

## Lecture N°. 6

### GASTROINTESTINAL STROMAL TUMORS - GISTs

Gastrointestinal stromal tumors, GISTs, are the most common forms of non epithelial neoplasms of the gastrointestinal tract.

In the past it was believed that most of the mesenchymal tumors originated from smooth muscle cells, but it was subsequently evident that only a small part of these gastrointestinal tumors presented the same characteristics of origin as smooth muscle cells. In fact, they showed structural and cytological peculiarities unlike those of smooth muscle cells. Furthermore, some aspects (degree of cellularity, atypisms, necrosis, mitosis, etc) might suggest a malignant type of behavior which was difficult to predict due to their histological aspects. Thus, these tumors were named STUMP (Smooth Muscle Tumors of Indeterminate Malignant Potential).

Based on these observations, Stout and Coll (1962) described neoplasms of the smooth gastric muscle characterized by round epithelioid cells, and in order to define them coined the term "leiomyoblastoma", believing they derived from primitive or immature muscle cells.

This term did not, however, describe the biological behavior of these tumors and, after a redefinition of the malignancy criteria, it was modified to "epithelioid leiomyoma" and "epithelioid leiomyosarcoma".

In 1983, Mazur and Clark demonstrated the absence of muscular markers and the unexpected presence of neural markers shown by immunohistochemistry in some of these lesions. They postulated different lines of differentiation which reflected some elements of the intestinal wall (muscle, autonomic nervous system) and coined the term "stromal tumors" in order to identify neoplasms originating from immature mesenchymal cells. This definition was further modified to "gastrointestinal stromal tumors (GISTs)", in order to distinguish them from other stromal neoplasias arising in other parts of the body such as the uterus or breast.

It has recently been demonstrated that these neoplasms have a similar phenotype to those of interstitial Cajal Cells (ICCs) -intestinal pacemaker cells-. This well-known system, which is found within the nervous structure of the autonomic system (Auerbach's myenteric plexus) and the muscles of the gastrointestinal walls is responsible for peristalsis (motility control, pacemaker function, and the regulation of enteric nervous transmission). A theory has been

put forward that ICCs might originate from precursor cells of the smooth muscle, or specialized muscle cells.

As a matter of fact, since all GISTs show immunoreactivity for c-kit (receptor with tyrosine kinase functions identified through immunohistochemistry, through the CD117 antigen), which is specifically expressed by the ICCs, a theory has been proposed whereby these tumors originate in the ICCs, or might possibly have immunophenotypic differentiation, which is typical of ICCs.

They are recognized through the immunohistochemistry expression of CD117 (tyrosine kinase receptor kit), which is identifiable in GISTs, but not in tumors of the smooth muscle. Based on this evidence, Kindblom (1999) went so far as to suggest the definition of "Gastrointestinal pacemaker cell tumors".

GISTs are generally found in middle-aged or elderly patients, and they mainly involve the stomach (around 70%), followed by the small bowel 30%, and other rare locations like the esophagus, colon and rectum.

GISTs tend to be intramural neoplasms developing externally and involving serosa and adjacent structures. They can remain clinically silent or manifest themselves through digestive tract bleeding, occlusions, and visceral ruptures. Metastases are rarely found in lymph nodes, more commonly in peritoneum and liver. The most common phenotypes are spindle or fusiform cells (neurinoma- or schwannoma-like aspect) and epithelial cells (leiomyoma-like aspect), while mixed and undifferentiated forms have also been described ("uncommitted GISTs").

It is widely believed that the behavior of GISTs depends on their site of origin: lesions in the stomach seem to have a better prognosis compared to lesions in the small bowel. The most important prognostic factors appear to be location, size, and mitotic activity.

Diagnosis is based on immunohistochemistry: positivity for CD117 (c-Kit) and the morphological characteristics support a diagnosis of GIST.

Many other authors believe that no GISTs can be considered benign with certainty. Still others prefer to define them as low malignancy risk tumors.

Surgical treatment requires complete excision of the neoplasm, avoiding lymphadenectomy, since GISTs do not metastasize in the lymph nodes. Accurate clinical follow-up is important in order to detect possible relapses and/or metastases that may appear even years after surgery.

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We will now present a few patients of our series operated on at the Surgical Clinic of the Università degli Studi di Genova.

