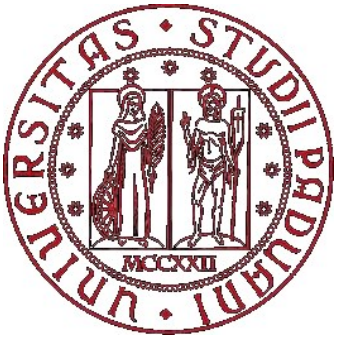

# UNIVERSITÀ DEGLI STUDI DI PADOVA


CORSO DI LAUREA MAGISTRALE IN MEDICINA E CHIRURGIA

DIPARTIMENTO DI SCIENZE CHIRURGICHE ONCOLOGICHE E GASTROENTEROLOGICHE

Unità di Chirurgia Generale 3

Direttore: Prof. Salvatore Pucciarelli


TESI DI LAUREA

# SMALL BOWEL NEOPLASM CHARACTERIZATION AND INFLAMMATORY-RELATED AND SPORADIC SMALL BOWEL ADENOCARCINOMA COMPARISON OF CLINICAL FEATURES


Relatore: Ch.mo Prof. Salvatore Pucciarelli

Correlatore: Dott. Marco Scarpa

Laureanda: Anna Andriani

# INDEX

# ABSTRACT

**Background:** Small bowel cancer (SBC) represents 1 to 5 % of all gastrointestinal cancer and is a rare cancer with a bad prognosis often arising in a Crohn's disease context.

Histopathologic types of small bowel cancer comprehend adenocarcinomas, gastrointestinal stromal tumors (GISTs), neuroendocrine tumors (NET), and lymphoma.

**Aim of the study:** This study first aims to assess if there are prognostic and clinical criteria to distinguish between adenocarcinoma, Net and Gist to create a possible algorithm for the diagnostic exams in patients with undefined small bowel neoplasm.

This study second aims to assess the burden of small bowel cancer (SBC) in patients with Crohn's disease (CD) and in those without IBD, and to identify possible factors associated with morbidity and with a poor prognosis.

**Materials and methods:** Records of all the consecutive patients who underwent small bowel resection for sporadic or CD-related adenocarcinoma from 01/01/2010 until 31/12/2022 will be reviewed.

Cancer cases occurring in CD will be compared with patients who underwent curative-intent surgery for a histologically confirmed sporadic SBC. Data will be collected in an anonymized database and will be compared with a non-parametric test.

**Results:** We evaluate the different presentation between adenocarcinomas, GISTs and NETS. In our series, adenocarcinomas occurred more frequently in males, 82% vs 18% of cases, while in GIST it occurred in males in 40% vs 60% in females and

in NET occurred in 16% occurred in males vs 84 % in females, p=0,0013. The presentation symptoms of diarrhea had different distribution depending on the pathology: in Adenocarcinoma is present only in 6% of cases, in GIST is absent, in NET is present 25%, p=0,04. Loss of Weight is present in 29,41% of patients with adenocarcinomas, 5% of patients with GIST and 25% of patients with NET. Pain is a common presentation in patients with small bowel neoplasm: in adenocarcinomas is present 17,04% of patients, in NETS in 58,3% of patients and in GISTS in 25% of patients. Subocclusion is a presentation symptom in 5,9 % of adenocarcinomas and in 25% of NET. Hemoglobin concentration (p= 0,04) was higher in NET, lower in the adenocarcinoma and medium in GISTs in comparison to the other two. In our series, NLR (p=0,0017) is higher in adenocarcinoma, medium in GIST and lower in NET. In our series, patient with adenocarcinomas were pN0 in 75% of cases, pN1 in 5% of cases and pN2 in 20% of cases, p=0,0009. In GIST patients, no nodal metastasis was observed. In NET patients, nodal metastasis were always present ( pN1 in 50% and pN2 in the other 50%). In Adenocarcinoma patients, distant metastasis were present in 19% of cases. In GIST patients, distant metastasis were never observed. In NETs metastasis were present in 84% of cases, p=0,0097. LVI (Lymphovascular invasion) was present in 66% of the adenocarcinoma, 100% of the NET and 0% in the GIST, p=0,04. DFS (Disease free survival) after 60 months is 42% in adenocarcinoma, 52% in NET and 83% in GIST, p=0,02. OS (Overall survival) after 60 months is less than 50% in adenocarcinoma, 62% in NET and 100% in GIST, p=0,26.

We also evaluated if there are difference between sporadic adenocarcinomas and IBD related adenocarcinomas. The oncological marker concentration of Ca19,9 and CEA is very different between patients with sporadic adenocarcinoma (Ca 19,9 < 2 kU/L and CEA < 0.5ug/L) and in patients with IBD-related adenocarcinoma the median of Ca19,9 is 350 U/L and the median of CEA is 440 ug/L, p=00,05. DFS (Disease free survival) is the same between sporadic adenocarcinoma and Crohn's disease related adenocarcinoma equal to respectively 32% and 0 % after 60 months, p=0,92. OS (Overall survival) is not different in patients with sporadic and IBD-related adenocarcinoma, p=0,40.

