

The morphological profile of small bowel tumors – our experience

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Abstract

Aim: The authors assessed the morphological profile of tumor masses belonging to the small bowel discovered in their daily practice. **Materials and Methods:** 31 tumor masses located in different segments of small intestine operated between 2002 and 2013 in the 1st Surgical Department, Emergency County Hospital of Craiova, Romania, were analyzed. The investigated parameters were: tumor location and number, tumor dimensions, gross assessment, tumor extension and histological assessment. **Results:** Tumor masses belonging to small intestine were rare. They usually expressed by their complications. In many cases, they were placed at the extremities of the small intestine. They were usually small but sometimes large and developing outwards intestinal wall. Commonly they had a fungating and ulcerated appearance. They were rather of mesenchymal origin than epithelial. However, some of them were inflammatory pseudotumors. Almost all neoplastic proliferations had a malignant phenotype, most often with regional extension. **Conclusions:** Our series of tumors had a morphological profile somehow similar with the profile described in the literature but with some particularities: the polarization to the extremities of the intestinal segment, a significant number of large tumors, clinical expression through different complications, the balance inclined in favor of mesenchymal origin of tumors and the clear predominance of malignant aggressive phenotype.

Keywords: small bowel, tumor, morphology.

Introduction

Despite of the fact that the small bowel represents about 75% of the total length of the digestive tract and more than 90% of the digestive mucosal surface, the small bowel tumors are very rare, accounting only 1–2% of the digestive tract neoplasms and only 0.3% of the digestive cancers [1–5].

Originating in all structures of the intestinal wall, there is a wide variety of tumors, over 35 histological types being described until now [6]. The small bowel tumors are benign and malignant; the most common being adenocarcinomas (30–50%), followed by carcinoid tumors (25–30%) and lymphomas (15–20%), and the segments with the highest risk of malignancy being the duodenum for adenocarcinomas and the ileum for carcinoid tumors and lymphomas [4, 7].

Despite of their great diversity of the histological types, the small bowel tumors have several common characteristics:

- Controversial and not fully understood pathogenesis, due to their rarity and great diversity of histological types,

so that practically there are multiple tumoral types, each of them with its origin and its own pathogenic mechanisms. It generally speaks separately about the pathogenesis of the adenocarcinomas and carcinoid tumors, lymphomas and gastrointestinal stromal tumors (GISTs) [8–16].

- Difficult diagnosis, most often established accidentally during some imaging tests performed for another clinical suffering, during surgery imposed by the complications appeared during disease progression (bowel obstruction, bleeding) or even at the necropsy; the diagnosis difficulties are due to the polymorphous and non-specific clinical picture and the relative inaccessibility of the small bowel to the endoscopic examination.

- The morphological diagnosis, established by the peri-operative exploration and by the morphological exam (macroscopic, histological and immunohistochemical) is essential for the diagnostic and therapeutic algorithm.

- Complex medical and surgical treatment, disposing of a wide range of therapeutic option, impossible to be standardized considering of the diversity of tumoral types, what do to be multiple therapeutic algorithms if not for

each type of tumor at least for certain classes or subgroups of tumors.

Materials and Methods

The study was a retrospective one and included 31 patients operated in the 1st Surgical Department, Emergency County Hospital of Craiova, Romania, between 2002 and 2013.

The diagnosis was a very difficult task, being established in only less than 30% of cases by chance, during the imaging tests performed for other suffering such as anemic syndrome of unknown cause, colon cancer, obstructive jaundice, ovarian tumor, gastric polypsis, or duodenal stenosis. In the rest of the cases, the diagnosis was established during the emergency surgery imposed by acute complications (bowel obstruction, bleeding, or peritonitis) appeared during the tumor evolution.

Thirty cases were operated, large resection in the oncological limits being the main surgical procedure.

The morphological diagnosis, based on the intraoperative examination and the study of surgical specimens, was based on a protocol, following elements of morpho-

logical diagnosis: tumor location, number, tumor dimensions, gross assessment, tumor extension and histological assessment which included where necessary immunohistochemical (IHC) investigation.

The materials were obtained from two different data sources:

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

Tumor dimensions were accurately determined both surgical specimens directly in the operation room and 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.

The surgically removed specimens were processed using the classical histological technique (fixation in 10% buffered formalin and embedment in paraffin) and then stained with Hematoxylin–Eosin for diagnosis orientation. Further, in some cases, a dedicated panel of antibodies was applied in order to precise the diagnosis. The antibodies used for the appropriate identification of each of these particular cases are summarized in Table 1.

Table 1 – Antibodies used in the study of small bowel tumors

Antibody	M/P	Clone	Source	Specificity	Dilution
SMA	M	1A4	DAKO	Smooth muscle cells and interstitial and arteriolar wall myofibroblasts.	1:50
CD34	M	QEnd 10	DAKO	Endothelial and interstitial cells.	1:50
Ki67	M	MIB-1	DAKO	Nuclear protein that is associated with and may be necessary for cellular proliferation, being thus a cellular marker for proliferation.	1:10
S100 protein	P	–	DAKO	Dendritic cells.	1:100
CD117	P	104D2	DAKO	Hematopoietic stem cells, melanocytes, mast cells, Cajal cells, epidermal basal cells.	1:400–1:600
Bcl-2	M	124	Novocastra	Oncoprotein which reacts with B-cells.	1:50
Cyclin D1	M	EP12	DAKO	Mantle lymphoma.	1:50
CD10	M	56C6	DAKO	Immature B-lymphocytes.	1:50
CD20	M	L26	DAKO	B-lymphocytes.	1:300
CD45Ro	M	UCH1	DAKO	T-lymphocytes.	1:20

SMA: Smooth muscle actin; M: Monoclonal; P: Polyclonal.

Tissue slides were analyzed using an Olympus CX 31 microscope equipped with a ColorView II camera and AnalySis Pro 5.0 software calibrated for this microscope.

All data were introduced and processed in Excel module of Microsoft Office Professional 2010. The graphs were done with the “Graph” tool included in the “Excel” module of the Microsoft Office Professional 2010 software package.

All patients were informed about their participation in this study and a written consent was provided by every patient.

Results

During the 12 years taken into consideration, there were only 31 tumors found in the small bowel from a total of 1683 of operated tumors belonging to the digestive tract (Figure 1).

The percentage of almost 2% is in accordance with the data presented in the literature that we already mentioned in the “Introduction” section.

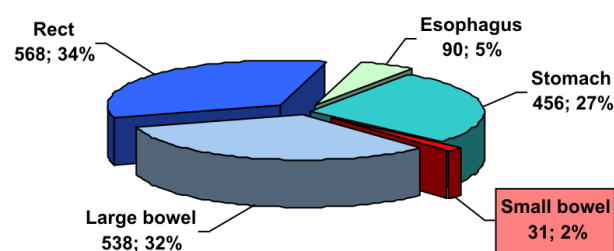


Figure 1 – The incidence of small bowel tumors.

Gross assessment

Tumor site

The most affected parts of the small intestine were the jejunum and the ileum who hosted together 80% of the studied tumors. It should be noted that the small intestine, excepting the duodenum, was affected in almost two-thirds of the cases at its extremities, especially the proximal segment of jejunum, followed by the terminal segment of the ileum.

Finally, almost all duodenal tumors involved the ampulla of Vater (Table 2).