**-Case N° 1 - V.C.- female - age: 65 yrs - gastric antral localization**

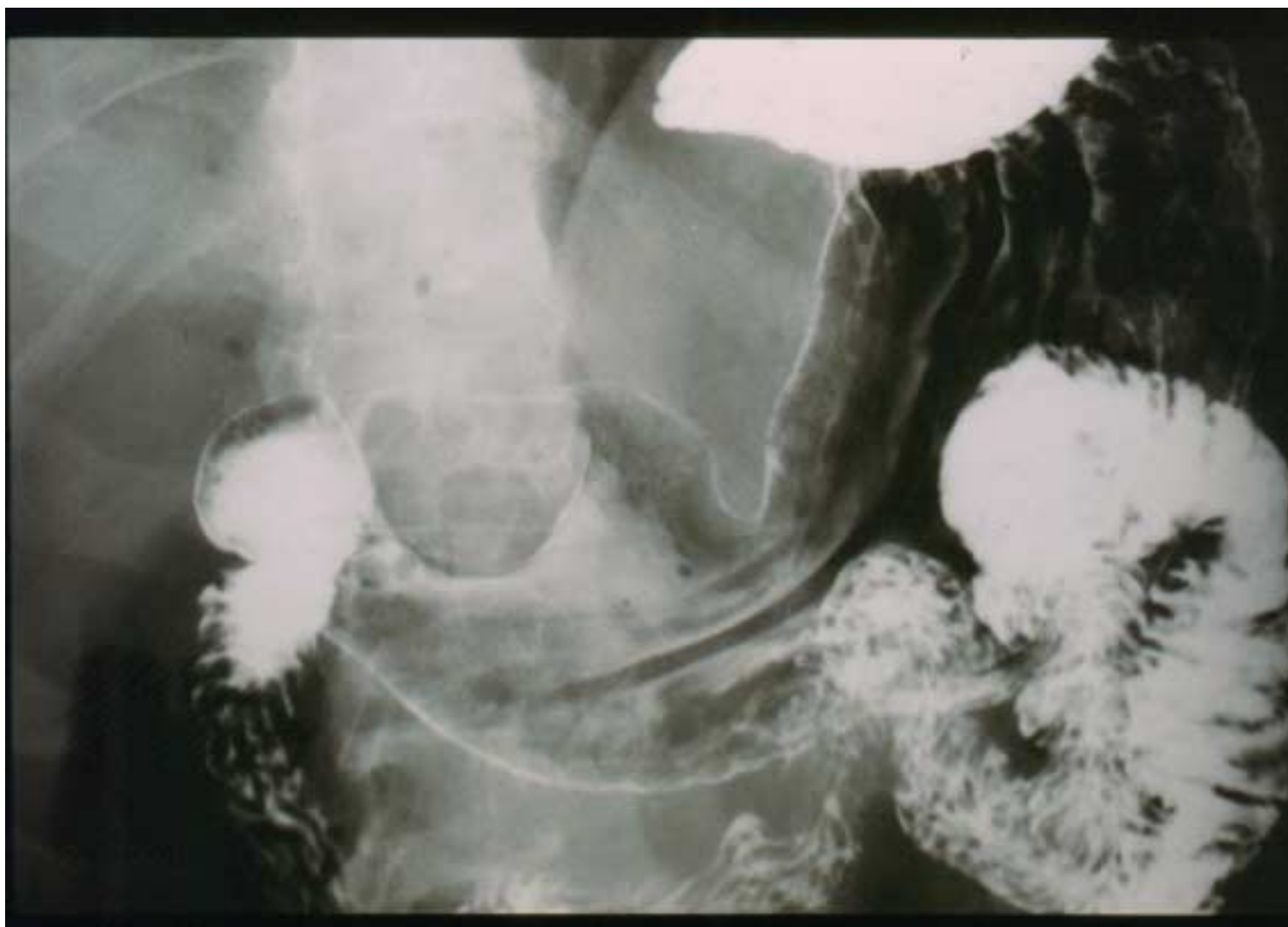


fig 1-a

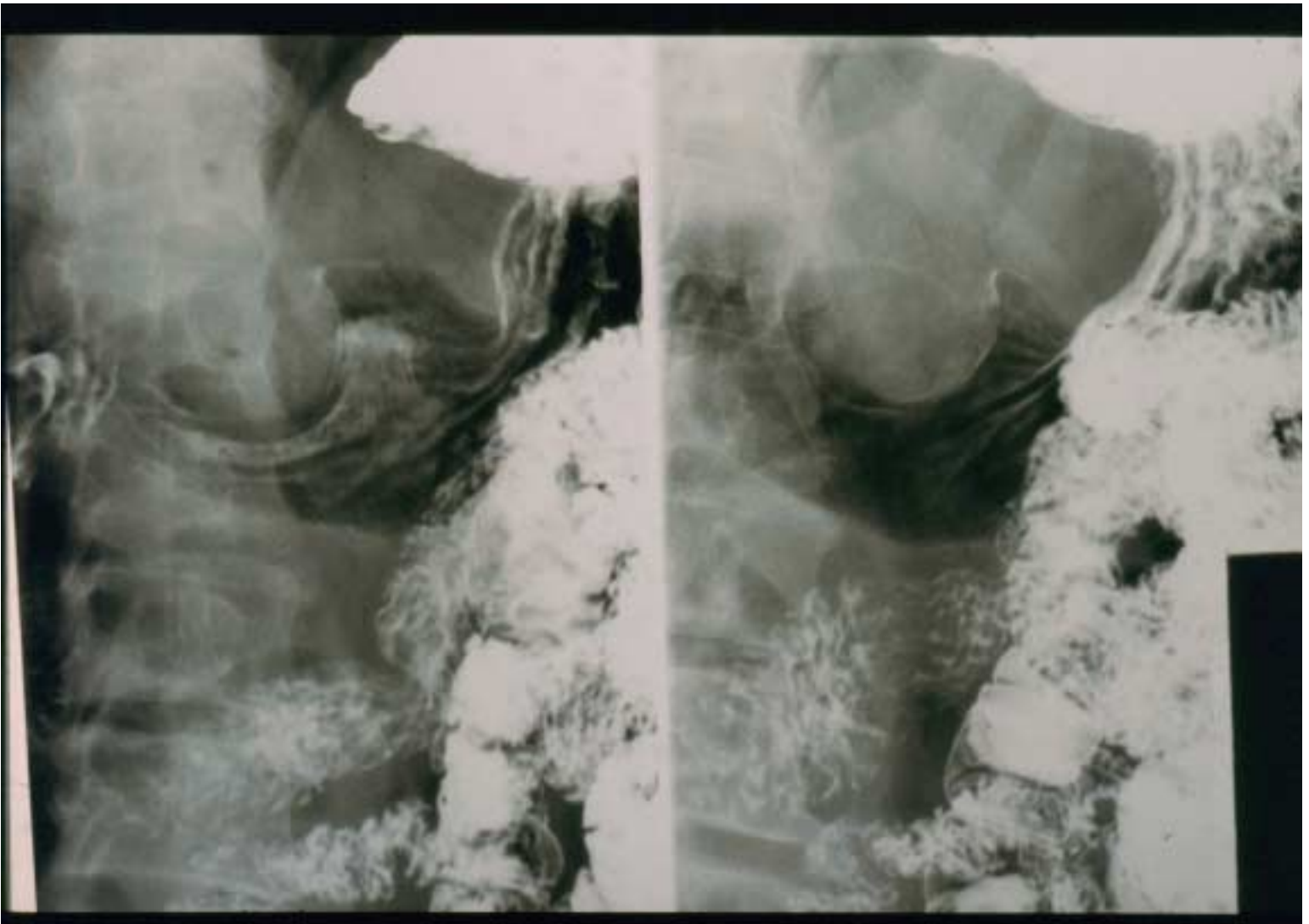


fig 1-b

Fig. 1 a-b - Stomach X-ray: observe antral impression on the lesser curvature



Fig. 2 - Antrum between two Ellis graspers impressed by the tumor

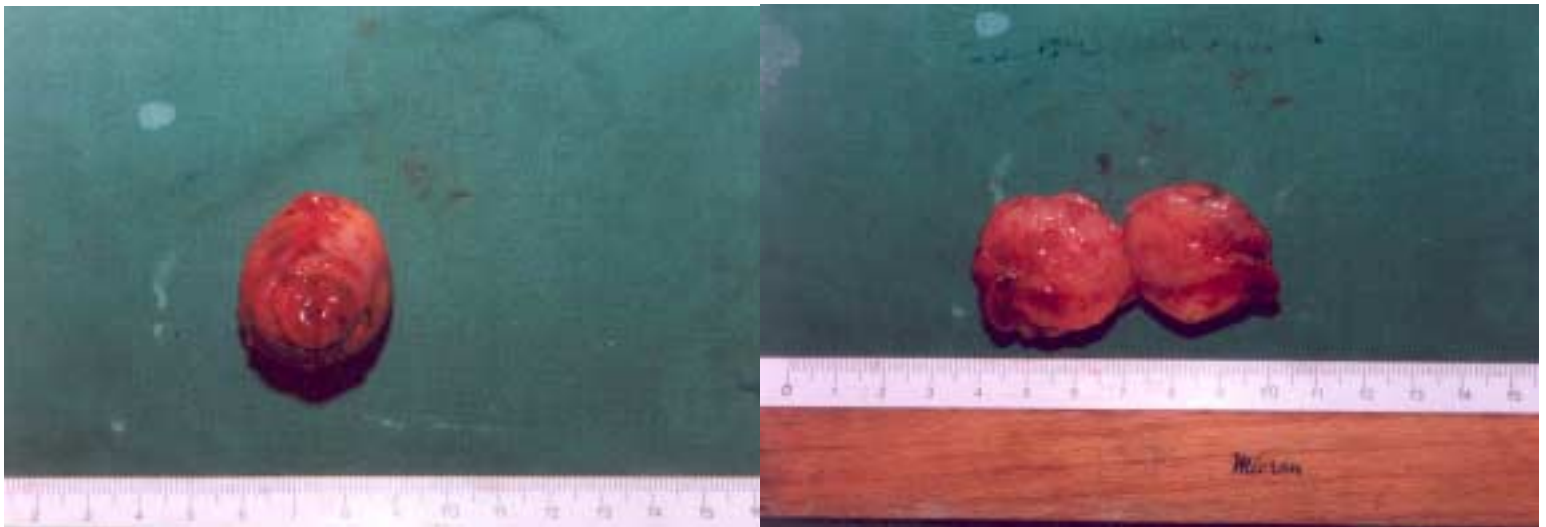


Fig. 3 – Tumor ablation after gastrotomy. Solid and fleshy aspect.

F.U. At 10 years from surgery the patient is alive and healthy with no relapse.

-Case N°. 2 - C. M. - female - age: 66 yrs. - site: gastric body on the greater curvature



Fig 4- a



Fig 4- b

Fig. 4 – Gastro-duodenal X-ray (b) shows irregular feature on the greater curvature corresponding to the endoscopic image (a).

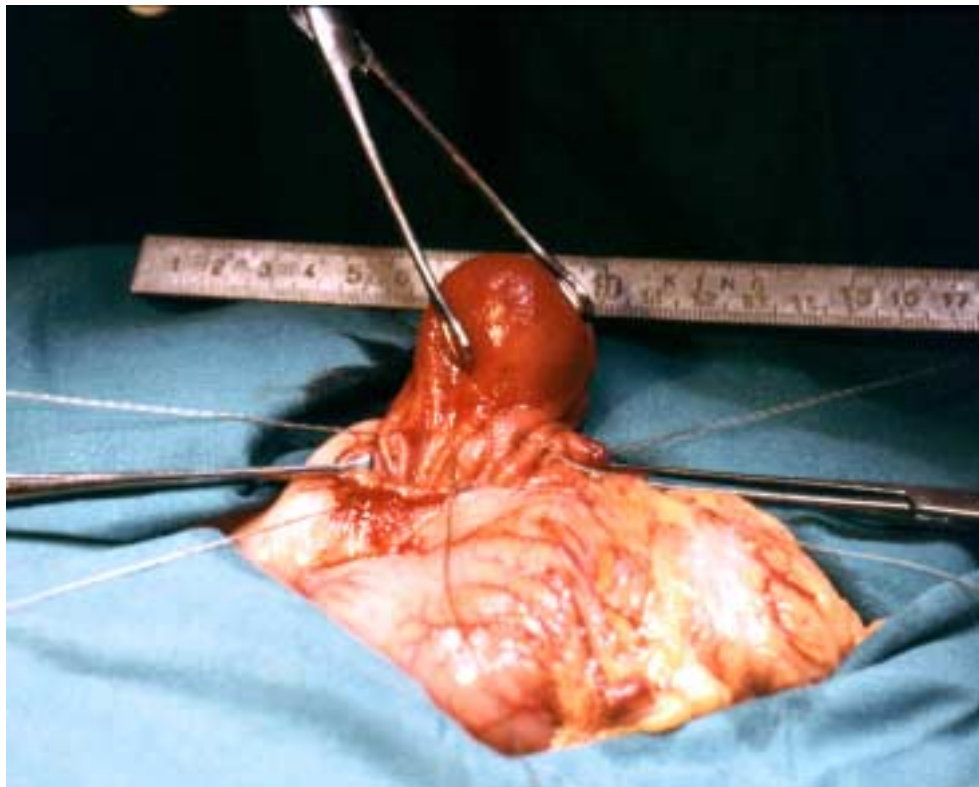


Fig.5 - Gastrotomy: the neof ormation is lined with the gastric mucosa

## **Pathology**

A 3.4 cm diameter nodular growth, lined with gastric mucosa, ulcerated in two locations. When cut the solid growth has an elastic-like tension and a wine red color with pinkish-white areas.

The neoplasm is located between the tunica submucosa and the tunica muscularis propria of the gastric wall and is made up in part of spindle-shaped cell bundles oriented in various directions and in part of epithelioid cells with cytoplasmic vacuolations and local nuclear pseudoinclusions, with moderate evidence of mixed degeneration and accentuated fibrosis. There is no evidence of necrotic focuses or infiltration of the overlying mucosa. Less than 5 mitoses per 50 HPF (High Power Fields) are observed. Proliferation index evaluated by immunohistochemistry (Ki67) is 5%. Oxyntic gastric mucosa lining the growth appears ulcerated but free from inflammatory lesions, with focal foveolar hyperplasia. *Helicobacter pylori* is absent.

The tumor presents the following immunophenotype :

Smooth muscle actin - (SMA) – negative

Desmin – negative

S-100 – negative

CD 34 – diffuse positivity (100%)

CD 117- diffuse positivity (100%)

The cytoarchitecture and immunophenotype findings define the diagnosis of gastrointestinal stromal tumor (GIST) with mixed epithelioid and spindle cells.

