

University of Medicine and Pharmacy
CRAIOVA

DOCTORAL THESIS

ABSTRACT

**POSSIBILITIES AND LIMITS FOR DIAGNOSIS AND
TREATMENT OF NONEPITHELIAL TUMORS OF DIGESTIVE
TRACT**

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A.OVERVIEW

INTRODUCTION

The structural complexity of the mesenchymal layer of the digestive tract can generate various types of tumoral lesions, which can progress to malignancy at any time. [1]

Mazur and Clark are the promoters of this disease, being the first to use the term gastrointestinal stromal tumors to name this group of nonepithelial neoplasms in 1983.[3]

These tumors originate from Cajal cells, cells that are the origin and the center of coordination for intestinal motility. [4]

Before 1990, all nonepithelial tumors of the digestive tract were classified as gastrointestinal stromal tumors, GIST, including leiomyomas, leiomyosarcomas, leiomyoblastoma, schwannomas.[6] Later studies of molecular biology and immunohistochemistry allowed the development of a strict clinical anatomical classification of these tumors, but studies are needed to clearly define the complex anatomopathological benign or malignant character of these tumors. [7]

That is why the thesis entitled " POSSIBILITIES AND LIMITS FOR DIAGNOSIS AND TREATMENT OF NONEPITHELIAL TUMORS OF DIGESTIVE TRACT" proposes a more complete approach to this problem, through an epidemiological, diagnostic and therapeutic study.

This thesis, respectively this study appeared due to the existence of a collaboration between the clinics of surgery, oncology and the pathology laboratory of the Emergency County Hospital Craiova.

CHAPTER 1

ANATOMY OF THE DIGESTIVE TRACT

1.1 ESOPHAGUS

Esophagus is the muscular-fibrous organ of the digestive tract that connects the mouth

and pharynx with the stomach. In adult individuals, it is approximately 25 cm. [10]

1.2 STOMACH

The stomach is an organ located intraperitoneally in the supramesocolic compartment, more precisely in the left subphrenic space, communicates with the esophagus through the cardia orifice and inferiorly stretches up to the duodenum. It has a total length of about 25 cm and a capacity of 1200 to 2200 cm³. [11]

1.3 SMALL INTESTINE

The small intestine is a tube that extends from the pylorus to the ileo-cecal valve and is divided into three parts: the duodenum, jejunum and ileum. The average length is between 4 and 6 m [10]

1.4 THE COLON

The colon consists of: cecum, appendix, ascending colon, transverse colon, descending colon and sigmoid, and has an average length of 1.3-1.8 m [16]

1.5 THE RECTUM

Represents the last part of the digestive tract with a size of 15 cm and ends with the anal canal. The upper limit of the rectum is given by sigmoid mesocolonum and corresponds to S3 vertebra and the lower limit is the junction of the analtegment with the perineal tegument. The rectum continues the colon, descending through the pelvis, crossing the perineum and opens outside through the anus. [12]

CHAPTER 2

NONEPITHELIAL DIGESTIVE TUMORS

2.1 DEFINITION

Nonepithelial tumors are tumors that develop in the wall of the digestive tract from undifferentiated mesenchymal cells or Cajal interstitial cells and are characterized by smooth muscle, nervous or mixed differentiation, [19] they are a chapter of pathology of the digestive tract with major importance because of regarding diagnosis, evolution

and treatment yet incomplete elucidated and unaccepted despite numerous clinical trials to date. [20]

2.2 CLASSIFICATION

Nonepithelial tumors the digestive tract are classified into:

Benign

- Leiomyoma,
- Schwannoma,
- Neuroma,
- Lipoma,
- Adenomyoma,
- Angioma,
- Endotelioma. [23]

Malignant

- leiomyosarcoma,
- leiomyoblastoma,
- malignant Schwannoma,
- liposarcoma,
- angiosarcoma. [24]

GIST tumors are classified as benign, borderline, malignant and potentially malignant. [27] Clinical studies available to date have not been able to clarify and establish with certainty the benign or malignant character of this group of tumors. [28]