Table 2 – Site of studied tumors

	Site	Cases	%
D 2	Segment	1	3.3
	Ampulla of Vater	4	13.4
D 3		1	3.3
Jejunum	Proximal	10	33.4
	Distal	1	3.3
	Entire length	1	3.3
Ileum	Middle	4	13.4
	Distal	3	9.9
	Terminal	5	16.7

D: Duodenum.

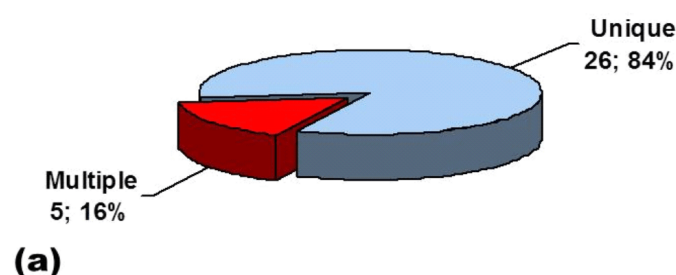


Figure 2 – Small bowel tumors: (a) Distribution by tumor number; (b) Distribution by tumor dimensions. NS: Not specified.

Tumor gross aspect

Almost 60% of the tumor masses had a protrusive aspect, either inside or outside the intestinal wall, most of them presenting ulcerations on the tumor surface. The next gross aspect as frequency was the infiltrative and stenosing one, encountered in one quarter of the cases (Figure 3). It should be pointed out also that the great majority of studied tumors, *i.e.*, around 70%, generated complications as obstruction, perforation of hemorrhage.

These complications brought the patients to the hospital, usually as an emergency situation (Table 3).

Tumor number and dimensions

In most of the cases, the tumors were solitary but there were, however, five cases with multiple tumors (Figure 2a).

Tumor dimensions had a wide range of variation, between 0.7 and 15 cm. Although almost one-third of the tumor masses had between 1 and 3 cm, in other words small tumors, almost 40% of the tumors were larger than 5 cm, meaning significant dimensions as compared with the small intestine's diameter (Figure 2b).

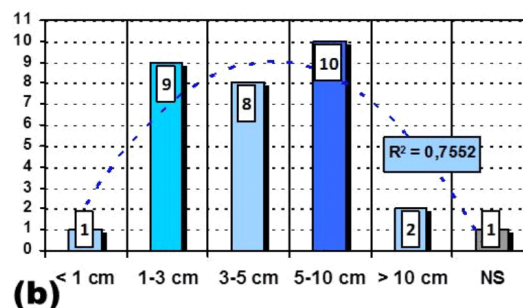


Table 3 – Types of gross aspects

Type	Complication	Cases	%
Fungating + Ulcerated	Not complicated	7	22.6
	Obstruction	3	9.7
	Perforation	3	9.7
	Hemorrhage	2	6.4
Infiltrative and stenosing	Obstruction	8	25.9
Complex tumor mass		5	16.1
Fungating	Not complicated	2	6.4
	Invagination	1	3.2

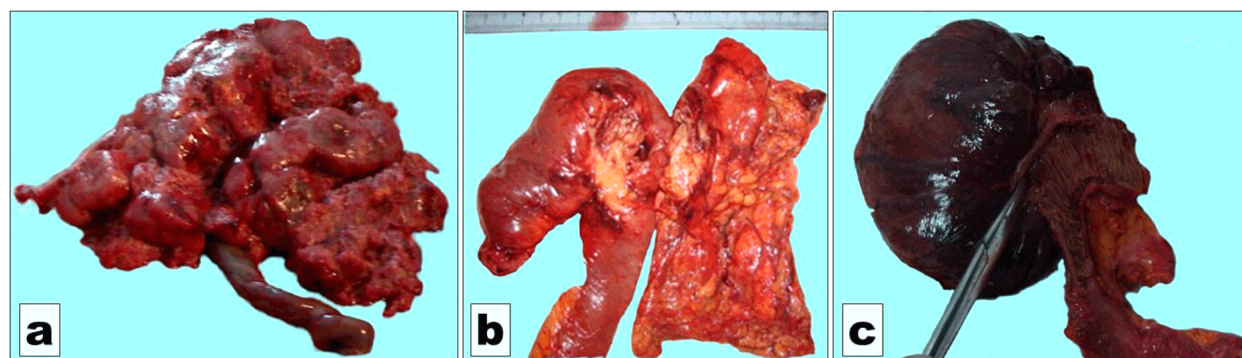


Figure 3 – Gross aspects: (a) Fungating and ulcerated; (b) Infiltrative; (c) Fungating outside the intestinal wall.

Histological assessment

Although the length of the small intestine, measured from the pylorus to the ileocecal valve, represents at least 75% of the length of the digestive tract (between 5 and 6 m) and the surface of its mucosa constitutes about 90% of the absorption surface of the gastrointestinal system, only 3 to 6% of neoplasms of this system develop within this segment and only 2% (1–6%) are malignant digestive neoplasms while, for example, approximately 57% of the digestive tract carcinomas develop from the lower intestine, which measures roughly 1.5 m. Even so, no less than 40

different tumor subtypes have been identified as having a starting point within the wall of the small intestine [17–19].

Most of the studied tumors (80%) have proven to be, from the histopathological point of view, neoplastic proliferations that developed from the small intestine wall structures (Table 4; Figure 4a).

Apart from one case, which was identified as a metastasis of a malignant melanoma, the neoplastic tumors were primary proliferations originating in the small intestinal wall structures. Also, we could not specify the morphological type of the tumors for two of the patients as they did not undergo therapeutic surgery.

According to the tissular origin, over half of the 23 examined tumor formations turned out to originate from the mesenchymal structures of the intestinal wall (Figure 4b).

On the other hand, the cellular phenotype found in most of the neoplastic tumors was the malignant one (92%) (Figure 4c). It is worth mentioning that we also included in the malignant subgroup the two inoperable tumors because their macroscopic appearance suggested their malignant nature.

Table 4 – Histological types of studied tumors

Tumor type		Epithelial		Mesenchymal	Total
		Benign	Malignant	Malignant	
Primary	Polyp	2			22
	Carcinoma		8		
	GIST			7	
	Lymphoma			3	
	Paraganglioma			2	
Secondary	Melanoma			1	1
Total surgically removed tumors		2	8	13	23
Inoperable				2	2
Tumors in total					
Total histogenetic types		2 (NP)	10	13	25
Total cellular phenotypes		2		23	
Pseudotumor	Inflammatory tumor		6		6
Total tumoral formations					31

GIST: Gastrointestinal stromal tumor.

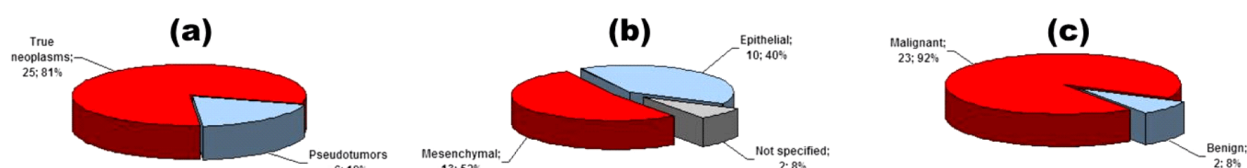


Figure 4 – Distribution of histological types of studied tumors.

Malignant neoplasms

The analysis of the different types of malignant neoplasms incidence within the study group has highlighted the predominance of carcinomas among epithelial neoplasms and the predominance of gastrointestinal stromal tumors (GISTs) among mesenchymal proliferative formations (Figure 5).