**-F.U.** Three years after surgery the patient, still being followed up, is in good health with no relapse.

The above pathology report is applicable in full to Case n° 1.

-Case N° 3 - R.N. – female – age: 74 yrs. - stenosing gastric localization

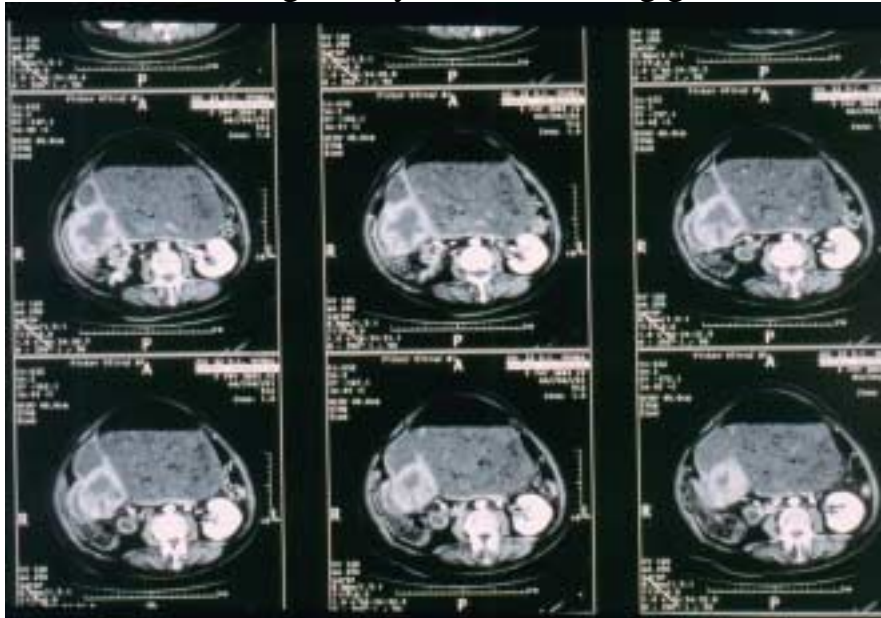


Fig. 6 - CT scan of abdomen : the antral lesion is stenosing.  
Gastrectasis with ingesta

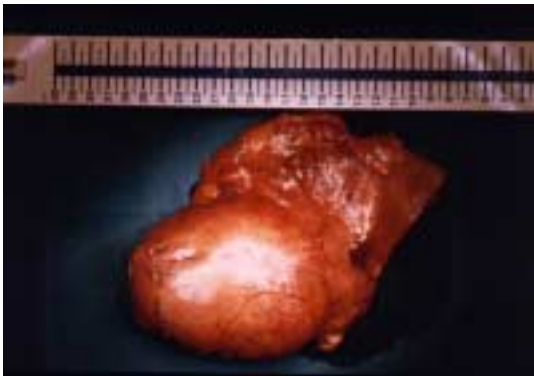


Fig.7 - Subtotal gastric resection . Tumor seen from the serous side.

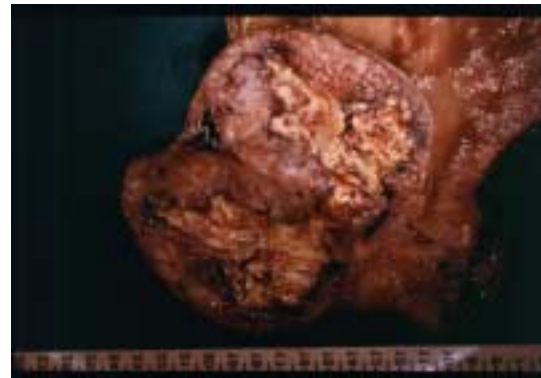
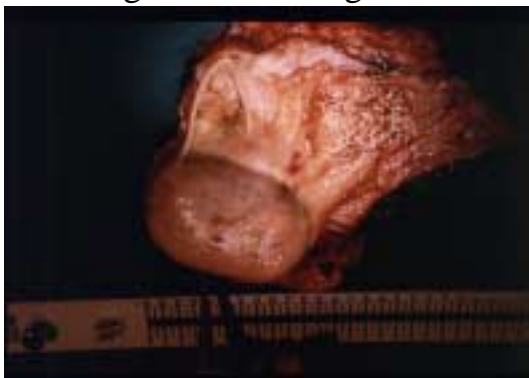


Fig.8 - Tumor as seen from the mucosal side. On the left the tumor appears to be covered by the gastric mucosa. On the right the sectioning shows non homogeneity of the neoplastic tissue with clear signs of necrosis.



## **Pathology**

The specimen, having a maximum diameter of 9.5 cm is lined with gastric mucosa, partly ulcerated: when cut the mass shows compactness and elasticity, with evident areas of necrosis. (Fig. 7-8)

The extramucosal neoplasia consists of epithelioid and spindle cells randomly distributed with cytoplasmic vacuolations and nuclear pseudoinclusions; necrosis is present in large areas. Mitosis is 1 per 10 HPF; proliferation rate is 1% (MIB-1).

The immunophenotype of the neoplasia is as follows;

SMA – expressed (5%)

Desmin – negative

S-100 – negative

CD 34 – diffuse positivity (100%)

CD 117 – diffuse positivity (100%)

The cytoarchitectural and immunophenotypic reports complete the diagnosis of gastrointestinal stromal tumor (GIST) with mixed epithelioid and spindle cells.

**-F.U.** Three years after surgery the patient is in good health with no relapse.

**-Case N° 4 - L.L. - female - age 79 yrs. - huge gastric tumor with perforation**

On admission the patient is undernourished and anemic with few subjective symptoms. Clinical examination: huge, palpable, painless growth in the epigastric region.

The first laboratory tests identify nutritional deficiency and intense anemia: parenteral nutrition (TPN) and transfusion therapy are started. Amongst the various exams, gastro-duodenal X-ray and CT scan proved to be decisive (Fig. 9-10).



Fig. 9 - Gastro-duodenal X-ray. Large calcified mass impressing the lesser curvature. Extragastric contrasting agent of the antral section, expression of perforation-fistulation.