In 1980, immunohistochemistry techniques have shown that some of the tumors do not have the characteristics of smooth muscle differentiation, while other tumors present markers of neuronal differentiation; [29]. Studies of molecular biology, electronmicroscopical and immunohistochemical examinations have shown that GIST chemicals do not belong to the category of leiomyomas or schwannoma, but represents an individual heterogeneous subset of mesenchymal tumors that originate from interstitial Cajal cells located mainly in the stomach and jejunum. [30]

In recent years the necessary clarifications were made to the nosologic classification of these tumors, their main features being described clinico-biological,

histological and evolutionary but even now all issues have not been clarified and fully understood. [31]

2.3 EPIDEMIOLOGY

GIST represents about 1-2% of all digestive system tumors and 80% of those of mesenchymal origin. [32]

Non-epithelial intestinal tumors can occur at any age but the highest frequency occurs mainly in decades 4-7 and more frequently in males. [34]

The average age of diagnosis of the GIST is between 58 and 63 years, and only 10% are diagnosed under age 40. [35] GIST presence in children is very rare and confined to the stomach, and less than 1% are diagnosed under the age of 18 years, especially in women. [36]

In 10% of cases, GIST is associated with other tumors: clear cell renal carcinoma, cervical, breast, gastric and lung carcinoma. [37]

Topographically, non-epithelial tumors can be located in the stomach (50-60%), small intestine (30-40%), colon (7%), and esophagus (1%). [40]

2.4 ETHIOPATOGENY

Cajal cell is the cell of origin for gastrointestinal stromal tumor cell and is characterized by emission of slow electric waves and is located between intramural neurons and smooth muscle cells of the digestive tract. This cell resembles the fibroblast and exhibits CD 117 receptors (c-kit +). [43]

GIST may develop in the entire gastrointestinal tract, predominantly in the stomach (40-70%), followed in order by the small intestine (20-50%), and in rare cases can be found also in the Meckel diverticulum 0.5 to 3, 2%, 5 to 10% and less than 5% of the cases were encountered in the esophagus. The esophagus is the only segment of the digestive tract where leiomyomas predominate compared with GIST (75% compared with 25%). [44]

GISTs are recognized by means of the proto oncogenic protein detected by immunohistochemistry, serving both as a diagnostic tool and as a marker to assess and initiate the treatment. This protein is the c-kit proto oncogene. [9]

CHAPTER 3

DIGESTIVE NONEPITHELIAL TUMOR DIAGNOSIS

3.1. CLINICAL DIAGNOSIS

Non-epithelial digestive tumors are characterized by uncertainty as regards to their clinical manifestation. Current clinical trials emphasize that only approximately 70% of the characteristic symptoms may occur, and in these cases the presence of signs depends on the location of tumor growth and size. [1]

Gastrointestinal stromal tumors may be asymptomatic until they reach large dimensions and may manifest with nonspecific abdominal pain, anemia and fatigue, leading to an erroneous diagnosis. [49]

Leiomyoma predominantly located in the esophagus, manifests through epigastric or retrosternal pain, loss of appetite, dysphagia, anorexia.

Lipoma localized in the gastrointestinal tract manifests mainly through occult or active bleeding, and in esophageal locations the clinical picture is dominated by dysphagia, reflux and vomiting. [51]

Digestive haemangioma defined clinically by bleeding under the form of hematemesis or melena. [4]

Leiomyosarcoma is manifested by bleeding especially in large, ulcerated tumors, but the patient can also present with abdominal pain, nausea, vomiting. In less than 15% of cases the tumor is palpable or accompanied by ascites. [52]

Gastrointestinal stromal tumors (GIST) are in the vast majority of cases (70%), symptomatic, the rest are asymptomatic, discovered accidentally during surgery or during investigations for other complaints, and in 10% of cases at autopsy. [5]

3.2. PARACLINICAL DIAGNOSIS

Clinical diagnosis is difficult because of the polymorphic and uncharacteristic clinical picture, which makes paraclinical examinations, particularly the imaging diagnosis to be very important in the management of these tumors. [56]