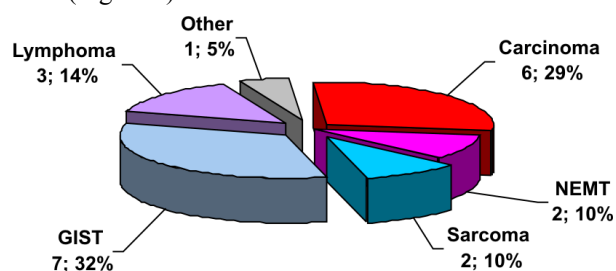


Figure 5 – Distribution of malignancies. NEMT: Neuroendocrine malignant tumor; GIST: Gastrointestinal stromal tumor.

Carcinomas

The most frequent type of primary malignant epithelial tumor that we have encountered in our study group was the common form of adenocarcinoma, found in five patients (Figure 7a).

For three of these patients the tumor was located near the Vater ampulla, measuring between 0.5 and 2 cm and

All neoplastic tumors, which originated from the mesenchymal structures of the intestinal wall, presented a malignant phenotype.

Benign neoplastic proliferations were very rare (only two cases) and were of epithelial origin.

Finally, the tumor formations identified as being non-neoplastic showed, according to the histopathological examination, only an intense inflammatory response within the intestinal wall (Table 4).

having an exophytic fungating aspect. Two of these tumors presented a glandular proliferation with a well-differentiated papillary appearance while the third presented a moderate glandular differentiation (Figures 6 and 7b).

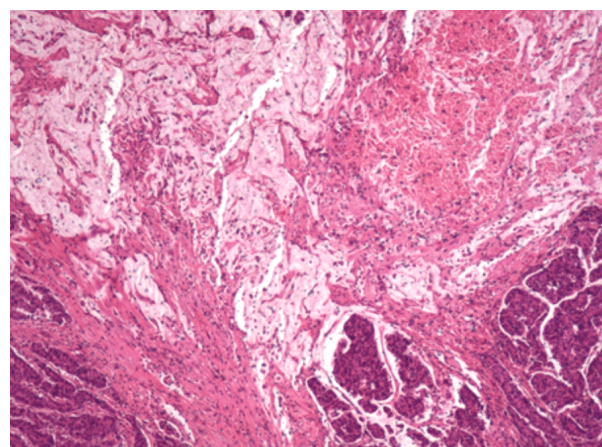


Figure 6 – Moderately differentiated adenocarcinoma, with secretory and necrotic areas. HE staining, ×40.

The other two patients had tumors located near the ileum. One of them was placed at 30 cm from the ileocecal valve, with a greater diameter of 6 cm, a solid, fungating macroscopic appearance, with a circumferential extension in the intestinal wall and a histological pattern of poorly differentiated glandular proliferation with

mucinous secretory areas. The other was placed at 10 cm from the ileocecal valve, with a greater diameter of 4.5 cm, an infiltrative and stenosing macroscopic appearance and a histological pattern of well-differentiated glandular proliferation with a solid papillary appearance and necrotic areas.

Apart from the common forms of adenocarcinoma, we encountered a case where we found an ampular tumor with fungating appearance, measuring 2/1 cm, and having microscopic appearance of poorly differentiated mucinous carcinoma (Figure 7, a and b).

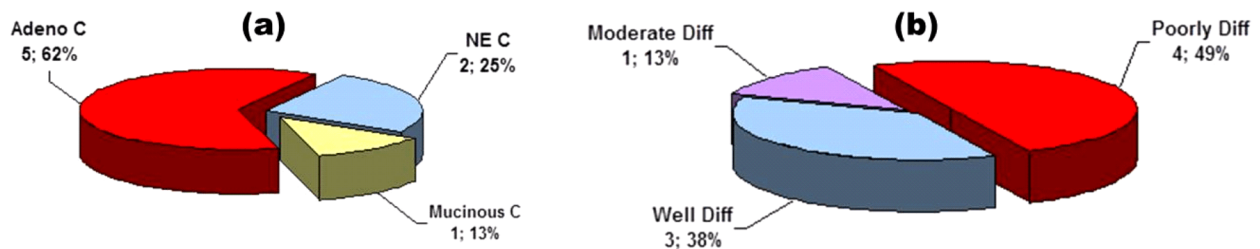


Figure 7 – Carcinomas of the small bowel: (a) Histological types; (b) Degree of differentiation. C: Carcinoma; NE: Neuroendocrine; Diff: Differentiated.

Generally, the macroscopic and microscopic characteristics of the six studied carcinomas fitted the classic descriptions in the literature [18, 20–22].

Finally, we included the two malignant neuroendocrine tumors in the carcinoma group. The first was located 150 cm from the ileocecal valve and measured 3/3 cm and the other was located 100 cm from the ileocecal valve and had considerable dimensions of 10/8 cm, which is

rather unusual since, in the literature, the most common maximal sizes do not exceed 3 cm. Both tumors presented an infiltrative and stenosing growth pattern, invading the entire intestinal wall and extending to the peri-intestinal tissue (Figure 8, b and d), the peritoneal and the retro-peritoneal lymph nodes in the first case and to the abdominal wall and urinary bladder in the second case.

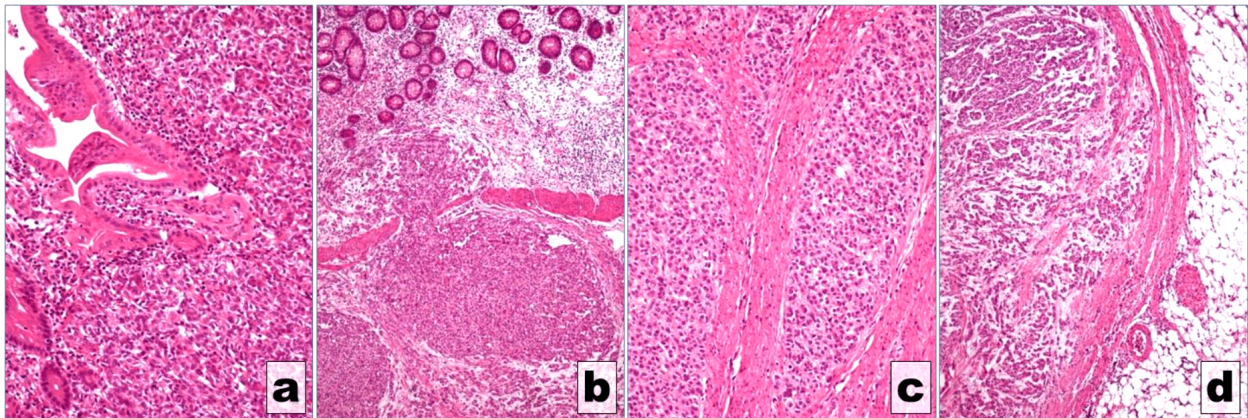


Figure 8 – Poorly differentiated neuroendocrine carcinoma of the small bowel: (a) Mucosa invasion; (b) Submucosa invasion; (c) Muscular layer invasion; (d) Peri-intestinal tissue invasion. HE staining: (a and c) $\times 100$; (b and d) $\times 40$.

From the histological standpoint, both tumors were characterized, according to *World Health Organization* (WHO) classification from 2004 [23] and the *National Cancer Institute* from 2011 [24] as atypical carcinoid tumors or poorly differentiated neuroendocrine carcinomas, resembling the poorly differentiated adenocarcinomas but with larger hyperchromatic nuclei, prominent nucleoli and visible nuclear pleomorphism (Figure 8, a and c), increased mitotic activity (2–10/10 HPFs – high-power fields) and, sometimes, presenting several necrotic areas.

