CT) was the main imaging test, carried out in all cases. It revealed the tumor and provided useful morphological data for the preoperative preliminary staging like the primary lesion site and size, the local invasion and the presence of metastases.

Tumor topography

The CT investigation was very accurate in establishing the tumor site along the gastrointestinal tract, topography confirmed further intraoperatively. Thus, the most frequent site of GISTs in our series was the small bowel, almost half of the patients having a tumor in this location. The next affected segment was the stomach, with a quarter of all patients, followed by the large bowel (Figure 4). In one case, the tumor has developed in the duodenal wall.

Tumor staging

The CT investigation was also useful in preoperative estimation of the degree of tumoral extension. Thus, in slightly more than half of the cases the imagistic investigation revealed a localized tumor, which seemed to be confined to the intestinal wall. However, a significant number of cases, representing less than one half but more than one third, showed features suggesting a local extension of tumoral proliferation, beyond the external limits of tumoral wall (Figure 5). In only one case, the CT examination pointed out the possible involvement of local lymph nodes.

In some cases, an endoscopic examination was performed in order to either collect tissue samples for preoperative histological assessment or to evaluate the hemorrhagic risk of the tumors.

Morphological profile

Tumor size

Studied tumors had significant dimensions in relation with the tissular structures where they were developed, almost 90% having more than 5 cm in the larger diameter.
and almost one-third being larger than 10 cm (Figure 6). The smallest one, a gastric tumor, had 4 cm and the largest one, in the small bowel, had 15 cm.

**Figure 6 – Distribution depending on tumor size.**

**Histological type**

The most frequent histological picture was that of a solid proliferation dominated by an interlacing fascicular and/or whirled arrangement of uniform spindle cells with elongated vesicular nuclei and eosinophilic cytoplasm (Figure 7).

**Figure 7 – GIST: spindle cell type. HE staining, ×40.**

This dominant histological pattern, accompanied by areas consisting of epithelioid rounded cells with a clear or lightly eosinophilic cytoplasm was identified in almost two thirds of the tumors (Figure 8).

**Figure 8 – Distribution depending on histological type.**

The morphological pattern dominated by large more or less cellular areas consisting of epithelioid cells (Figure 9) was twice less frequently observed, being encountered in slightly more than one fourth of the cases (Figure 8).

Only two tumors presented a mixture of areas dominated by spindle cells pattern with areas rich in epithelioid cells.

Tumoral mass may involve all layers of the intestine and may either grow extramurally or extend intraluminally. In both cases, the risk of ulceration is present, with subsequent bleeding either in the lumen, resulting in an upper gastrointestinal hemorrhage or in the peritoneal cavity resulting in a hemoperitoneum.

Both situations were present in one third of the studied cases, the former in two gastric tumors (Figure 10) and the latter in two small bowel tumors and one duodenal tumor.

**Figure 9 – GIST developed outside the colonic muscular layers: epithelioid cell type. HE staining, ×40 (left) and ×100 (right).**

**Figure 10 – Gastric GIST: (a) The tumor pushes the gastric mucosa into the gastric lumen, with ulceration on the tumor surface; (b) Necrotic debris covering the ulcerated tumor (HE staining, ×40).**

Excepting one of the two gastric tumors who had only 4 cm, all the other tumors that have ulcerated had the larger diameter between 6 and 8.5 cm.

**Immunohistochemical assessment**

The studied tumors reacted to the application of the standard panel of antibodies for GIST recognition following a positivity distribution pattern similar to those encountered in the literature (Figures 11 and 12).

In order to exclude the event of an undifferentiated epithelial tumor, the covering pancytokeratin AE1/AE3 was used, the immunostaining being negative in all tumors (Figure 12, a and b).

Then, the specific CD117 immunomarker was positive in all tumors (Figure 12, c and d).

The CD34 immunomarker was positive in a significant number of cases, almost three quarters, in accordance with the literature (Figure 12, e and f). It is interesting to point out that there are authors that were recommending to use the term “GIST” only for those stromal tumors that were lacking differentiation toward either smooth muscle phenotype or neural-type elements or both, but which show instead, almost all, immunoreactivity for CD34 [12–14].

Smooth muscle differentiation, indicated by the SMA
immunomarking was observed to only one quarter of the cases (Figure 12, g and h) while the neural differentiation, indicated by the positivity for S100 protein was even less encountered, in only 20% of cases.