**Conclusions:** This study investigated presentation characteristics, and diagnostic features of adenocarcinomas, GISTs and NETs to address the diagnostic exams. In case of small bowel should value patients sex, hemoglobin concentration, presence of positive and metastasis. According to our data in case of absence of anaemia, diarrhea, nodes metastasis at the CT diagnostic, diagnosis should be address to GIST tumors. In case of small mass and lymphonode involvement, Net should be suspected and $^{68}$Gallium PET should be done to investigate the presence of tumor.

This study also aimed to set if there are significant differences in presentation, prognosis and survival, between sporadic adenocarcinomas and Crohn's disease-related adenocarcinomas. Differential diagnosis remain difficult due to the aspecific symptoms like diarrhea, abdominal pain and anemia that are common presentation of IBD disease. Moreover, survival analysis showed no difference in prognosis and overall survival between sporadic adenocarcinomas and concomitant OBD adenocarcinomas.

# RIASSUNTO

**Presupposti dello studio**: Il carcinoma dell'intestino tenue (SBC) rappresenta dall'1 al 5% di tutti i tumori gastrointestinali, è un tumore raro con una prognosi sfavorevole che spesso si manifesta nel contesto della malattia di Crohn.

I tipi istopatologici di carcinoma dell'intestino tenue comprendono adenocarcinomi, tumori stromali gastrointestinali (GIST), tumori neuroendocrini (NET), linfomi.

**Scopo dello studio:** Questo studio si propone innanzitutto di valutare se esistono criteri prognostici e clinici per distinguere tra adenocarcinoma, Net e Gist per creare un possibile algoritmo per gli esami diagnostici in pazienti con neoplasia dell'intestino tenue indefinita.

Questo studio mira inoltre a valutare l'onere del carcinoma dell'intestino tenue (SBC) nei pazienti con malattia di Crohn (CD) e in quelli senza IBD e identificare i possibili fattori associati alla morbilità e alla prognosi infausta.

**Materiali e metodi**: Verranno riviste le registrazioni di tutti i pazienti consecutivi che sono stati sottoposti a resezione dell'intestino tenue per adenocarcinoma sporadico o correlato a MC dal 01/01/2010 al 31/12/2022.

I casi di cancro che si verificano in CD saranno confrontati con pazienti sottoposti a chirurgia con intento curativo per un SBC sporadico confermato istologicamente. I dati saranno raccolti in un database anonimizzato e saranno confrontati con test non parametrici.

**Risultati**: In questo studio abbiamo valutato la diversa presentazione tra adenocarcinomi, GIST e NETS. Nella nostra serie, gli adenocarcinomi si sono verificati più frequentemente nei maschi, 82% vs 18% dei casi, mentre nel GIST si è verificato nei maschi nel 40% vs 60% nelle femmine e nel NET si è verificato nel 16% nei maschi vs 84% nelle femmine, p=0,0013. Il sintomi di presentazione diarrea ha avuto distribuzione diversa a seconda della patologia: nell'Adenocarcinoma è presente solo nel 6% dei casi, nel GIST è assente, nel NET

è presente nel 25%, p=0,04. La perdita di peso è presente nel 29,41% dei pazienti con adenocarcinomi, nel 5% dei pazienti con GIST e nel 25% di pazienti con NET. Il dolore è una presentazione comune nei pazienti con neoplasia del piccolo intestino: negli adenocarcinomi è presente nel 17,04% dei pazienti, nei NETS nel 58,3% dei pazienti e nei GISTS nel 25% dei pazienti. La subocclusione è un sintomo di presentazione nel 5,9% degli adenocarcinomi e nel 25% dei NET. La concentrazione di emoglobina era più alta nei NET, più bassa nell'adenocarcinoma e media nei GIST rispetto agli altri due, p=0,04. Nella nostra serie, l'NLR è più alto nell'adenocarcinoma, medio nel GIST e più basso nel NET, p=0,0017. Nella nostra serie, i pazienti con adenocarcinomi erano pN0 nel 75% dei casi, pN1 nel 5% dei casi e pN2 nel 20% dei casi, p=0,0009. Nei pazienti con GIST non è stata osservata metastasi linfonodale. Nei pazienti con NET erano sempre presenti metastasi linfonodali (pN1 nel 50% e pN2 nel restante 50%). Nei pazienti con adenocarcinoma, metastasi a distanza erano presenti nel 19% dei casi. Nei pazienti con GIST non sono mai state osservate metastasi a distanza. Nei NET le metastasi erano presenti nell'84% dei casi, P= 0,0097. LVI (Lymphovascular invasion) era presente nel 66% degli adenocarcinomi, nel 100% dei NET e nello 0% dei GIST, p=0,04. La DFS (Sopravvivenza libera da malattia) dopo 60 mesi è del 42% nell'adenocarcinoma, del 52% nel NET e dell'83% nel GIST, p=0,02. L'OS (sopravvivenza globale) dopo 60 mesi è inferiore al 50% nell'adenocarcinoma, al 62% nel NET e al 100% nel GIST, p=0,26.