Malignant mesenchymal tumors

Mesenchymal tumors of the small intestine can be divided into two larger categories [20, 25–27].

- entities that have a histological appearance similar to that of the benign and malignant soft tissue tumors, mesenchymal with a different location (schwannoma, leiomyoma, lymphoma);
- neoplasms with spindle-shaped cells that often express CD117 (c-kit) in excess, called gastrointestinal stromal tumors (GISTs).

The **gastrointestinal stromal tumor** (GIST) was the most frequent type of malignant mesenchymal tumor that we encountered, being found in seven patients (Figure 9).

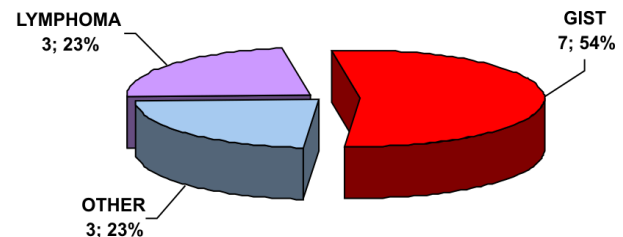


Figure 9 – Types of malignant mesenchymal tumors.

In two of the patients, the tumor was located near the jejunum, measured between 10 and 15 cm, a fact due to which we can fit them in the category of tumors with a high degree of malignancy according to the modifications proposed by Joensuu, in 2008 [28], to the classification ensued in 2002 by the *National Institutes of Health* (NIH) [29], and had a fungating and ulcerated appearance.

In both tumors, the tumor proliferation had a

predominantly storiform aspect, one of them presenting epithelioid areas and the immunohistochemical panel confirmed the diagnosis of high degree of malignancy (Figure 10).

For the other five patients, the tumors were located

near the ileum, between 100 and 150 cm from the ileocecal valve, the greater diameter varying between 5 and 10 cm. In other words, these were also large tumors that could fit, judging only by this criterion, in the category of intermediate or higher degree of malignancy.

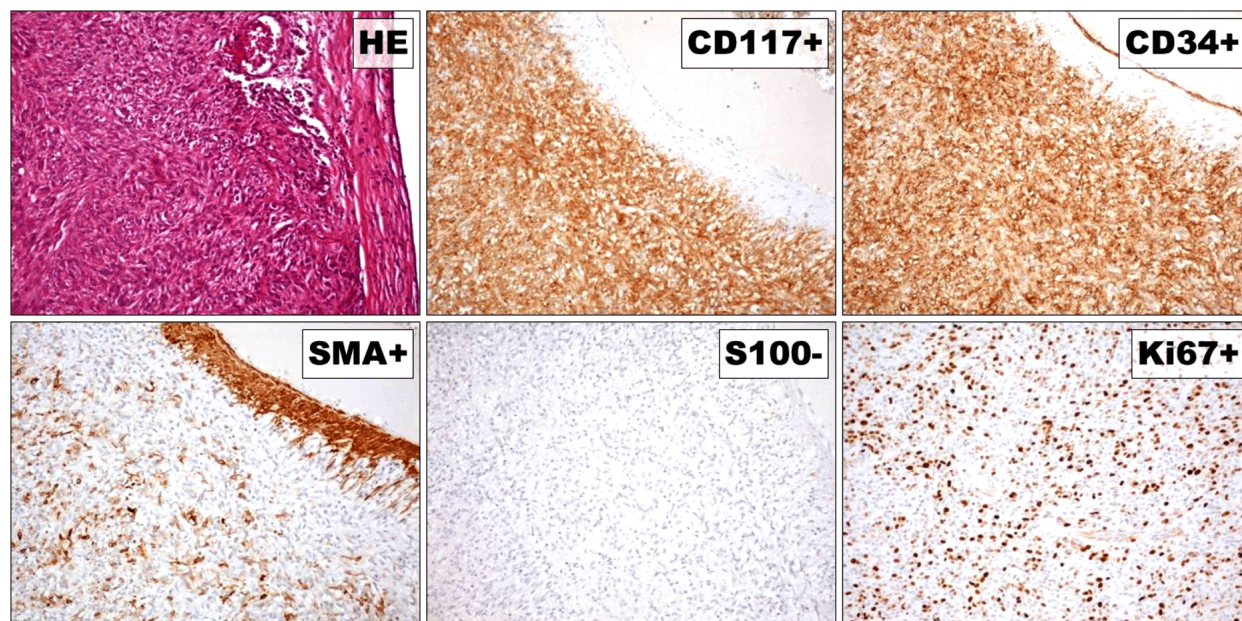


Figure 10 – GIST with storiform pattern and the immunohistochemical panel which confirms the diagnosis, $\times 100$.

All tumors had a fungating or fungating and ulcerative macroscopic appearance with a tumor cell proliferation with storiform pattern.

However, in one case we also found the epithelioid pattern (Figure 11).

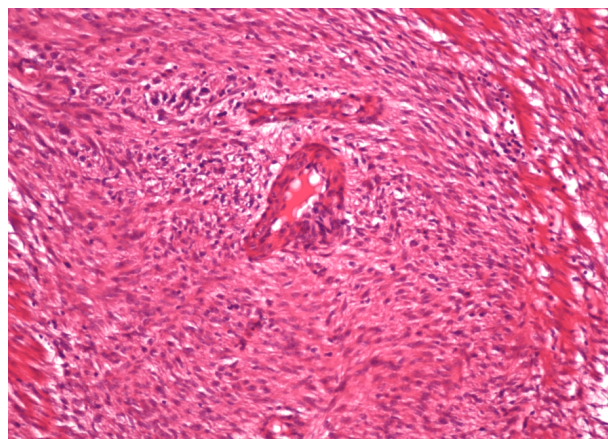


Figure 11 – GIST with mixed epithelioid and storiform pattern. HE staining, $\times 100$.

The immunohistochemical analysis confirmed in these cases too both the type of mesenchymal proliferation and the degree of malignancy.

Intestinal lymphoma. The gastrointestinal tract is a common location for extranodal lymphomas, the most frequently affected organ being the stomach, followed by the small intestine and the colon. The most common are the B-cell lymphomas [20].

In the studied cases, we encountered malignant lymphoid proliferations in three patients.

The **first case** had a tumor formation measuring 3/2 cm, located at 40 cm from the duodeno-jejunal angle, with a firm consistency, fungating and ulcerated and semicir-

cumferential. The histological examination highlighted a proliferation comprised of small-cleaved cells associated with larger cells (Figure 12a), widely spread throughout the intestinal mucosa and submucosa, having an ulcerated surface and a tendency to congest (Figure 12b). The strong positivity of malignant cells for the bcl-2 oncoprotein (Figure 12c) that marks the translocation (14, 18) oriented the diagnosis towards the follicular variant of a B-cell lymphoma.

The **second case** had a tumor mass that measured 3/2 cm and was located 150 cm from the duodeno-jejunal angle, having a fungating and ulcerated aspect and perforating the intestinal wall.

The histological examination revealed a diffuse proliferation of small atypical cleaved lymphocytes that almost effaced the architecture of the lymphoid structures from within the intestinal wall.

The immunohistochemical assessment was positive for CD20, suggesting the origin from the B-cells and for cyclin D1, suggesting the translocation (11, 14), panel that pleaded for the diagnosis of mantle cell lymphoma.