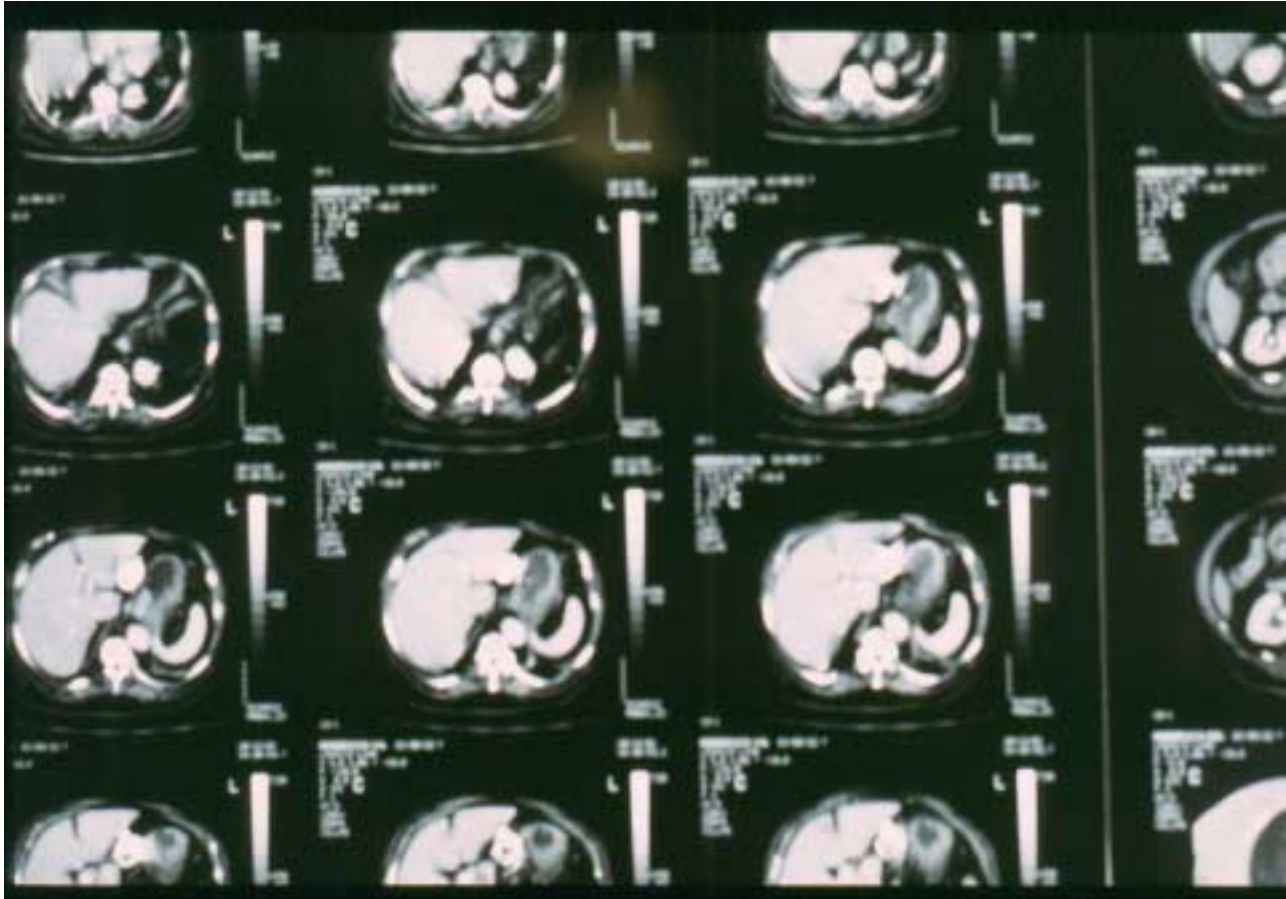


Fig. 10 - CT scan of the abdomen. Same findings as previous figure.  
The lesion appears to have extra-gastric development

Surgery is scheduled after acceptable general conditions of the patient have been restored.

**Surgical report:**

“Xipho-subumbilical median laparotomy. Confirmation of a large growth almost entirely affecting the lesser curvature. Colo-epiploic detachment. Altered omentum due to gross inflammatory phenomena (intraoperative histologic examination). The epiploon retro-cavity has become impervious due to inflammation with large necrotic areas. Omentectomy. The rear wall of the stomach is dissected free to give access to the large, partly calcific mass, growing from the lesser curvature. The gastric wall, found to have thickened uniformly, is heavily compromised. The duodenum is isolated and an interruption at the pylorus is performed by GIA 60. We proceed with the isolation of the posterior wall of the stomach, interruption at the left gastric artery and skeletonization of the greater curve is obtained. The conditions of the fundus and body gastric wall do not allow for conservative surgery and total gastrectomy is therefore chosen.

Preparation of Roux-en-Y loop; mechanical anastomosis (GIA60+TA30 green) of [www.mattiolifp.it](http://www.mattiolifp.it) (Lectures - GASTROINTESTINAL STROMAL TUMORS - GISTs) Page 10 / 22

the loop foot at 60cm; mechanical end-to-side esophago-jejunal anastomosis (purse-string + PCEA 21 + green TA50) Once the tube is positioned, testing for leakage is carried out using methylene blue. Suturing of the mesentery.

Hemostasis check, surgical cleansing of the abdominal cavity, right subhepatic and left subdiaphragmatic tubular drainage. Suturing of abdominal wall.

Examination of the specimen confirms that the whole gastric wall has been compromised by a serious thickening, especially in the region of the body-antrum where the largest portion of the extramucosal growth, which is partly calcific, is located.(Fig. 11a) On sectioning, the extramucosal location of the mass is confirmed, and a large mucosal erosion is observed in the antrum on the lesser curvature, with wide central perforation, confirming preoperative radiologic findings.” (Fig. 11b)