Initial evaluation of non-epithelial tumors digestive requires imagistic investigations as the following: gastric esophageal barium examination, ultrasound, endoscopic examination, abdominal and pelvic CT scan with contrast. [55]

3.3. HISTOPATHOLOGICAL DIAGNOSIS

GIST vary widely in size from a few millimeters to more than 30 cm, with an average size of between 5 and 8 cm. Macroscopic GIST has usually exofitic growth and intraoperative appearance is that of a mass attached to the stomach, projecting into the abdominal cavity. [9]

CHAPTER 4

DIGESTIVE NONEPITHELIAL TUMOR TREATMENT

The treatment of non - epithelial digestive tumors is complex both medical and surgical, and also chemotherapy and radiotherapy for malignant tumors. [4.49]

Management of these tumors is determined by a complex team consisting of a surgeon, gastroenterologist, oncologist, pathologist and anesthesiologist according to location, extension, the presence of complications, metastatic foci and the patient's condition. Thus, if the tumor is less than 1 cm with gastric localization and no signs of malignancy, and the patient's condition allows delaying the surgery until a full investigation and anatomopathological confirmation, dynamic endoscopic surveillance is preferred and if the tumor tends to change dimensions or ulcerate is surgically removed. [4,42,49] If the tumor is less than 8 cm laparoscopic resection can be performed, but it should be done with integrity pseudocapsule and protective bag to avoid intra-operative dissemination. [38,42,90]

CHAPTER 5

NATURAL EVOLUTION. COMPLICATIONS

Very long time, it was considered that small gastrointestinal stromal tumors have a benign evolution but current studies have shown that they can behave unpredictably with late metastasis. [63]

Basically, from an evolutionary standpoint, stromal tumors are divided into four categories: very low risk, low risk, intermediate risk and high risk for malignant development.

B. PERSONAL CONTRIBUTION

CHAPTER 6

MOTIVATION AND OBJECTIVES, MATERIALS AND METHODS

6.1 MOTIVATION AND OBJECTIVES

I chose this topic because of the major importance that this pathology presents through many uncertainties regarding the diagnostic, therapy and prognosis currently related to these tumors.

The purpose of this study is to investigate the risk factors involved in the occurrence of these tumors, to find the best optimal diagnostic and treatment methods. Another aim of my thesis is the evaluation of prognostic factors of the non epithelial digestive tumors.

This was achieved by analyzing both clinical and pathological characteristics of non – epithelial digestivetumors and by analyzing and investigating the feasibility of the current treatment of these diseases.

6.2 MATERIAL AND METHODS

This thesis represents a multicenter retrospective study conducted on a total of 46 patients with nonepithelial tumors of the digestive tract hospitalized and operated in 2008-2013 in the Emergency County Hospital Craiova and University Hospital of Valencia, Spain, from which we formed 2 groups: nonepithelial tumors of the digestive tract classified as GIST and the rest of nonepithelial tumors.

The largest and most significant category is represented by GISTs with a total of 38 patients from both academic centers, 15 patients from Craiova and 23 patients from Valencia. The category of nonepithelial tumors and non GIST consists of 8 patients from the center of Craiova University.

Patients were followed based on a form that included:

- Epidemiological data: sex, age, origin, occupation, occupational and environmental pollutants
- Ethiopatogenic data: family history, risk factors, comorbidities
- Clinical diagnosis: incidentally, symptomatic or by complications (intestinal obstruction, gastrointestinal bleeding)
- Preoperative imaging diagnosis: abdominal ultrasound, computerized tomography, endoscopy
- Treatment: Surgery - emergency or scheduled, endoscopic, adjuvant therapy
- Evolution
- Postoperative morbidity

- Mortality

For the microscopic evaluation of parameters were used two types of digestive tissue fragments:

- Digestive tissue fragments taken from the casses included in the lot and operated during the study
- Paraffin blocks from cases included in the lot that were operated prior to the study.

Tumor tissue fragments were subjected to conventional histological processing techniques (fixation and paraffin inclusion) then serial sections were made from each block.