The strongly positive expression of Ki67 suggested a high degree of malignancy for the proliferation (Figure 13).

The **third case** presented a large infiltrative and stenosing tumor mass, measuring 6/4 cm and located 10 cm from the duodeno-jejunal angle, accompanied by numerous modified mesenteric lymph nodes, near the vicinity of the ileocecal valve.

The histological examination revealed, within the entire depth of the intestinal wall and the peri-intestinal adipose tissue as well as in some mesenteric lymph nodes, the presence of a proliferation that contained large malignant cells and Reed–Sternberg cells as well as some necrotic areas, an aspect which pleaded for the diagnosis of Hodgkin's lymphoma.

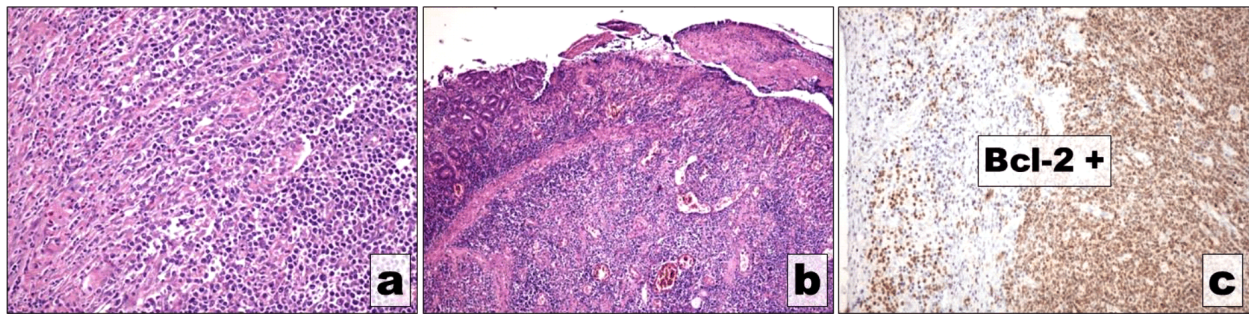


Figure 12 – B-cell lymphoma with follicular pattern, HE staining: (a) $\times 40$, (b) $\times 100$; (c) Bcl-2 immunomarking, $\times 100$.

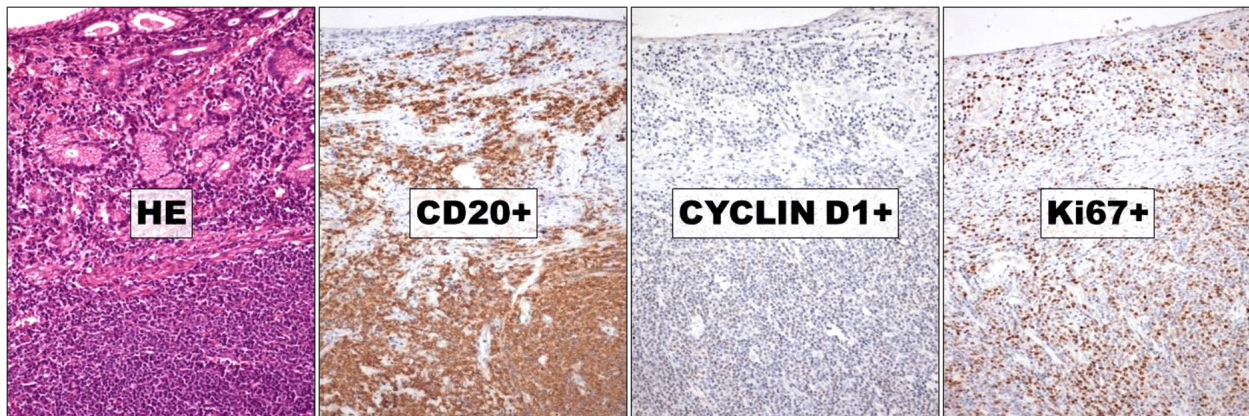


Figure 13 – Mantle-cell lymphoma – immunohistochemical panel, $\times 100$.

Malignant melanoma. Another case from the group of malignant mesenchymal neoplasms had the form of multiple tumor masses storeyed starting from 100 cm from the ileocecal valve and spanned until 30 cm from it, measuring between 1 and 5 cm, the last having a stenosing appearance.

The histological examination revealed a tumor proliferation made of polygonal cells with abundant cytoplasm, arranged in separate nests by rows made of vascular and

connective tissue, and which presented melanic pigment (Figure 14, a and b).

Sometimes, the cellular proliferation destroyed the mucosa entirely and produced ulcerations (Figure 14c).

The proliferation also extended within the wall, invading the entire muscular layer and the peri-intestinal adipose tissue, and often presented numerous tumoral vascular emboli (Figure 14d).

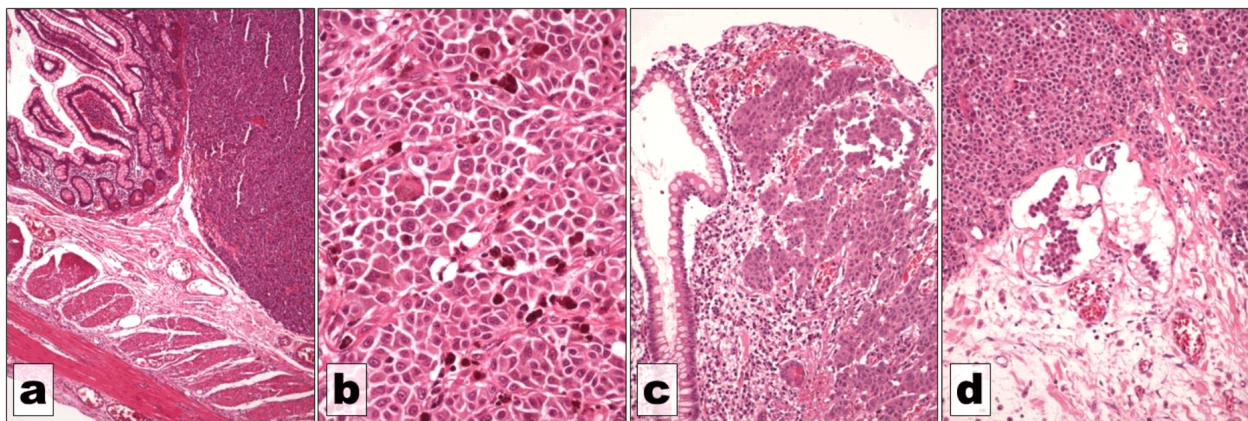


Figure 14 – Malignant melanoma: (a) General aspect; (b) Polygonal malignant cells with melanic pigment; (c) Ulceration of the invaded mucosa; (d) Lymphatic emboli. HE staining: (a) $\times 40$; (c and d) $\times 100$; (b) $\times 200$.

The histological appearance confirmed the diagnosis of malignant melanoma.

Paraganglioma. One tumor that is rarely encountered is the paraganglioma, which originates within the paraganglial structures of the autonomic nervous system. We found, however, such tumors among our cases in two of the patients.

In the *first case*, the tumor proliferation took the shape of multiple nodular formations, measuring 1–2 cm, and

located near the ileum where they infiltrated the wall and produced stenoses. The histological examination revealed the typical aspect of large cube-shaped malignant cell proliferation, cells that are also known as “Zellballen”. These cells have a specific disposition in well individualized nests, separated by fibrous septa which were strongly vascularized.