fig 11- a

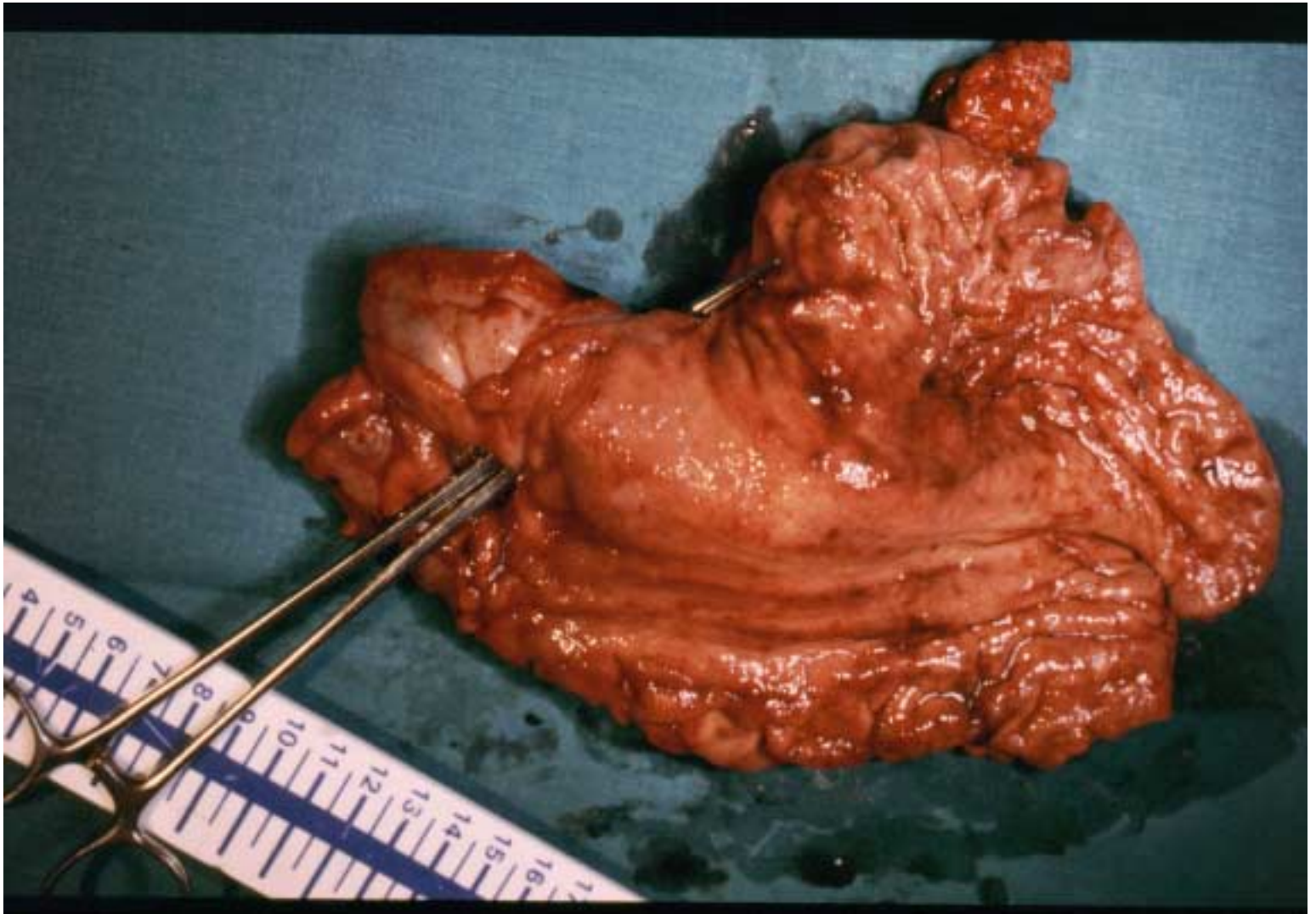


fig 11- b

Fig. 11 a - b - see text.

### Pathology

The tumor, with extramucosal development, consists of spindle cells, and shows necrotic and calcific processes, and high (100%) CD 34 and CD117 positivity.

On the 20th day after surgery death occurred due to multi-infarctual encephalopathy, cardiac and respiratory failure.

- Case N° 5 - C.B.- female - 66 yrs. - location: jejunum (Treitz)

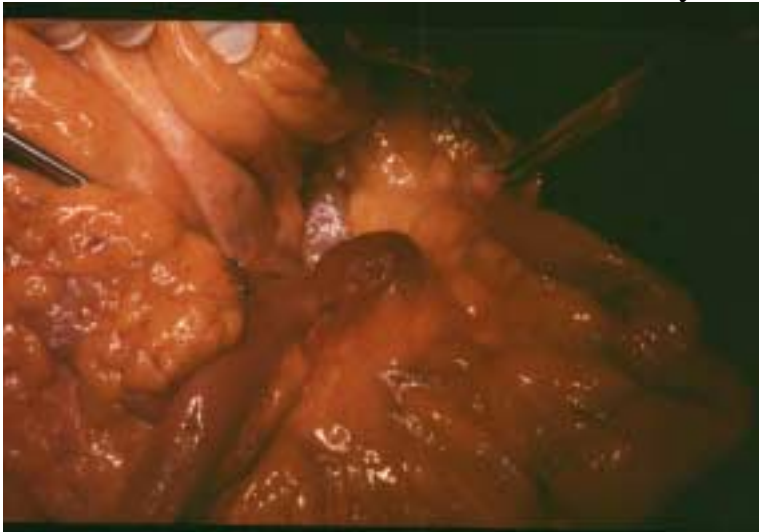


Fig. 12 - Extramucosal neoplasm. Extraluminal resection.  
(open-laparoscopy/conversion)

### Pathology

Extramucosal neoplasm consisting of spindle cells, smooth muscle actin positive (10%), CD 34 negative, CD 117 highly positive (100%).

- F. U.- The patient has been under observation for three years with no recurrences.

**-CASE N° : 6 - F. M. - male. - 60 yrs. location: colon-rectum**

Large mass with pelvic development hindering canalization.  
Miles abdomino-perineal colorectal amputation.

### Pathology

Large volume, extramucosal, stenosing neoplasm of the rectum , with spindle cells (G2 atypia), MIB-1: 10, 3X10 mitoses HPF, characterized by necrosis, with highly positive (100%) CD34 and CD117.

- F. U. Death occurred after three years due to hepatic and peritoneal metastases.

The above mentioned cases are the most significant of our series. A study on the whole case series is in press.