Abbiamo anche valutato se ci siano differenze tra adenocarcinomi sporadici e adenocarcinomi correlati a IBD. La concentrazione del marker oncologico di Ca19,9 e CEA è molto diversa tra i pazienti con adenocarcinoma sporadico (Ca 19,9 < 2 kU/L e CEA < 0,5ug/L) e nei pazienti con adenocarcinoma correlato a IBD la mediana di Ca19,9 è 350 U/L e la mediana di CEA è 440 ug/L, p=0,05. La DFS (Sopravvivenza libera da malattia) è la stessa tra adenocarcinoma sporadico e adenocarcinoma correlato alla malattia di Crohn pari rispettivamente al 32% e allo 0% dopo 60 mesi, p=0,92. L'OS (sopravvivenza globale) non è diversa nei pazienti con adenocarcinoma sporadico e correlato a IBD, p=0,040.

**Conclusioni:** Questo studio indaga le caratteristiche di presentazione e le caratteristiche diagnostiche di adenocarcinomi, GIST e NET per indirizzare gli esami diagnostici. In caso di intestino tenue occorre valutare il sesso dei pazienti,

la concentrazione di emoglobina, la presenza di positività e metastasi. Secondo il nostro studio in caso di assenza di anemia, diarrea, metastasi linfonodali alla diagnostica TC, la diagnosi dovrebbe essere indirizzata ai tumori GIST. In caso di piccola massa e coinvolgimento linfonodale, deve essere sospettata la rete e deve essere eseguita la PET con 68Gallium per indagare la presenza del tumore.

Questo studio mira anche a stabilire se ci sono differenze significative nella presentazione, prognosi e sopravvivenza, tra adenocarcinomi sporadici e adenocarcinomi correlati alla malattia di Crohn. La diagnosi differenziale rimane difficile a causa dei sintomi aspecifici come la diarrea, il dolore addominale e l'anemia che sono una presentazione comune della malattia IBD. Inoltre, l'analisi della sopravvivenza non ha mostrato differenze nella prognosi e nella sopravvivenza globale tra adenocarcinomi sporadici e adenocarcinomi OBD concomitanti.

## 1.1. INTRODUCTION: SMALL BOWEL NEOPLASM

Small bowel carcinomas (SBC) are remarkably uncommon neoplasms, mostly sporadic. There are several predisposing conditions such as hereditary syndromes –familial adenomatous polyposis, Lynch syndrome, Peutz-Jeghers syndrome, juvenile polyposis syndrome and chronic immune-mediated intestinal disorders—coeliac disease and Crohn's disease (CrD) (1). The underlying intestinal disorder, i.e., CD or CrD, has been demonstrated to be a stage-independent prognostic factor in patients undergoing surgery for SBC (2).

The incidence of small bowel neoplasm is 1.5 per 100.000 inhabitants and represents 2% of gastrointestinal tumors(3). This pathology is incredibly rare in consideration of the length of the small bowel or of his extension for 75% of the total digestive tract length and for 90% of the mucosal surface area. Several hypotheses are justifying the low incidence of small bowel neoplasms: chemical-physical characteristics of the intraluminal content that is less alkaline and more fluid in this tracts, produce a minor inflammatory insult on the mucosae surface; low density of bacteria and lack of anaerobic germs causes minor production of injurious catabolites; the reduced transit time shortens the contact between mucosa and luminal cancerogenic; the rapid turnover and metabolic activity of enterocytes against numerous cancerogenic substance. The lymphatic tissue seems to have a protective effect in the inset through an action of immune surveillance on the onset of neoplastic disease confirmed also by the evidence of a higher neoplastic risk in patients with immune dysfunction or chronic inflammatory disease as CrD (2).

Adenocarcinoma is rare. It usually arises in the proximal jejunum and causes mild symptoms (3). In patients with CrD involving the small intestine, tumors tend to occur distally and in bypassed or inflamed bowel loops. A primary malignant lymphoma that develops in the ileum can cause a long, rigid intestinal segment. Small bowel lymphomas can develop in patients with longstanding, untreated celiac disease. Carcinoid tumors (also called gastrointestinal neuroendocrine tumors or NET) most often arise in the small intestine, particularly in the ileum and appendix; in these locations, larger lesions can become malignant. Multiple tumors are present in 50% of cases. Of those with a diameter > 2 cm, 80% have already metastasized locally or to the liver at the time of surgery. Kaposi's sarcoma occurs aggressively in Africans, transplant recipients, and AIDS patients, who present with

gastrointestinal tract involvement in 40-60% of cases. Lesions can be located anywhere in the gastrointestinal tract but are usually found in the stomach, small intestine, or distal colon. GI lesions are usually asymptomatic, but hemorrhage, diarrhea, protein-losing enteropathy, and intussusception may occur.