**Mitotic index**

The evaluation of the mitotic index, proved to be one of the main prognostic predictors, revealed that slightly more than one half of the cases had less than 5 mitoses/50 high-power fields (Figures 13 and 14).

**Ki67 labeling index**

The evaluation of the cellular activity using the Hasegawa’s scoring system [11] described above revealed that two thirds of the studied tumors had an Ki67 LI higher than 10% and more than one quarter of the cases had an even higher index, which exceeded 30% (Figure 12, k and l; Figure 15).

**Risk of recurrence**

The estimation of the patients’ possible evolution in the future as realized using the modified NIH Consensus Risk classification described above.
The first striking observation was that most of the patients had tumors with a high risk of recurrence (Figure 16; Table 5).

Only one patient, with a gastric tumor, the smallest of all, was included in the “low risk” category and two patients, one with a large enough gastric tumor and one with a small tumor of the small bowel but a somehow “agitated” one, have met the criteria for inclusion in the “intermediate risk” category.

It should be pointed out that, in one case with a small bowel tumor, the presence of a tumor rupture, “moved” the patient in the “high risk” group even NIH consensus criteria would have placed it in the “intermediate risk” group.

No patient with “very low risk” of recurrence was present in the study.

**Table 5 – Risk stratification of studied GISTs**

<table>
<thead>
<tr>
<th>D_R</th>
<th>T_SZ</th>
<th>MI</th>
<th>T_ST</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td></td>
<td>≤5</td>
<td>Gastric</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>6–10</td>
<td>Small bowel</td>
<td>1</td>
</tr>
<tr>
<td>Intermediate</td>
<td>&gt;5.0–10.0</td>
<td>≤5</td>
<td>Non-gastric</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>&lt;5</td>
<td>Small bowel</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>8.5</td>
<td>2</td>
<td>Duodenum</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>&lt;5</td>
<td>Large bowel</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>5</td>
<td>Small bowel</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>&gt;5.0</td>
<td>&gt;5</td>
<td>Any</td>
<td>5</td>
</tr>
<tr>
<td>High</td>
<td></td>
<td>8</td>
<td>Gastric</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>&gt;5</td>
<td>Small bowel</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>&gt;5</td>
<td>Small bowel</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>&gt;5</td>
<td>Large bowel</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>&gt;5</td>
<td>Large bowel</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>&gt;10</td>
<td>Any</td>
<td>Any</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>5</td>
<td>Small bowel</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Any</td>
<td>&gt;10</td>
<td>Any</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>&gt;10</td>
<td>Gastric</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Any</td>
<td>Any</td>
<td>TR</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>&lt;5</td>
<td>Small bowel</td>
<td>1</td>
</tr>
</tbody>
</table>

D_R – Degree of risk; T_SZ – Tumor size [cm]; MI – Mitotic index (/50 HPFs); T_ST – Primary tumor site; TR – Tumor rupture.

**Treatment**

The therapeutical algorithm included two main steps: the first one was the surgical intervention and the second one, the adjuvant medical therapy with Imatinib.

**Surgical therapy**

All patients went through the first step. The surgical strategy has been adopted depending on patient’s condition on admission.

Thus, five of the patients were operated as an immediate emergency, imposed by evolutionary threatening complications: bowel obstruction and intraperitoneal bleeding as it was mentioned above.

The remaining ten patients were operated after clinical and imagistic investigation as programmed interventions.

R0 type excision, based on oncological principles (a macroscopic excision margin of 1–2 cm without tumor cells histologically confirmed and without rupturing the tumor thin pseudocapsule especially in the case of large tumors) [15] which is, however, the goal, was the main surgical procedure, the resection type being chosen according to the tumor size and stage.

Thus, for the gastric tumors, two total and two partial gastrectomies were performed. For the small bowel, the intraoperative situation allowed in six cases the segmental enterectomy and imposed in two of the cases an enlarged resection.

Finally, for the colon, two of the tumors, developed in the intestinal wall of the left colic flexure, required a left colectomy and the third tumor, belonging to the transverse colon wall, imposed a right colectomy.

**Adjuvant medical therapy**

In the second step, the therapeutical protocol with Imatinib, using a standard dose of 400 mg/day, was
given only to the 12 patients with an assessed high risk of recurrence/progression.

Follow up

A postoperative morbidity rate of 13.3%, meaning two patients (one with gastric tumor and one with colic tumor) with anastomotic fistulas which were solved until hospital discharge and a "0" postoperative mortality could be considered as encouraging results of the surgical step within the therapeutic algorithm.