The most significant aspects of histology and immunohistochemistry investigations are illustrated below:



Fig. 13

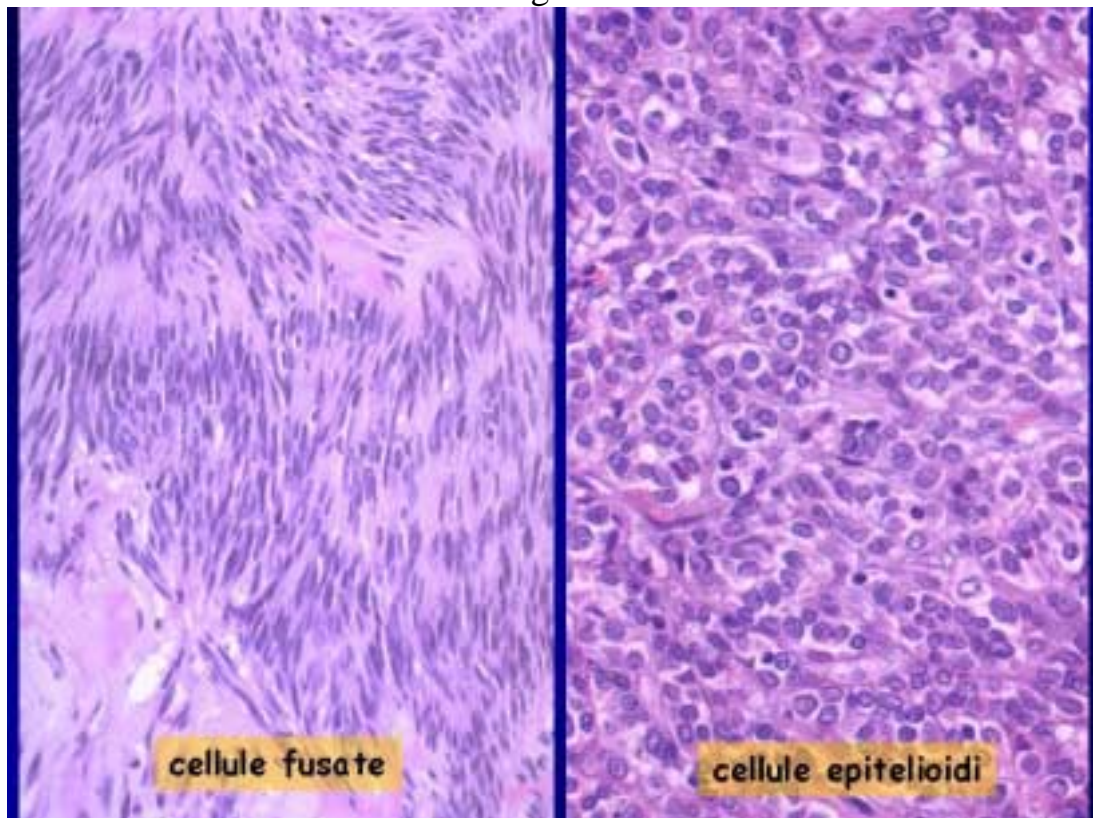


Fig. 14

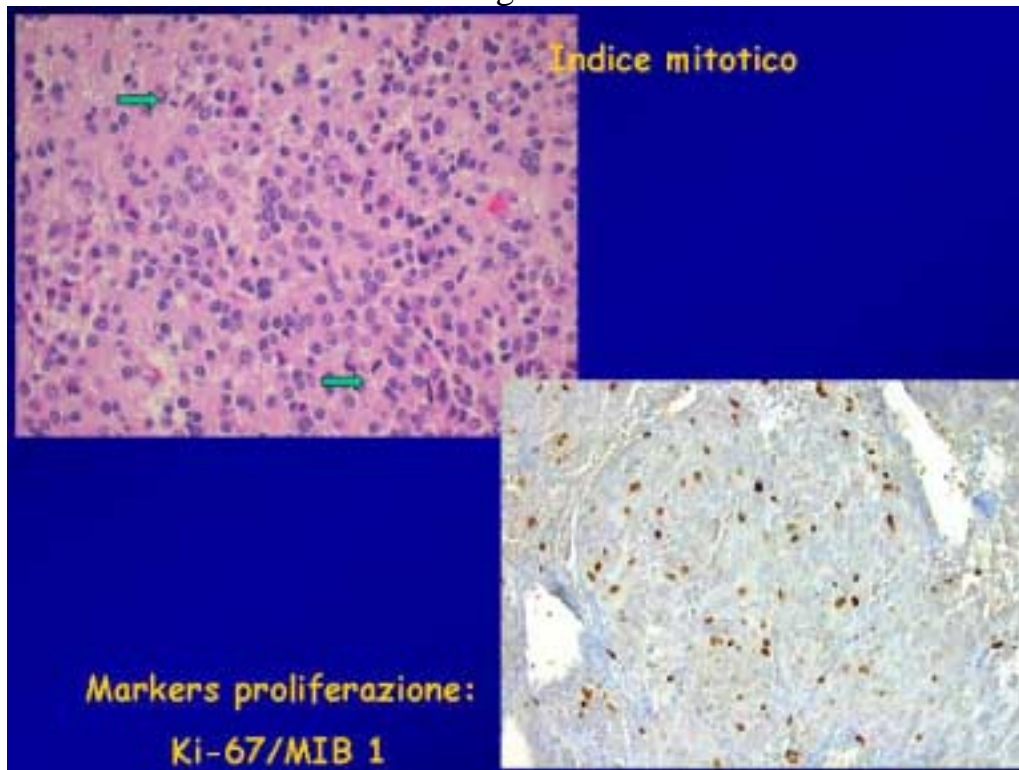


Fig. 15

## IMMUNOISTOCHIMICA

- CD117+
- CD34 + (60-70%)
- SMA + (30-40%)
- Desmina: molto rara
- S-100: + (5%)

C-KIT (CD 117)

CD 34

This figure is a slide titled 'IMMUNOISTOCHIMICA' in green. It features a list of immunohistochemical markers on the left and two corresponding IHC images on the right. The top image shows brown staining for C-KIT (CD 117), and the bottom image shows brown staining for CD 34.

## Fig. 16

GISTs are a relatively new chapter in oncology and are still being studied. Oncologists, pathologists and surgeons have not been able to identify clear parameters to assess the degree of malignancy and aggressiveness of these tumors. (Workshop 2002- National Institutes of Health (NIH) Bethesda), and to consequently define guidelines for their surgical and oncological management.

The biological behavior of these tumors makes it impossible to use the normal parameters of distinction between malignant and benign, unless obvious evidence of malignancy is present (invasiveness, metastization, etc).

A conservative surgical approach has often been taken towards benign forms like the frequently encountered leiomyomas, considered benign on the basis of morphological and clinical parameters, only to discover evidence of biological aggressiveness much later (with relapse and/or metastases after a long time) which are impossible to define beforehand. It would therefore be advisable to describe the biological behavior by means of risk factor grading and by parameters of evaluation.