### 1.1.1. Incidence of malignant tumors

The incidence of small bowel cancers has slightly risen in recent decades. It increased from 1.18 per 100,000 (4) in 1973 to 2.27 per 100,000 in 2004 in the United States. Likewise, in France, the incidence increased during the period 1976–2001 (5) but also during the period 1996–2015(6-7-8). Four main histologic types are present in the small bowel: adenocarcinomas, neuroendocrine tumors, stromal tumors and lymphomas (8)

The distribution of histologic types of small bowel malignant tumors is changing, largely because of the increasing incidence of NETs (9). In 1987, the most common histologic types of malignant tumors of the small intestine in population-based registry data from the Surveillance, Epidemiology and End Results (SEER) program of the National Cancer Institute (NCI) were adenocarcinoma 45%, NET 29%, lymphoma 16%, and sarcoma 10% (10). In the year 2000, NETs surpassed adenocarcinomas as the most common small bowel tumor reported to the National Cancer Database (NCDB) (11). Between 1985 and 2005, the proportion of patients with NETs increased from 28 to 44%, while the proportion of adenocarcinoma decreased from 42 to 33%. The proportion of patients with stromal tumors and lymphoma remained essentially stable (17% and 8%t, respectively) (12, 13).

## 1.2. SMALL BOWEL ADENOCARCINOMA

Adenocarcinomas of the small bowel (SBA) are rare tumors. They are two times more frequent in males and preferentially located in the proximal jejunum. Ileal localization is mostly found in association with Crohn's disease (CrD), a condition which brings the neoplastic risk to 40-100 times that of the general population after about 15 years of the disease. The underlying intestinal disorder (CrD) has been demonstrated to be a stage-independent prognostic factor in patients undergoing surgery for SBC (1).

Although both Coeliac disease (CD) and (CrD) are sustained by similar pathogenic mechanisms, CD-associated SBA (CD-SBA) and CrD-associated SBC (CrD-SBA) represent distinct entities in terms of clinical, histopathological, and molecular features (Table 1) (14).

| Feature | CD-SBC | CrD-SBC | Spo-SBC |
|---|---|---|---|
| **Age at diagnosis** | 53–62 yrs | 42–73 yrs | 56.5–72.1 yrs |
| **Site** | Jejunum and duodenum | Ileum | Jejunum and duodenum |
| **Tumor cell phenotype** | Intestinal | Non-intestinal | Intestinal |
| **MSI status** | 65–73% | 0–16% | 9–35% |
| **Oncogenic viruses** | Unknown | EBV latent infection | No association with EBV infection |

*Table 1 Clinical, histopathological and molecular features of small bowel carcinomas according to the subgroup. (2)*

*CD-SBC, small bowel carcinoma associated with coeliac disease; CrD-SBC, small bowel carcinoma associated with Crohn's disease; EBV, Epstein-Barr Virus; MSI, microsatellite instability; spo-SBC, sporadic small bowel carcinoma; yr, year.*

### 1.2.1. Epidemiology and risk factors

Incidence of small bowel adenocarcinoma has increased in the United States and Europe, particularly small bowel adenocarcinoma of the duodenum (15). In a population-based study in France, the age-standardized incidence rate of small bowel adenocarcinoma was 0.69 per 100,000 in the 1996–2000 period and increased to 0.8 per 100,000 in the 2011–2015 period in men and it increased from

0.37 per 100,000 in the 1996–2000 period to 0.51 per 100,000 in the 2011–2015 period in women (16-17). The duodenum is the most frequently affected segment, accounting for 55–82% of cases, followed by the jejunum (11–25%) and ileum (7–17%) (18). The increasing incidence is mainly due to duodenum adenocarcinoma. In a population-based study the Netherlands, a twofold increase in duodenal cases was observed from the 1999–2003 period to the 2009–2013 period. small bowel adenocarcinoma is most often diagnosed during the sixth decade and a slight male predominance is observed (18,20,21). There are 3,595 new cases of small bowel adenocarcinoma each year in Europe according to the EUROCARE database (19).

The epidemiological features of small bowel adenocarcinoma differ based on underlying chronic immune-mediated intestinal disorders. The median age for Crohn's disease-small bowel adenocarcinoma (CrD-SBA) diagnosis seems to be younger varying from 42 to 53 years in most studies in American, British, Dutch and Italian patients. Sporadic small bowel adenocarcinoma (spo-SBA) patients generally have a higher median age at diagnosis -between 56.5 and 72.1 years- in comparison to CrD-SBA (16).