The overall results of the therapeutic strategy, including both surgery and adjuvant medication, at the end of the six years of surveillance are also encouraging:

- Four patients, i.e., the three ones belonging to the “low risk” and “intermediate risk” categories and a fourth one, operated and treated with Imatinib, were declared as cured;
- One patient, treated after operation with Imatinib, developed a recurrence of the tumor, meaning a recurrence rate of 6.6%;
- Nine patients are in different phases of the adjuvant therapy protocol, all of them having a favorable evolution up until now;
- Finally, one patient died during the therapy with Imatinib but the cause of death was related neither with the adjuvant therapy nor with a tumor recurrence. He is mentioned here only to have the entire picture of the studied group outcome. Thus, the overall mortality is of 6.6% but with the specification that patient’s death had no relation with GIST or its treatment.

Discussion

Gastrointestinal tumors are an interesting type of tumors which, even if rare, drew attention seriously in the last decades to the medical world, becoming nowadays not only a distinct family of mesenchymal proliferations but also the most frequent one – almost 20% of all soft tissue sarcomas [16].

They still keep the interest of both researchers and practitioners because of their spectrum of specific features.

Clinical profile

Concerning the age of patients diagnosed GIST, our series is fitting with the literature data which show that more than 80% of the patients are older than 50 years, with a median age widely ranging between 55 and 65, usually slightly over 60 years, and including all locations [16–19].

Concerning the gender, some series show equal gender distribution, but others propose a male predominance, as we observed in our series [20–26].

A first specific feature of GISTs is their wide clinical expression, ranging from virtually benign to highly aggressive tumors but which appears in only 70% of the patients. Moreover, the particularity is represented by the fact that symptoms and signs are not disease specific, but they seem to be related more to the site, size and aggressiveness of the tumor [3, 6, 27, 28–30].

The most frequently encountered symptoms are: (vague) abdominal pain/discomfort (60–70%), gastrointestinal bleeding (30–40%), abdominal mass, and intestinal obstruction. Other symptoms at presentation are also unspecific like nausea, vomiting, anorexia or early satiety and weight loss. Intestinal perforation can also occur uncommonly [3, 6, 28, 30].

However, 20–25% of GISTs are asymptomatic, the tumors being therefore detected incidentally during imaging or surgery for other disorders and, finally, about 5–10% of the lesions are found only at autopsy [6, 28, 29, 31–33].

Even a small one, our series of patients fulfilled all the clinical particularities of a GIST tumor.

However, it could be some comments concerning the accuracy of the imagistic investigation.

It is already well established that imaging investigation and particularly the contrast enhanced computed tomography (CECT) is the most useful tool at the initial staging workup in order to describe the lesion size and size, evaluate its extent, and assess the presence or absence of metastasis [3].

It is true that in terms of tumor site, imagistic investigation indicated accurately the location of all tumors in our series. An interesting observation was that the distribution along the gastrointestinal tract has not respected the frequency hierarchy reported by the great majority of authors, but there are anyway reports in which small bowel is more frequently affected than the stomach (Table 6).

Table 6 – Comparison of site distribution with other studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Stomach</th>
<th>Small bowel</th>
<th>Colon</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>[25] – 2013</td>
<td>42.9</td>
<td>34.2</td>
<td>20</td>
<td>2.9</td>
</tr>
<tr>
<td>[26] – 2013</td>
<td>31.8</td>
<td>33.6</td>
<td>34.6</td>
<td></td>
</tr>
<tr>
<td>Our study</td>
<td>26.6</td>
<td>46.7</td>
<td>6.7</td>
<td></td>
</tr>
</tbody>
</table>

As for the tumor extension, CT examination should be interpreted with caution, no more than a preliminary estimation, which has to be confirmed by the post-operative histological examination.

In our series, the tumor extension was overestimated by the CT examination in 26.7% of cases and in other 26.7% the extension was underestimated (Table 7).

Table 7 – Correlation between tumor extension assessment by CT and by histopathological (HP) examination

<table>
<thead>
<tr>
<th>CT T Ext</th>
<th>HP T Ext</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lc</td>
<td>Le</td>
</tr>
<tr>
<td>Lc</td>
<td>4</td>
</tr>
<tr>
<td>Le</td>
<td>3</td>
</tr>
<tr>
<td>M</td>
<td>1</td>
</tr>
</tbody>
</table>

As for the tumor extension, CT examination should be interpreted with caution, no more than a preliminary estimation, which has to be confirmed by the post-operative histological examination.