- The first section was stained with the classical HE coloration
- The following sections have been used for IHC marking.

CHAPTER 7

ETIOPATHOGENY ELEMENTS

7.1 AGE; GENDER; ORIGIN AREA

Age and gender are epidemiological factors involved in the etiopathogenesis of non epithelial tumors of the digestive tract.

Our study conducted on the 2 groups of patients diagnosed with GIST tumors showed a distribution by age, with maximum incidence at 50-59 years for group I (RO) (GIST - Craiova) and 60-69 years for group II (SP) (GIST - Valencia)

Analyzing the two groups of patients diagnosed with GIST in terms of average age I noticed that it consists with data from the literature, converging to the age of 60 years.

The preponderance of males was evident in both study groups with GIST having 29 men and 9 women with sex ratio 3.22, so in the group I (RO) were 66.67% males with a sex ratio of 2 and in group II (SP) we recorded 82.61% males with the sex ratio of 4.75

Regarding the environmental origin of the patients we found no significant differences with etiopathogenetic connotations, the percentage of patients from rural and urban areas being approximately equal in the study groups.

7.2COMORBIDITIES

Non epithelial tumors of the digestive tract do not show a direct association with the existence of comorbidities, thus studied groups have met the following comorbidities.

Most common comorbidities were cardiovascular with hypertension found in 17 patients, followed by hepatic pathology and obesity. In a significant number of patients (16 patients) we found previous surgery.

CHAPTER 8

DIAGNOSIS

8.1CLINICAL MANIFESTATIONS

Most patients in group I (RO) presented at admission with intestinal obstruction or bleeding; five of them presented with intestinal obstruction as complication of the disease, 4 had hemorrhage two of them upper gastrointestinal bleeding and the other two with haemoperitoneum. In 2 cases the patient presented to the hospital with another condition and GIST was discovered incidentally as the result of investigations for the accused symptomatology. Only four of the patients had been diagnosed before admission.

On admission, patients in group II (SP) were diagnosed in a larger number compared to group I (RO); 9 patients were hospitalized already diagnosed, yet a large

number of patients being hospitalized as a result of complications, four of them having intestinal obstruction, 5 upper gastrointestinal bleeding and three with haemoperitoneum.

Patients in group III (non GIST) were admitted with complications of the disease or the illness was discovered incidentally as follows: four of them were hospitalized with intestinal obstruction, one with upper gastrointestinal bleeding, one was diagnosed incidentally and 2 patients were admitted with the diagnosis of gastric tumor, respectively small bowel tumor without specifying the nature of the tumor.

8.2 PARACLINICAL INVESTIGATIONS (IMAGING)

Laboratory investigations used were: computer tomography, upper and lower endoscopy, simple abdominal ultrasound.

Computerized tomography was performed in all patients included in the studied groups, establishing the topography, size, local invasion and ultimately the evolutionary stage of the disease.

In the GIST lots after CT examination we discovered for the lot I (RO) gastric localization of the tumor in 4 cases, small intestine location was found in 7 cases and 4 cases had other sites, respectively, a case localized in the duodenum and 3 cases localized on the colon. In group II (SP) gastric location dominated with a number of 15 cases followed by the small intestine with 6 cases while in two cases we found another location respectively one case on the duodenum and another on the esophagus.

Proportion of GIST localization in the two studied groups was significantly different, thereby in group I (RO) the highest proportion was found belonging to the small intestine with 46.67% followed by the stomach with 26.67% thus being in contradiction with the literature and in group II (SP) predominated the gastric localization with 65.22% followed by the small intestine with 26.09% percentages that are consistent with the literature. Although GIST's localization at the level of the two groups differ significantly overall the studied tumors localization was consistent with the literature, respectively 50% gastric and 34.21% small bowel.

8.3. HISTOPATHOLOGY, IMMUNOHISTOCHEMISTRY

Microscopically with hematoxylin-eosin staining was determined for all GISTs the histological type from both study groups I (RO) and II (SP). We found predominance of fusiform type in group II (SP) with 17 cases followed by epithelial and mixed type with the same number of cases and in group I (RO) we noticed the predominance of mixed type with 9 cases followed by the fusiform type with 5 cases.