Risk factors reported for CrD-SBA include a long disease duration, a small bowel involvement, a stricturing phenotype and bypassed segment(s) of the small bowel (22). As regards long disease duration, in a French study involving 1935 patients affected by CrD with small bowel involvement at diagnosis a cumulative risk of SBC has been assessed as 0.2% and 2.2% after 10 and 25 years of follow-up, respectively (23). Small bowel resection and use of salicylates for more than two years protect against SBC in patients with CrD (24). As regards gender, the rates of female prevalence are extremely heterogeneous in CrD-SBA (29–60%) (25,26,27,28,29,30,31,32,33,34,35,36) so it is hard to assess a gender predominance in either condition. However, considering the strong prevalence of CD in women, these data may suggest that the male gender is at higher risk to develop CD-SBA (16).

### 1.2.2. Risk factor: Crohn's Disease

CD is a type of inflammatory bowel disease (IBD) that may affect any segment of the gastrointestinal tract characterized by chronic inflammation of digestive tract mucosae. The colon and distal small bowel are the most frequently involved

digestive tract segments. In Crohn's disease, any part of the small or large intestine can be involved. It may involve multiple segments, or it may be continuous. The inflammation involves all layers of the intestinal wall (37).

CrD may be categorized by the disease presentation as it progresses in stricturing, penetrating, and inflammatory. Stricturing disease causes narrowing of the bowel that may lead to bowel obstruction or changes in the caliber of the feces. The penetrating disease creates abnormal passageways (fistulae) between the bowel and other structures. Inflammatory disease (or non-stricturing, non-penetrating disease) causes inflammation without causing strictures or fistulae. These three different types of lesions may coexist or evolve one in another in the same patient at different stages of the disease. Although the precise causes of Crohn's disease are unknown, it is believed to be caused by a combination of environmental, immune, and bacterial factors in genetically susceptible. Crohn's disease affects about 3.2 per 1,000 people in Europe, North America and the UK (38). It is less common in Asia and Africa. In Italy incidence is 6,9/100.00 inhabitants/year and prevalence 86/100.000 people without difference between men and women.

### 1.2.3. Risk factor: Coeliac Disease

Coeliac disease is an autoimmune disorder that primarily affects the small intestine, and is caused by the ingestion of gluten in genetically susceptible individuals. Prevalence in the general population ranges from 0·5% to 2%, with an average of about 1%. The development of the coeliac enteropathy depends on a complex immune response to gluten proteins, including both adaptive and innate mechanisms. Clinical presentation of coeliac disease is highly variable and includes classical and non-classical gastrointestinal symptoms, extraintestinal manifestations, and subclinical cases. The disease is associated with a risk of complications, such as osteoporosis and intestinal lymphoma. Diagnosis of coeliac disease requires a positive serology (IgA anti-transglutaminase 2 and anti-endomysial antibodies) and villous atrophy on small-intestinal biopsy. Treatment involves a gluten-free diet; however, owing to the high psychosocial burden of such a diet, research into alternative pharmacological treatments is currently very active. (140)

### 1.2.4. Clinical presentation and diagnosis

The diagnosis of small bowel adenocarcinoma is often difficult due to the rarity of these lesions and the nonspecific and variable nature of the presenting signs and symptoms. This is the reason why the delay in diagnosis is common and explains the discovery of disease at a late stage and a poor treatment outcome .

Symptoms are aspecific and include abdominal pain, occlusion or sub-occlusion and bleeding mostly when the tumor is diagnosed after emergency treatment. According to localization, there are different symptoms: there is less bowel obstruction in the case of duodenal tumors compared to jejunoileal tumors. A chronic small bowel sub-obstruction that is not improved by medical treatment should be considered for surgical resection.

Between 1978 to 1998 an Overman, Kunitake, Tanabe and Sonali study, the diagnosis was made mainly by upper endoscopy (28%), during surgery (26%), by a small bowel barium transit (22%), by a CT scan (18%), ultrasound examination (3%) or physical examination (3%) (40). In a more recent Japanese multicenter study, 43% of the duodenum adenocarcinomas were diagnosed without symptoms but this may be related to the gastric cancer screening ongoing in Japan (41). In the NADEGE cohort, the contribution to diagnosis varied according to small bowel segments. Upper endoscopy gave a diagnosis for 49% of the duodenal adenocarcinoma, colonoscopy for 41% of the ileum adenocarcinoma and capsule endoscopy or CT scan with enteroclysis for 26% and 34% of the jejunum adenocarcinoma (42). In CrD, the diagnosis of small bowel adenocarcinoma is often difficult because the symptoms are similar to those of the underlying pathology and is frequently reached postoperatively after resection of an obstructed small bowel segment (31). Even in patients with predisposing disease, early diagnosis is a challenge and no specific screening is recommended.