Some pathologists believe that GISTs cannot be safely classified as benign, above all once they appear as a tumoral mass. Others, on the other hand, think that it is safer to classify them as low risk malignant tumors. This opinion is confirmed by the fact that GISTs that are found in and removed from the stomach or small bowel and that are smaller than 5 cm, rarely recur. This has led them to be classified as tumors with benign behavior.

Research is aimed at identifying parameters that may help oncologists and surgeons in the management of these tumors.

These parameters, which have not been, as yet, unanimously agreed upon, might be :

Phenotype :epithelioid neoplasms are thought to lead to a more unfavorable diagnosis, even though data are inconclusive.

Necrosis : rather unreliable since it is absent in small lesions, and appears only in large volume tumors already denoting a high risk factor.

Cellularity: High cellularity characterized by frequent areas of cells arranged in a storiform pattern are indicative of a high risk factor.

Nucleus- cytoplasm atypicality. No significant data are available

Mitosis: Mitotic count, associated with the tumor size



and location, is presently considered one of the most reliable parameters.

Immunohistochemical markers: while confirming the validity of what has been said about markers CD 34 and CD 117, some studies have demonstrated that loss of such specific immunoreactivity might suggest malignant clinical behavior. Loss of both alleles of the c-KIT gene would seem to be associated with increased metastatic risk. This assessment is not unanimously shared and some authors would even deny the diagnostic value of the two markers.

Site : This parameter should be associated with the mitotic count and with tumor size: stomach GISTs are frequently assumed to have a low risk factor. According to some authors, stomach GISTs smaller than 5cm should be considered for the most part benign as long as they show a low mitotic count: <5 out of 50 high power fields (HPF).

The small bowel seems to be a high risk site depending on tumor volume and mitotic count.

Volume: depending on the location and mitotic count, the 5 cm limit appears to be a reliable figure (<5 cm = low risk or benign).

Macroscopic features : (semeiologic, ultrasound, CT scan, MR and surgical evidences) degree of wall involvement, bleeding and/or necrotic areas, local invasion and relapses, etc. are reliable factors for the identification of potential aggressiveness.

Anamnesis : young age, presence of symptomatology, or detection within one year from onset are considered favorable data.

- Molecular Parameters ( KIT mutation, tumoral ploidy, p53, etc.): these and others are some of the areas of on-going research.

Although many doubts remain to be cleared, we can assume that some parameters are reliable. While distinction between benign and malignant tumors is to be avoided, GISTs can be classified as "tumors with borderline biological behavior". The parameters that are currently available for classifying at-risk categories include: tumor size, mitosis count, and site (Fig.17)

## FATTORI PROGNOSTICI

RISCHIO di MALIGNITA'	DIMENSIONI	MITOSI
MOLTO BASSO	< 2 cm	< 5/50HPF
BASSO	2-5 cm	< 5/50HPF
INTERMEDIO	< 5 cm	6-10/50HPF
	5-10 cm	< 5/50HPF
ELEVATO	> 5 cm	>5/50HPF
	> 10 cm	Qualsiasi
	Qualsiasi	>10/50HPF

Fig. 17 - NIH CONSENSUS CONFERENCE

Some considerations also need to be made from a clinical point of view. As for most tumors, surgery is the treatment of choice for GISTs, but does the surgeon have the elements to diagnose, to evaluate the degree of risk, and consequently to choose the best management course?

Whilst symptomatology (the lesion can be asymptomatic or appear only occasionally) could be not a diagnostic factor, instrumental semeiotics can be of help in the diagnosis. The observation of an exophytic developing process and an endoluminal shift of the mucosa with no involvement of the mucosa itself and possible involvement of adjacent structures is highly indicative of stromal tumor. These data can be obtained by US, CT, spiral CT, MR, endoscopy, echo-endoscopy.

This diagnostic phase offers two of the parameters that are useful for determining the degree of risk: site and size.

Preoperative detection of GIST could be obtained in favorable sites through endoscopic US- or CT-guided needle biopsy, maybe even through videolaparoscopy (exploratory and/or (bioptic)). Should it be possible to identify the immunohistochemical markers and the cytomorphological characteristics from the biopsy sample (this is difficult to obtain prior to surgery), we would then be able to count on a precise diagnosis and make a pre-operative prognosis of the pathology. With the availability of diagnostic and risk parameters (cellular

immunocytopenotype, site, and size) it would thus be possible for the surgeon to define the most suitable surgical procedure according to the severity of the lesion.

As mentioned above, GISTs have been described as tumors with borderline biological behavior. On one hand, small lesions, that are often found incidentally, and which are surgically removed and managed conservatively can relapse over the long term (long-term follow-up is recommended): surgical case records show a large number of not so small "Leiomyomas" which have been enucleated by thorascopy- or video-laparoscopy. On the other hand, extensive lesions have been found involving both adjacent structures and organs, as well as at distant sites.

In such cases surgery is not possible or is inadequate, and besides, these tumors are resistant to radiotherapy and to antiproliferative chemotherapy. Data on systemic chemotherapy carried out on GISTs in various centers, and collected in 1999 in the Italian Registry of Rare Tumors, confirm "the unsatisfactory performance of standard procedures", while eagerly awaiting new, effective treatment.

Clinical trials, started in 2001-2002, are now showing the therapeutic validity of imatinib (imatinib mesylate)/STI-571, which is able to selectively inhibit some tyrosine kinases. As is known, the proliferation of stromal cell in GISTs is based on the expression of the activated tyrosine kinase receptor c-KIT (self activated mutation). The action of imatinib is based on a competitive anti receptor mechanism, which strongly depends on what type of mutation the KIT gene has undergone.

Recent reports indicate that treatment with imatinib has been most effective when mutation of exon 11 is involved.

There are several reports in the literature regarding this kind of treatment, that may be classified as "target therapy", and that show encouraging prospective results. The ways in which the tumor responds, reaction time in particular, are still being clinically and pathologically analyzed, and are the object of biological and oncological research.

With regards to the interaction between this therapy and surgery, adjuvant and/or complementary and neoadjuvant treatment are being investigated. Cases where antiproliferative treatment had yielded limited results have been satisfactorily approached by "for residual disease surgery", even with regards to debulking, and further treatment with imatinib therapy.

Even within a context of new evidence and proof, surgery maintains its fundamental role requiring, nevertheless, a better perspective of this issue that may help to understand and treat other difficult-to-define tumors such as lung microcytoma, prostate cancer, or medullary thyroid carcinoma.

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