In order to calculate the risk of relapse was also studied the number of mitosis from GIST at the level of the two groups of patients, thus for group I (RO) in a patient we recorded no mitosis, in 3 patients we recorded under 5 mitoses, in 3 patients we recorded over 5 mitosis and for 8 patients the number of mitoses was not counted, and for lot II (SP) 4 patients showed no mitosis, 13 patients had under 5 mitosis while 6 patients registered more than 5 mitoses.

Analyzing the results of each antibody, we obtained values similar to those in the literature for most antibodies, thus for antibodies used the results were:

- For CD 117 antibody we obtained positive values for all tumors analyzed
- For CD34 antibody we obtained positive values for 11 cases in group I (RO) and 18 cases in group II (SP) values that are close to those in the literature
- Desmin was positive in a few cases, 1 case in group I (RO) and 2 cases in group II (SP) and the percentage values are higher than those quoted in the literature (desmin positive <2%), probably due to the low number of patients included in the study (Table 32).
- Very high Ki67 tumor proliferation index values was obtained in 6 cases in group I (RO) which means great potential for malignancy of the tumor while in group II (SP) we have not registered any case with very high proliferation index, registering only cases with high, medium and small proliferation index. However, a significant number of cases from both groups did not benefit from

Ki67 tumor proliferation index determination more precisely 6 cases of each lot of GIST (Table 33).

Accurate diagnosis of leiomyomas was made based on immunohistochemical examination which confirmed the histological examination using specific antibodies, thus we obtained positive CD117 in rare mesenchymal cells, CD34 negative, S100 protein negative, positive α -actin, desmin-positive, Ki67 positive in under 3% of the tumoral cells.

CHAPTER 9

TREATMENT

9.1 SURGICAL TREATMENT

The most commonly used surgical approach was the classic laparotomy, for patients in groups I (RO) and III (non GIST) this method was used exclusively. For patients in group II (SP) classic laparotomy was used in 11 cases, laparoscopic surgery was used in 10 patients and for one patient was used an endogastrically laparoscopic approach. For a patient whose tumor had esophageal localization thoracoscopy was used for tumor excision.

For patients whose disease was discovered before the occurrence of complications and investigations prior to surgery showed clear localization of the tumor, without invasion, laparoscopic intervention was performed (Fig 26, 27).

Practiced surgeries for GIST were:

- For the case with esophageal GIST local resection of the tumor was performed.
- For gastric GISTs the procedures used were : gastrectomy in 3 cases in group 2 and 2 cases in group 1, local resection of the tumor in one case in each group; Wedge resection was performed in 7 cases from group 2, partial gastrectomy was performed in 4 cases from group 2 and one case from group 1.

- For cases of intestinal GIST enterectomy was performed in 6 cases of each of the 2 groups, tumor excision was performed in one case from group 2, and in 2 cases from group 1 was performed an extensive excision due to local invasion of the tumor.

- For colonic GISTs 2 left colectomy and one right colectomy were performed (Table 35).

In group I (RO) we found a predominance of large tumors and in group II (SP) large tumors are almost equal to those of small size.

9.2. MEDICAL TREATMENT

To evaluate patients which required adjuvant therapy with imatinib we calculated the risk of recurrence of the operated tumor following the criteria of GIST consensus conference of 2012 that takes into account the tumor size, the mitotic rate and tumor localization, thus in group I (RO) we had a number of 3 patients with low risk of relapse who received adjuvant therapy and 12 patients were classified in the medium, and high relapse risk group and received standard treatment with imatinib 400 mg / day 3 years. In group II (SP) we recorded 11 patients with low risk of recurrence which did not require adjuvant therapy while 12 patients were classified with medium and high relapse risk and underwent the same imatinib regimen.

Patients in group III (non GIST) excepting the patient with leiomyosarcoma, which received specific chemotherapy and radiotherapy, were not included in any specific postoperative treatment as tumors were classified as benign.