We noticed in some proliferations microulcerations of the mucosa.

The histological appearance pleaded for a rare form of malignant paraganglioma.

The **second case** presented an impressive tumor of 14/10 cm located near the first jejunal loop, which was perforated and had metastasis in the hepatic parenchyma. The histological aspect was, again, evocative for the malignant form of paraganglioma.

Tumor extension. Most of the malignant proliferations whether they were mesenchymal or epithelial, extended beyond the intestinal wall structures. The extension involved more frequently the neighboring organs and the structures of peritoneal cavity like peritoneum and great omentum. However, the metastatic process was also significant, mostly in the regional lymph nodes (Table 5).

Table 5 – Extension of malignant neoplasms

Extension	Region	Cases	%
Local		4	17.4
	<i>Neighboring organs</i>	5	21.7
Regional	<i>Peritoneum</i>	10	43.5
	<i>(carcinomatosis)</i>		
	<i>Great omentum</i>		
		2	8.7
Distant	<i>Mesenteric lymph nodes</i>	9	39.1
	<i>Liver metastasis</i>	1	4.3

Benign neoplasms

Benign neoplastic proliferations have been rarely encountered in the study group, in only two patients respectively.

In the **first patient** we identified two sessile tumor masses measuring 0.8 cm and located in the second duodenal segment and peripapillary respectively and a third sessile circumferential tumor, measuring 2 cm and located within the jejunum, 110 cm from the duodeno-jejunal angle, having a hyperemic mucosa and central ulceration. The histological examination revealed the

aspect of tubular adenomatous polyp with areas of mild dysplasia.

For the **second patient**, we identified only one fungating tumor measuring 5 cm, located in the second duodenal segment. The histological examination revealed a tubulovillous ulcerated polyp with a high degree of dysplasia.

Non-neoplastic tumor formations

We encountered among studied cases six where the macroscopic appearance was very diverse, raising the suspicion of a neoplastic proliferation.

Thus, in two of the cases the appearance was that of a tumoral block with signs of inflammation, one in the jejunum, 60 cm from the duodeno-jejunal angle, and the other located within the terminal ileum near the ileocecal valve.

For two other cases, the appearance was infiltrative. In one of the cases, the area measured 1/1 cm and was located 25 cm from the duodeno-jejunal angle. In the second one, we identified multiple infiltrative lesions along the jejunum, up until the proximal ileum, which raised the suspicion of a carcinomatosis.

Finally, in the last two cases, the tumor formation had a fungating aspect. One of the tumors had a pediculated appearance, was located in the distal ileum and, through its rather large measurements, 4/3 cm, determined an intestinal invagination. The other one was located in the third duodenal segment, presented a central ulceration and determined a luminal stenosis due to its size.

However, the histological examination revealed in all cases only a chronic non-specific and non-systemized inflammatory response, sometimes with vascular congestion and edematous distension of the lax interstitial spaces from within the corium of the mucosa and submucosa and with the tendency to cluster the inflammatory cell population in lymphoid aggregates that resembled the lymphoid follicles (Figure 15, a–c).

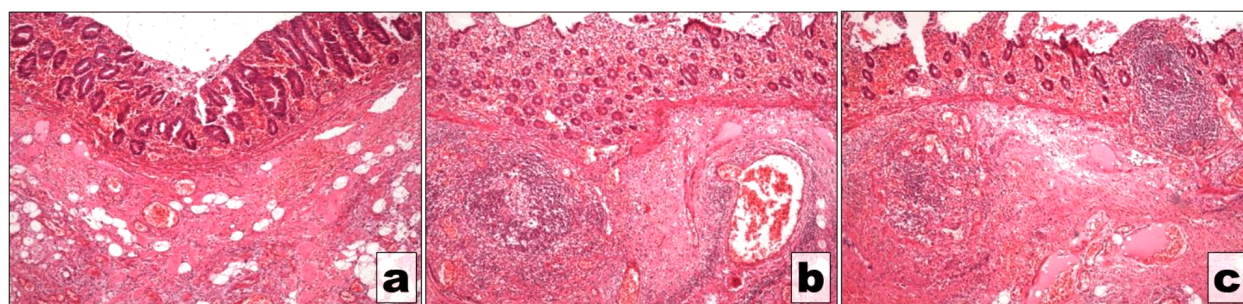


Figure 15 – Inflammatory pseudotumor: different aspects. HE staining, ×40.

This morphological appearance, which lacked myofibroblastic proliferation with spindle-shaped cells, however with frequent but typical mitosis and myxoid stroma [30], led in all cases to the diagnosis of chronic inflammatory reaction, excluding the diagnosis of inflammatory tumor of the small intestine.

Discussion

Gross assessment

Tumor site

Comparing the distribution according to the tumor location with two other studies [18, 31], both of them with a consistent number of cases we observed, on one

hand, that the involvement of the ileum is almost the same (Figure 16).

On the other hand, our series differed from the two other series of patients by a larger number of tumors harbored by the jejunal segments as compared with a larger number of cases with tumors located in the duodenum in the other series.

As we already mentioned, our group of tumors included almost entirely malignancies. If we take into consideration the location, our duodenal tumors were exclusively carcinomas. The comparison with other studies [18, 31] showed that the duodenal segment of the small intestine is usually affected by epithelial malignancies, followed by the neuroendocrine tumors.

The second intestinal segment – the jejunum – hosted in our series only sarcomas, especially gastrointestinal stromal tumors and lymphomas. In the other studies, the carcinomas went down around 40% and the presence of lymphomas became more prominent.

Finally, in our study, sarcomas dominated in the third segment, most of them being again gastrointestinal stromal tumors whereas in the other studies the most frequent malignancies were by far the neuroendocrine cancers (Figure 17).

The two benign tumors were found, as we mentioned above, in the duodenum and jejunum.

The inflammatory lesions were encountered usually in the jejunal segment, as we also already mentioned.

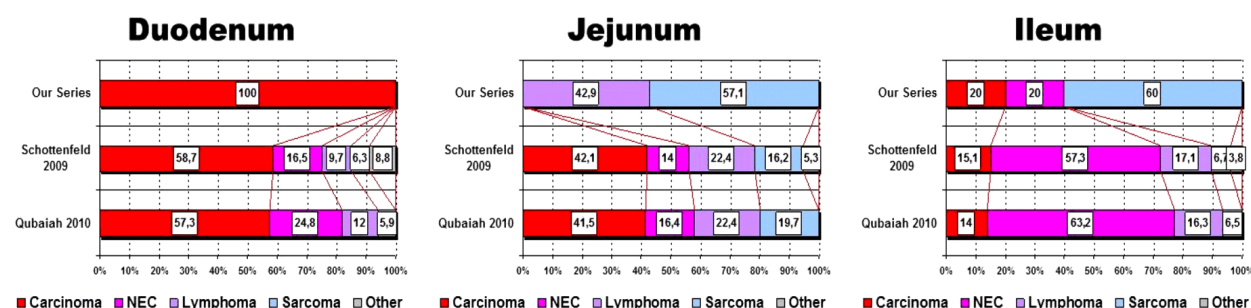


Figure 17 – Comparison with other studies of malignancies' location [18, 31].

Tumor number and dimensions

The analysis of tumor dimensions according to tumor location revealed that duodenal tumors had small dimensions smaller than 3 cm whereas in the other intestinal regions the tumors were usually larger than 5 cm. We remind again the two-jejunal tumors larger than 10 cm, one gastrointestinal stroma tumor and the paraganglioma (Figure 18).