Improvement of imaging techniques may allow differential tumor-type diagnosis, as was suggested by a small study assessing small bowel adenocarcinoma and primary small bowel lymphoma with spectral CT imaging. According to a prospective study on 150 patients with a suspected small bowel disease, magnetic resonance (MRI) enterography is more accurate than CT enterography for tumor detection (43). Guidelines recommend an initial basic workup and some more specific examinations according to localization or predisposing disease. The basic assessment includes a contrast-enhanced thoracic-abdominal-pelvic CT scan to

evaluate local and metastatic extension. Liver MRI may be useful in case of contra-indication for iodine contrast agents or if liver metastases are suspected on CT scan examination (44,45). Positron emission tomography (PET) scanning is not routinely indicated but may be considered if there is doubt about metastasis on initial CT staging (46). A gastric endoscopy and colonoscopy looking for other tumors are indicated in case of suspicion of genetic predisposition. In the case of duodenal adenocarcinoma, an endoscopic ultrasound is recommended to assess vascular invasion and discern duodenal lesions from ampullary, biliary or pancreatic primary (47).

The dosage of CEA and CA 19-9 is useful at the initial workup, particularly in the event of a metastatic tumor (44,141,142). Monitoring the concentration markers at the moment of the diagnosis allows to evaluate the subsequent changes of concentration after therapy to monitor the prognosis and progress of the neoplastic disease, particularly in case of metastatic progress or relapse of the disease (143). The not detectable concentration of markers is related to the remission of the tumor while the increase of the marker could indicate the presence of metastasis or relapse of disease (144).

In CrD, exploration of the entire intestine with MRI enterography or capsule endoscopy should be done to diagnose other synchronous tumor lesions. Testing for anti-transglutaminase A antibodies and duodenal biopsies are routinely recommended to detect celiac disease (49).

Follow-up with clinical examination, imaging and tumor marker dosage for a total duration of 5 years are recommended after diagnosis and a curative resection(44).

### 1.2.5. Staging

Staging is based on TNM staging (Table 2). It is recommended to assess a minimum of eight lymph nodes to have adequate staging.

**Primary tumor (T)**

T0 There is no evidence of a primary tumor

Tis Carcinoma in situ

T1 Tumor invades the mucosa, muscularis mucosa or submucosa

T1a Tumor invades the lamina propria or muscularis mucosa

T1b Tumor invades the submucosa

T2 Tumor invades the muscularis propria

T3 Tumor invades the subserosa or into the non-peritonealized perimuscular tissue (mesentery or retroperitoneum)

T4 Tumor perforates the visceral peritoneum (T4a) or directly invades other organs or structures (T4b), including:

- other loops of the small intestine, mesentery or retroperitoneum

- through the serosa into the abdominal wall

- the pancreas (only for tumors in the duodenum)

**Regional lymph nodes (N)**

N0 No regional lymph node metastasis

N1 Metastasis in 1–2 regional lymph nodes

N2 Metastasis in 3 or more regional lymph nodes

**Distant metastasis (M)**

M0 No distant metastasis

M1 Distant metastasis

**Cancer staging**

Stage 0: Tis, N0, M0

| |
|---|
| Stage I: T1 or T2, N0, M0 |
| Stage IIA: T3, N0, M0 |
| Stage IIB: T4, N0, M0 |
| Stage IIIA: any T, N1, M0 |
| Stage IIIB: any T, N2, M0 |
| Stage IV: any T, any N, M1 |

*Table 2 TNM staging from 8th edition 2017 (48)*

### 1.2.6. Prognosis

Small bowel adenocarcinoma prognosis is generally poorer than that of colorectal carcinoma (50). This finding seems true even in CrD patients, in whom small bowel adenocarcinoma is more aggressive than large bowel cancers (51). The primary reason for this bad outcome is that patients are often asymptomatic until late disease, and metastases are often already present at small bowel adenocarcinoma diagnosis. The tumor stage has been considered the single most important prognostic factor in all small bowel adenocarcinoma (52). Poor prognosis is also associated with further factors: poor differentiation, positive margins, duodenal site, male gender, black ethnicity and older age at small bowel adenocarcinoma diagnosis (10). High positive lymph nodes-to-total lymph node ratio and a low number of assessed lymph nodes have been correlated with reduced survival (40,53,52).