CHAPTER 10

RESULTS

The postoperative evolution of patients was favorable in 36 cases (78.26%).

Postoperative mortality rate was 0 in all three studied groups.

Postoperative morbidity was 21.74% (10 cases), we recorded six local immediate postoperative complications (fistula in 3 cases, wound suppuration in 3 cases) and 4

cases with general complications (2 thromboembolic and 2 respiratory) and late postoperative complications, trocar 1 and 2 postoperative incisional hernias after laparotomy and esophageal stenosis.

Regarding the survival rate and remote evolution, these parameters are difficult to measure because the short study did not allow five years evaluation of survival for all cases, though 7 of 8 patients with nonepithelial non GIST tumors could be considered cured being confirmed histologically with benign tumors.

For GIST, remote survival following complex treatment with surgery and adjuvant imatinib was:

- Group I (RO) 4 patients were declared cured following therapy with imatinib or did not required adjuvant therapy because they were classified as low-risk for relapse. One patient showed relapse after treatment with imatinib. One patient died during treatment with imatinib, but death had other causes. 9 patients are under therapy with imatinib in various stages but with a favorable outcome to date
- Group II (SP) 18 patients were declared cured following therapy with imatinib or did not required adjuvant therapy because they were classified as low-risk for relapse. One patient showed relapse after treatment with imatinib. One patient died during imatinib therapy, but death had other causes. 3 patients are under therapy with imatinib in various stages, but with a favorable outcome to date.

CHAPTER 11

CASE REPORT

Patient aged 39 years is admitted in the Clinic of Surgery of the Emergency County Hospital Craiova with ulcer dyspepsia, epigastric pain, nausea, vomiting and

pyrosis. Symptoms onset was 3 months ago with enhancement starting a week ago. Normal physical examination, normal biological tests, normal lung Rx.

Abdominal ultrasound examination finds at the cardia a 17-18 mm circular thickening with marginal elevation suggestive of infiltrative process. Endoscopy identifies a tumor of 2.5 cm localized at cardial level with coverage mucosa of normal appearance in conventional endoscopy and autofluorescence examination, rapid urease test positive. A 5 mm pyloric ulcer with central fibrin exudation and hyperemia of the surrounding mucosa is found. At the endoscopic examination about 40 cm from the dental arch a hyperechoic formation is visualized, inhomogeneous, with calcification of 3/1, 5 cm and origin in the 4th muscle layer, previously located in the vicinity of the left hepatic lobe with weak signals on Doppler examination, 4 mm hypoechoic adjacent ganglion formation.

Patient present on admission the following comorbidities: nodular goiter, dorsal cervical-lumbar spondylosis.

The preoperative diagnosis being esophageal-gastric tumor with extramucosal starting point (stromal tumor) is proposed for xifo-umbilical laparotomy. Following exploration at the eso-gastric junction a well-defined tumor 2/2 cm was found, and a submucosal 1/1 cm tumor in the abdominal esophagus, enucleation of the tumors is attempted through gastric exploratory incision, but fails, thus requiring the practice of an upper esophageal gastrectomy with gastro esophageal anastomosis end-to-side. Postoperative local and general positive development.

On histopathology were found mesenchymal tumors with starting point in the muscular tunic and immunohistochemical examination was recommended to establish the exact type of mesenchymal tumor; leiomyoma is confirmed through positive CD117 in rare mesenchymal cells, CD34 negative, negative S100 protein, α actin positive, desmin positive, Ki67 positive in under 3% of the tumor cells.

CHAPTER 12

DISCUSSIONS

Regardless of the anatomopathological form, the main features of non epithelial tumors of the digestive tract are:

- Low incidence
- Plurifactorial etiopathogeny incompletely elucidated
- Difficulties in diagnosis
- Mainly surgical treatment

This multicenter study conducted on a total of 46 nonepithelial tumors of the digestive tract, which were treated in The Emergency County Hospital Craiova and University of Valencia Hospital, Spain, in a period of five years (2008-2013), has allowed some observations and comments.

First I noted the rarity of these tumors representing 1.8% of all digestive tumors.