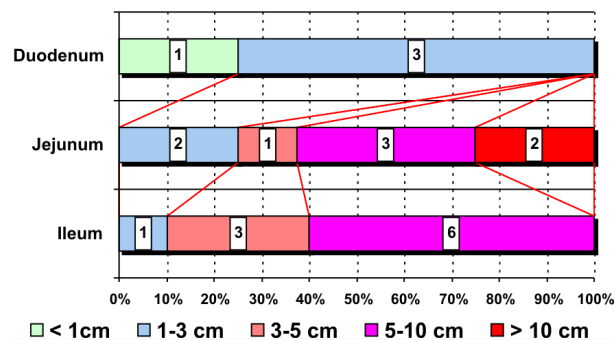


Figure 18 – Distribution in different intestinal segments according to tumor dimensions.

The two benign tumors were smaller than 5 cm and as well as the pseudotumoral inflammatory lesions.

Histological assessment

In the recent literature that we had access to, we only found two studies in which the inclusion criterion was the macroscopic appearance, meaning that of a tumor formation in the intestinal wall. A first observation would be that in both ours and the other two studies, the malignant neoplasms were predominant (Figure 19). In our series, however, the percentage of malignant neoplasia was higher.

A second observation is that the benign neoplasms

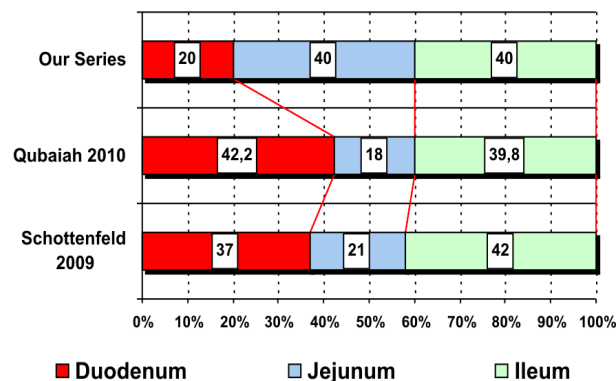


Figure 16 – Comparison with other studies [18, 31].

had a variable incidence, the highest value being found in the Polish group [32].

A third observation is concerning the non-neoplastic tumor formations, which were present in all three groups with nearly similar frequencies.

It should be noticed however that both foreign groups but especially the American group [33], also contained a number of tumor formations, which had no mentions regarding their histopathological pattern.

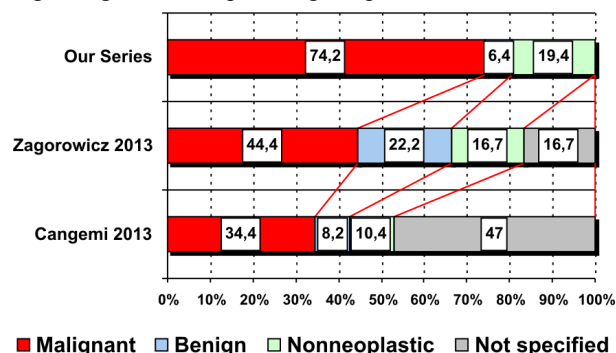


Figure 19 – Distribution of cellular types and comparison with other studies [32, 33].

The comparative evaluation according to tissue origin criterion has shown, on one hand, that within the foreign groups, the epithelial neoplasms were predominant, unlike our group where the mesenchymal neoplasms were more numerous and, on the other hand, within the epithelial neoplasms, both in our group and in American group [33] the malignant neoplasms were predominant while, in Polish group [32], the benign neoplasms were more frequent (Figure 20).

It is also worth mentioning that, for this evaluation, the lymphomas were included in the category of mesenchymal neoplasms.

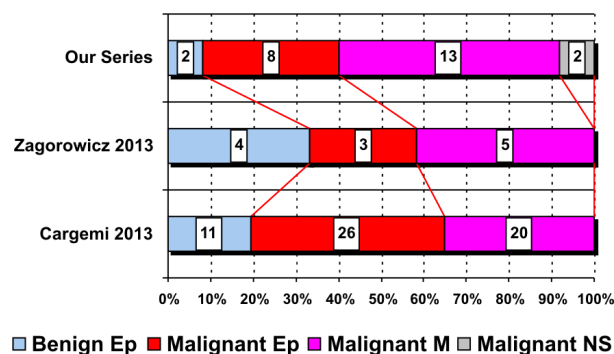


Figure 20 – Distribution of histogenetic types and comparison with other studies [32, 33]. Ep: Epithelial; M: Malignant; NS: Not specified.

Malignant neoplasms

In order to compare our results with data from the literature, we used this time a larger number of studies we found in the literature, throughout a longer time span, where the inclusion criterion was the neoplastic nature of the analyzed tumor formations (Figure 21).

Thus, with the exception of the Partridge *et al.* study [34], where the malignant epithelial proliferations were dominated by malignant neuroendocrine tumors, all the other studies, including ours, highlighted a higher frequency of carcinomas ranging, however, from 28.5% (our group) and 54.7% (Ojha *et al.*, 2000) [35]. Generally, in the literature, retrospective studies performed on larger groups reported only the presence of common form of adenocarcinoma and put this on the first place with a frequency of 30% to 40% among primary malignant neoplasms of the small intestine [18, 36].

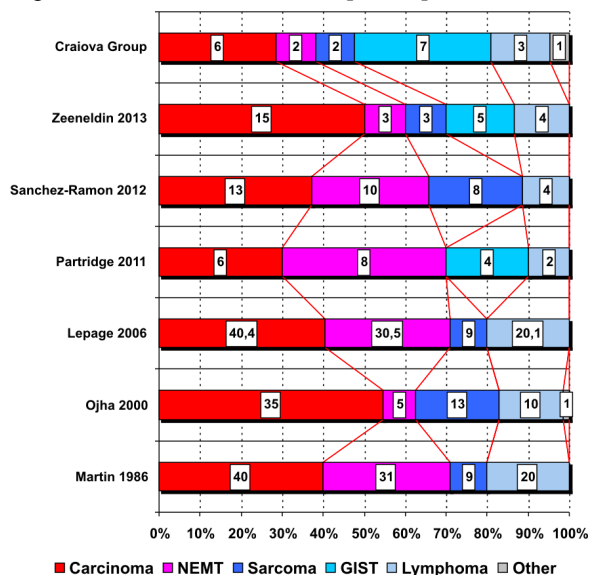


Figure 21 – Comparison with other studies [4, 34, 35, 37–39]. NEMT: Neuroendocrine malignant tumor; GIST: Gastrointestinal stromal tumor.

Regarding the group of epithelial neoplasms, it is worth mentioning that, in order to compare, we have separately taken into consideration, as in the cited studies, the group of malignant neuroendocrine tumors (carcinoid tumors) although the *National Cancer Institute* classification from 2011 places the carcinoid tumors as neuroendocrine carcinomas with a higher or lower degree of differentiation [24]. In our comparative analysis,

which included studies performed on small groups, the frequency of neuroendocrine carcinomas was extremely variable, ranging from 7.8% (Ojha *et al.*, 2000) [35] to 40% (Partridge *et al.*, 2011) [34]. This type of tumors is quoted in the recent literature as the second malignant neoplasia of the small intestine, with an average frequency of 20–25%, but with a constantly increasing incidence over the last three-four decades, reaching 42% of small intestinal neoplasia, in some studies performed on larger groups [18, 36, 40].