The underestimation was determined, in two cases, by the CT’s inability to discriminate the microscopic early invasion of tumor cells in the peri-intestinal tissue, and, in other two cases, by the CT’s inability to discriminate the early invasion of tumor cells in some small regional lymph nodes.

On the other hand, the overestimation was determined,
in three cases, by the misinterpretation of the inflammatory response in the peri-intestinal tissues and, in the third case, by the misinterpretation of some of the regional reactive lymph nodes.

**Morphological profile**

As an overall morphological assessment of our series, studied tumors could be described as large tumors, or rather too large for their site of origin, not too extended beyond the intestinal wall, with a morphological pattern dominated by spindle cells, many of them with a high mitotic index, features that put together, present the group as a mostly high risk of recurrence/progression group. This imbalance is probably the cause of the “discouraging” results of the statistical assessment of the correlations between the main morphological parameters (Table 8).

However, even in these conditions, we could attempt to draw an “organ profile”.

Thus, the gastric tumors were large enough, usually localized, composed more often of spindle cells, rather not so “agitated” but in spite of this, many of them with a high risk of recurrence.

The small bowel tumors, the most numerous subgroup, were mostly large and very large, almost half of them extended beyond the intestinal wall, consisting very often of spindle cells, most of them with a high mitotic index and, therefore, almost all of them with a high risk of recurrence/progression.

The colon tumors, were large, all of them extended beyond the intestinal wall, consisting rather of epithelioid cells, often with a high mitotic index and, therefore all of them with a high risk of recurrence/progression.

Concerning other correlations, the “tumor size” seemed not to correlate with the tumor extension and histology. Somehow (the \( p \) value was closer to the alpha value of 0.05) it seemed to correlate with the mitotic index, in the sense that very large tumors had all a mitotic index greater than “5” whereas tumors smaller than 10 cm had a mitotic index rather smaller than “5”.

However, the only statistically confirmed correlation was found between the “tumor size” and the “degree of risk of recurrence/progression”.

“Tumor extension” showed no correlation neither with “histological type” nor with “mitotic index” or the “risk of recurrence/progression”.

“Histological type” seemed to correlate with the “risk of recurrence/progression” and, what was the most surprising, “mitotic index” did not correlate with the “risk of recurrence/progression”.

**Table 8 – Morphological profile and prognosis of studied GISTs**

<table>
<thead>
<tr>
<th>T_ST</th>
<th>T_SZ</th>
<th>T Ext</th>
<th>HP</th>
<th>MI</th>
<th>D_R</th>
</tr>
</thead>
<tbody>
<tr>
<td>G</td>
<td>1</td>
<td>4</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SB</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LB</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p ( \chi^2 )</td>
<td>0.347</td>
<td>0.270</td>
<td>0.499</td>
<td>0.530</td>
<td>0.588</td>
</tr>
</tbody>
</table>

**Ki67 as a possible predicting marker**

The system using multiple histopathological parameters for GIST prognosis is, on one hand, widely accepted and used but, on the other hand, there are many attempts to improve it, being authors that consider it subjective and lacking reproducibility [34]. One of the reasons that make this system still not a robust one is that until to date, there are no standardized data concerning the appropriate methods for mitotic counting in GIST. The three major questions: where to count, how to count and how large the 50 HPFs area should be, are still open [35]. Moreover, there exists a subset of GISTs with a high intratumoral heterogeneity leading to a great discrepancy in mitotic rates based on the area used for this purpose [36].

Meanwhile, Ki67, a nuclear protein associated with cell proliferation, expresses in all cell cycle phases except for G0 [27]. Recent studies proved its utility as prognostic marker in breast cancers [37]. Even the prognostic value of Ki67 as a potential biomarker has
not been fully investigated in GISTs [38, 39], Jiang et al. proved that Ki67 expression is significantly associated with many clinicopathological features and malignancy in GISTs and, therefore, it could be used as a putative prognostic marker in GISTs [27].

Following Jiang’s advice, we tested all tumors with Ki67 and then used both Hasegawa’s new scoring system and relative risk system in assessing our tumors. A good surprise was to see that “Ki67 score” correlated with the determined “mitotic index”. Not so good surprise was the lack of correlation with the “tumor size”, Jiang et al. stated in their paper (Table 9).