Overall survival significantly differs between patients with CD-small bowel adenocarcinoma and those with CrD-small bowel adenocarcinoma. In particular, the predisposing chronic immune-mediated intestinal disorder CrD has been demonstrated to be a stage-independent prognostic factor in patients undergoing surgery for small bowel adenocarcinoma in the largest study systematically comparing CrD-small bowel adenocarcinoma and spo-small bowel adenocarcinoma (25). The five-year overall survival rate is relatively high in CD-SBA, i.e., 64.2% and 83% in an American study and in an Italian study recruiting 17 and 26 patients, respectively (54,25). Conversely, the five-year overall survival

rate appears to be worse in CrD-SBA patients, ranging from 26% to 38%, in French, Danish and Italian studies. In keeping with that, two-year overall survival in CrD-SBA has been reported to be 52% and 56% in an American study and in a French study, respectively (27,35), even lower than five-year overall survival in CD-SBA. Overall survival is more favorable in CD-SBA in comparison with spo-SBA, whereas no survival difference has been demonstrated between CrD-SBA and spo-SBA. However, in the large study by Wieghard et al. (36) patients with CrD-SBA were diagnosed at an earlier stage (I/II) compared with spo-SBA (55% vs. 32%,$p < 0.0001$) and were more likely to undergo surgery (81% vs. 72%, $p = 0.0016$).

Independently of the clinical group prognostic factors for SB include stage, tumor histotype and high Tumor-infiltrating lymphocyte density (TIL density) (25, 55). Tumour histology by itself is clinically relevant, as it has been shown how diffuse-, mixed- and solid-types cumulatively considered tend to have a worse prognosis compared to glandular-type and medullary-type cancers (55,56). Amongst prognostic factors within the CD-SBC group, both MSI and high TILs have been also identified and they correlate one each other. However, only TIL density retains a prognostic power in a multivariable model, presumably because several high-TIL SBC showing a good prognosis miss MSI. High TILs in SBC can be induced by additional factors besides MSI status, such as oncogenic viruses. In these regards, it is interesting to note that two non-MSI high-TIL small bowel adenocarcinoma with EBV latent infection described in CrD seem to be associated with a favorable outcome (57,58), probably due to the anti-tumor immune response induced by abnormal peptide production from EBV. Therefore, although these findings need to be confirmed by further evidence, EBV latent infection should be considered in CrD-SBC for a better prognostic evaluation.

### 1.2.6. Treatment

Surgery is the mainstay of curative treatment for SBC without distant metastasis (M0), whose possible benefits from adjuvant chemotherapy are controversial (1). Surgical resection with suitable lymph node sampling is necessary for long-term survival in resectable SBC. Surgery is the only curative

therapy for SBC at stage I, whereas it should be followed by adjuvant chemotherapy, such as FOLFOX4 or LV5FU2 or oral fluoropyrimidine for SBC at stage II or III (44). Systemic chemotherapy is the treatment for non-resectable or metastatic SBC, namely those at stage IV (44).

Several molecular alterations may suggest the response to novel therapies. In particular, *KRAS* wild-type mutational status has been demonstrated to predict responsiveness to anti-epidermal growth factor receptor monoclonal antibodies cetuximab and panitumumab alone or combined with chemotherapy in metastatic SBC in several case reports (59,60).

Immunotherapy has been changing the therapeutic scenario in several solid tumors, in particular PD-1/PD-L1 pathway blockade should be considered in advanced MSI small bowel adenocarcinoma, as mismatch repair deficiency has been demonstrated to predict response to anti-PD-1 antibodies in eleven types of solid tumors, including small bowel adenocarcinoma (61).

## 1.3. GIST

Gastrointestinal stromal tumors (GISTs) are rare clinical entities, representing less than 0.2% of all gastrointestinal tumors and only 0.04% of small intestinal malignant neoplasms. GISTs may occur anywhere along gastrointestinal tract, but most commonly arise in the stomach (40–60%) and jejunum/ileum (25–30%) (62,63).

### 1.3.1 Epidemiology

The overall incidence of GISTs from 2001-2015 was 0.70 per 100,000 people per year. The overall incidence of GIST from 2001 to 2015 was 0.70 per 100,000 people per year according to the data obtain by The United States Cancer Statistics (USCS) by Patel and Benipal (64). Males had an overall incidence rate of 0.80, which was greater than females who had an incidence of 0.63. When stratified by location within the gastrointestinal tract, the incidence was greatest in the stomach, followed by the small intestine and lastly the colorectum) (64).

### 1.3.2 Clinical presentation and diagnosis

GISTs exhibit a broad spectrum of clinical behavior ranging from at times long-term fatigue to a rapid degeneration of a variety of symptoms in just a few months (65,66). The tumors most commonly originate in the stomach (50–70%), followed by the small intestine (25–35%), the colon and rectum (5–10%) and the esophagus (<5%) and between 15% and 50% are metastatic at diagnosis (67).