Another observation is that lymphomas, which were regarded as the third most frequent neoplasia of the small intestine [36], were constantly found with an incidence varying from 10% to 20%.

Regarding the malignant mesenchymal proliferations other than lymphomas, a first observation is their constant presence, with a variable incidence, as with lymphomas, yet with a wider range, between 9% and almost 40%. A second observation is the occurrence, over the last few years, of the individualization of GISTs as a distinct group within the malignant mesenchymal tumors, currently being considered as the fourth major group of primary malignant neoplasms of the small intestine [36, 41].

Something in particular that we found in the compared groups would be the presence of a case with melanoma metastasis in our group and the presence of a case with two synchronous neoplastic proliferations of the small intestine in the Ojha *et al.* group [35], one adenocarcinoma and one lymphoma.

Carcinomas

Comparing the results, we have obtained with those from the literature, we established, on one hand, the predominance of adenocarcinomas within the group of carcinomatous proliferations, except, as shown, Partridge *et al.* study [34], in which neuroendocrine carcinomas accounted for two-thirds of the study group chosen by the authors and, on the other hand, the constant presence of neuroendocrine adenocarcinomas. It is also worth pointing out the fact that, both in our study and in Partridge *et al.* and Ojha *et al.* [35], there were also carcinomas with different histological pattern than that of the common form of adenocarcinoma (Figure 22).

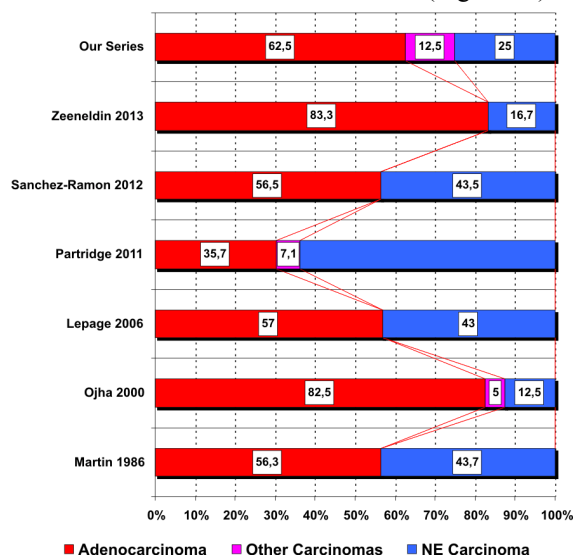


Figure 22 – Comparison with other studies [4, 34, 35, 37–39]. NE: Neuroendocrine.

Malignant mesenchymal tumors

The comparison with other studies from the literature revealed several aspects. Thus, we can observe that, in the last decade the stromal tumors are starting to be reported as a separate group from the rest of the sarcomas. Another observation is that lymphomas, which are a constant presence in the reports of malignant proliferations of the small intestine, seem to suffer a decrease of their incidence (Figure 23).

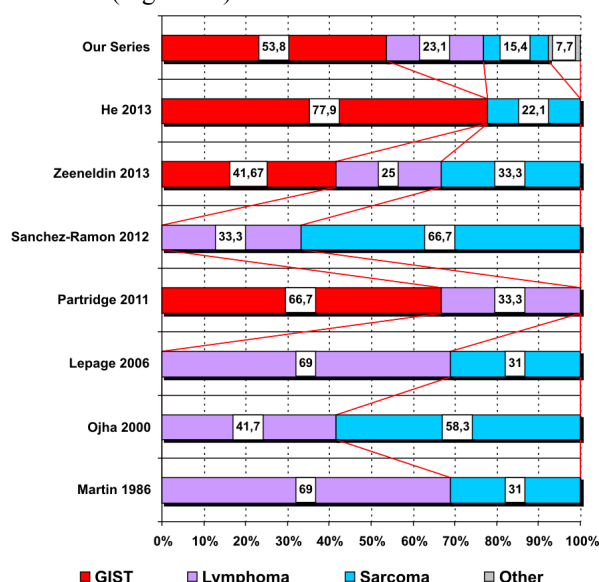


Figure 23 – Comparison with other studies [4, 34, 35, 37–39, 44].

Tumor extension

Comparing the degree of extension of our malignant tumors with other studies, we observed that only few of our proliferations had only local extension.

Usually, they were extended in the neighboring regions and very often distant metastases were present (Figure 24).

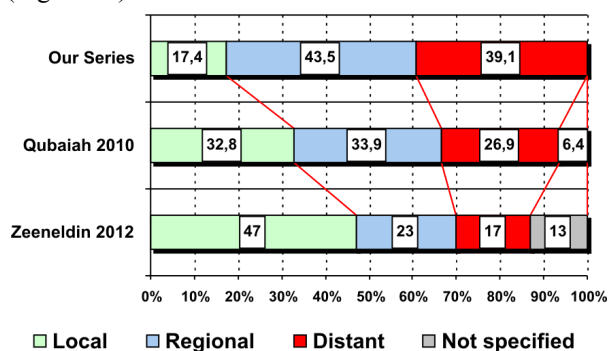


Figure 24 – Comparison with other studies [31, 37].

Non-neoplastic tumor formations

Concerning the chronic inflammatory reactions discovered in some of our cases, sometimes, the presence of an abundant lymphocytic cellular component (Figure 25) could have raised the suspicion of an immunoproliferative disease of the small intestine, a distinct form of B-cell lymphoma, considered to be a special form of mucosa associated lymphoid tissue (MALT) lymphoma of which some speculated to originate from a lymphoplasmacytic reactive infiltration as a response to the

permanent stimulation with possible infectious antigens, a hypothesis sustained by the polyclonal nature of the proliferation and the response to tetracycline therapy [42, 43].

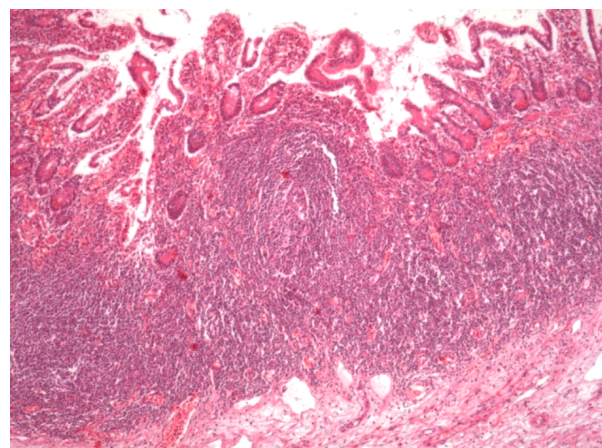


Figure 25 – Inflammatory pseudotumor mimicking a lymphoma, HE staining, ×40.

Conclusions

The morphological profile of our series of tumors was similar in many of its aspects with the profile described in other studies but with some particularities: the polarization to the extremities of the intestinal segment, a significant number of large tumors, clinical expression through different complications, the balance inclined in favor of mesenchymal origin of tumors and the clear predominance of malignant aggressive phenotype. Besides the fact they are rare, tumors of the small intestine are also difficult to diagnose. Therefore, any non-specific abdominal distress or inexplicable anemia should raise the suspicion of a possible tumor mass belonging to the small intestine and set off further as soon as possible an algorithm of thorough investigations followed by therapeutic sanction whose golden standard is the surgical intervention.

Conflict of interests

The authors declare that they have no conflict of interests.

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The first and the second authors had equal contribution to the achievement of this paper.

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