Table 9 – Correlations of Ki67 score and the main morphological features

<table>
<thead>
<tr>
<th>Ki67 score</th>
<th>T_ST</th>
<th>TSZ</th>
<th>T Ext</th>
<th>HP</th>
<th>MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>G</td>
<td>SB</td>
<td>LB</td>
<td>&lt;5</td>
<td>5–10 &gt;10</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2   0</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>4   2</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>4   0</td>
</tr>
</tbody>
</table>

| p2 | 0.775 | 0.127 | 0.082 | 0.403 |

T_ST – Primary tumor site; T_SZ – Tumor size [cm]; T Ext – Tumor extension; HP – Histopathology; MI – Mitotic index (/50 HPFs); G – Gastric; SB – Small bowel; LB – Large bowel; Lc – Localized; Le – Local extension; M – Metastasis; SpC – Spindle cell type; EpC – Epithelioid cell type; MXD – Mixed.

An explanation could be the tumoral heterogeneity invoked by Agaimy et al. [36], heterogeneity we also found in some of our cases (Figure 17) while testing Ki67 labeling. Another explanation could be the reduced number of cases in our study.

However, finally, we compared statistically the Ki67 Related Risk System and the NIH Modified Consensus Risk System (Table 10) and they were somehow very close to correlate. This allow us to hope that if we analyze a larger group of cases and then if we improve both the mitotic counting procedure and the Ki67 LI determination by taking into consideration larger tumoral areas and all morphological distinct parts of a tumor the two systems will correlate in the assessment of tumor prognostic.

Table 10 – Correlation between Ki67 related risk and NIH modified Consensus Risk

| D_R | L   | I   | H   |
|     |     |     |     |
| L   | 0   | 0   | 3   |
| I   | 1   | 0   | 1   |
| H   | 0   | 2   | 8   |

p2 | 0.096 |

D_R – Degree of risk; L – Low; I – Intermediate; H – High.

Treatment

The treatment of the gastrointestinal tumors is a complex one, disposing of surgical and medical methods [40, 41].

Surgery is the main therapeutic option whose goal is the complete removal of the tumor through an R0 resection type, which for GIST means resection with free-tumor margins, histological confirmed, lymphadenectomy being not necessary, taking into account that this type of tumor rarely gives lymph node metastases.

Timing of surgery, surgical tactics and procedures are different, depending on the site, size and stage of the primary tumor, presence or absence of evolutionary complications, age and biological status of the patient [18, 42–44]. Following this strategy, we succeeded in obtaining a low postoperative morbidity rate that anyway was solved until patients’ discharge and no postoperative mortality.

The reasons why we did not use the laparoscopic procedures were three:

1. Many of our cases were hospitalized for an acute complication (intraperitoneal or intraluminal bleeding, or intestinal obstruction);
2. Tumor located in a place that contraindicates the laparoscopic approach;
3. Local invasion of the tumor, which involves an extensive intervention.

However, up to 30% of GISTs recur and progress to metastatic disease even after the complete excision of tumors [27].
Therefore, even the surgical step was a success, we continued for patients belonging to the “high risk of recurrence/progression” group with the second step, consisting of adjuvant therapy with Imatinib, one of the first and promising examples of targeted therapy in cancer. As we mentioned above, there are still nine patients undergoing medical adjuvant therapy in different phases.

The general recommendations are to continue indefinitely the treatment, since treatment interruption is undergoing medical adjuvant therapy in different phases. As we mentioned above, there are still nine patients first and promising examples of targeted therapy in cancer. consisting of adjuvant therapy with Imatinib, one of the study and preparing and writing this article.

All authors had equal contribution in realizing this study and preparing and writing this article.

Conclusions

GIST has been imposed over the last decade as the main type of non-epithelial tumor of the digestive tract. Therefore, any clinician should be aware that beyond a non-specific digestive symptomatology or an abdominal emergency condition could be hidden a GIST. The pre-nospecific digestive symptomatology or an abdominal main type of non-epithelial tumor of the digestive tract. previously surgically excised [45].

Indefinitely the treatment, since treatment interruption is undergoing medical adjuvant therapy in different phases. As we mentioned above, there are still nine patients first and promising examples of targeted therapy in cancer. consisting of adjuvant therapy with Imatinib, one of the study and preparing and writing this article.

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References

Gastrointestinal stromal tumors – a clinical-morphological study on 15 cases

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Received: March 25, 2014
Accepted: July 29, 2014