Most tumors were GIST (38 cases - 82.61%), other non epithelial tumors non GIST are represented by leiomyoma one case, leiomyosarcoma one case, lipoma 3 cases, 1 case of schwannoma and 2 cases hemangioma.

Topographically, non epithelial tumors were found in all segments of the digestive tract, the predominant location of GIST was different for the two groups: in accordance with the literature [40] for the Spanish lot (mainly gastric tumors followed in order by the small intestine, esophagus and duodenum) and somewhat inconsistent with the literature (mainly in the small intestine, followed in order by gastric tumors, colonic and duodenal) for the group from Romania. With regard to non epithelial tumors non GIST, they were located in the small intestine in 4 cases, 2 cases in the colon, esophagus and stomach 1 case each.

Immunohistochemical examination is essential for GIST diagnosis of certainty; we used a wide range of specific antibodies (AE1/AE3, actin, desmin, vimentin, S100protein, CD34, CD117) with different specificity. The most constant antibody has

been CD117 shown to be present in all studied cases in both groups. CD34 antibody positivity (11 cases in group I (RO) and 18 cases in group II (SP)) is an indicator of tumor progression to malignancy [61]. For other antibodies (actin, desmin, S100 protein) positivity was located above the average assessed in the literature constituting an element of certainty in the diagnosis of GIST [62].

În cea ce privește tumorile non epiteliale non GIST examenul histopatologic (efectuat la toate cazurile) confirmă diagnosticul, stabilește tipul histologic al tumorii caracterul benign sau malign și invazia locală.

With regard to non epithelial tumors non GIST, histopathology (performed in all cases) confirms the diagnosis, determines the histological type, the benign or malignant nature and local invasion.

Treatment of non epithelial tumors of the digestive tract is complex, medical and surgical. Surgery is the main treatment option whose main objective is to remove the tumor through a R0 resection type, which for non epithelial tumors and especially for GIST means resection with free margins verified by histopathology extemporaneously, lymphadenectomy not being necessary because this type of tumor does not give lymph node metastases, timing of the intervention and the surgical technique and tactics are based on the topography of the tumor, size and its evolutionary stage, presence or absence of evolutive complications, biological status and patient's age.

CHAPTER 13

CONCLUSIONS

1. The incidence of nonepithelial tumors of the digestive tract is low, representing 1.8% of all digestive tumors in our study.
2. GIST is the main anatomical and clinical form in our study totaling 82.61% of all non epithelial tumors the rest being represented by leiomyoma 1 case, 1 case leiomyosarcoma, lipoma 3 cases, 1 case of schwannoma and hemangioma 2 cases.

3. The peak incidence of non epithelial tumors in general and especially GIST occurs mainly in male patients and in the decades VI and VII of age (62.96 years).
4. The presence of cardiovascular, pulmonary and hepaticcomorbidities is significant with implications in determining operative risk, the timing of surgery and postoperative care of patients.
5. Topographically non epithelial tumors can be found in all segments of the digestive tract.
6. Computed tomography imaging is the most complete investigation that allows preoperative staging of GIST in the localized disease, local invasion and metastasis.
7. Morphological examination of the resectedfragments (histopathology and immunohistochemical examination) is essential in the diagnosis of certainty.
8. CD117 antibody positivity (100% in our study) is the most constant sign of immunohistochemical diagnosis of GIST, while positivity for CD34 (76.32%) and increased Ki67 index are the main indexes consistent with tumor malignancy
9. Surgery is the main treatment option, timing of the intervention, the surgical technique and tactics depending on the topography, size and evolutionary stage of disease, presence or absence of complications, patient age and status.
10. The main goal of surgery is to remove the tumor through a R0 resection type, which for non epithelial tumors and especially for GIST means resection with free margins verified by histopathology extemporaneously, lymphadenectomy is not necessary because of the absence of such tumorsextension trough the lymphatic system.
- 11 The results are superimposable to those in the literature. Favorable outcome in 78.26% of cases, postoperative morbidity in 21.74% of cases, 0 postoperative mortality, 29 patients (63%)disease-free after three years.

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