The fact that the disease can occur in many areas of the GI tract can, in part, explain the broad spectrum of its clinical presentations that span from gastrointestinal bleeding, hemoperitoneum, anemia, abdominal mass, to the complete absence of symptoms (68). A large number are discovered incidentally during imaging, endoscopy, or laparotomy for unrelated problems. A population-based study reported that 69% of GISTs were symptomatic, 21% were discovered incidentally during surgical procedures, and 10% at autopsy (69). Hereditary forms, which represent only a small minority of cases, have their own particular manifestations such as skin hyperpigmentation, dysphagia, and multicentric paragangliomas (70,71).

The diagnosis of GISTs may involve imaging tests such as computed tomography scan and MRI, endoscopy with or without endoscopic ultrasound, and biopsy. Only biopsy, however, can yield a positive diagnosis. As most GISTs express KIT protein, immunostaining for KIT and/or molecular genetic testing for mutations in KIT can diagnose 95% of GISTs. Regorafenib, a drug that inhibits various protein genes that lead to GIST development is a relatively new treatment modality (72).

#### 1.3.3. Prognosis

Despite therapeutic advances, nearly one third of patients with GISTs, including those with extended TKI therapy, will experience a recurrence. In these patients, careful management and follow-up is essential (73,74). The follow-up schedule differs depending on the risk of recurrence. For example, in high-risk patients, there is a risk of recurrence in 1–3 years after the end of adjuvant therapy. In low-risk patients, the risk of recurrence is lower, and the time to recurrence is longer (75,76). Patients at very low risk may not require postoperative follow-up, although the risk of recurrence is not zero. In low-risk patients, a CT scan examination is recommended every 6 months for 5 years. Intermediate–high risk patients require

postoperative follow-up by CT examination at 3–4 months in the first 3 years, then at 6 months for 5 years, then annually (74,75,76). There is a consensus that abdominal ultrasonography can replace CT evaluation once a year. In patients that are undergoing TKI therapy, PET-CT is more sensitive for assessing treatment response, treatment resistance or tumor recurrence (77). Negative prognostic factors are young age, higher tumor size, increased mitotic index, aneuploidy and tumor location. Gastric tumors have a better prognosis than those localized in the intestinum (78,79).

### 1.3.4. Treatment

Surgery is the mainstay of the therapeutic approach to patients with non-metastatic GISTs (80,65). Chemotherapy and irradiation appear to have no impact on the natural history of these tumors (81,82,83,). GIST resistance to chemotherapy is pronounced, a phenomenon that has been linked to the higher expression of multidrug resistance proteins (84). Furthermore, the abdominal location of GISTs compromises the benefit of radiation therapy because of toxicity to adjacent structures. Patients with advanced GISTs require the assessment of mutational status for personalized chemotherapy with TKIs. The use of TKIs has led to an improvement in survival rate and quality of life of these patients. Proper treatment can improve the prognosis of patients and the epidemiological indicators, such as morbidity and mortality (85).

## 1.4. NET

Neuroendocrine tumors (NETs) are cancers of the interface between the endocrine (hormonal) system and the nervous system (86). While they are found at numerous anatomic sites, most occur within the gastroenteropancreatic axis. These tumors can be further classified according to their site of origin: the foregut, the hindgut, or the midgut (the second portion of the duodenum, the jejunum, the ileum, the caecum, and the appendix) (87). These latter are the most common subtype of gastrointestinal NETs.

### 1.4.1. Epidemiology

The incidence of NETs is rising, and recent studies have reported rates approaching 3 per 100,000 (88,89,90). The most common cause of death in these patients is advanced metastatic disease, and both clinical and epidemiological data indicate that the more effectively the disease is ablated, the more long-lasting the benefit.

### 1.4.2. Clinical presentation and diagnosis

The behavior and clinical presentation of midgut NETs vary depending on their site of origin, and their symptoms tend to be nonspecific. NET tending to be slow-growing, carcinoids present with either local manifestations or systemic symptoms. The most common symptoms of a midgut NET are abdominal pain, dyspepsia, nausea and/or vomiting, weight loss, blood loss, diarrhea, and carcinoid syndrome (91). More rarely, it presents as an acute event with clinical features resembling those of appendicitis, intestinal obstruction, intestinal perforation, or gastrointestinal hemorrhage. Although NETs smaller than 1 cm in diameter and especially those arising within the small intestine may be metastatic at presentation, the primary size is correlated with the presence of lymph-node involvement with or without liver metastases and an early diagnosis is imperative.

A significant number are also discovered incidentally during surgery for presumed small bowel or colonic inflammatory or neoplastic disorders, such as Crohn's disease, lymphoma, or adenocarcinoma(92).

The most common hematological, biochemical and radiological testing procedures prescribed when there is any index of suspicion are: serum Chromogranin A. urinary 5-Hydroxy Indole Acetic Acid (5-HIAA), serotonin and catecholamine excretion, angiography, (93) computed tomography (CT) or magnetic resonance imaging (MRI), endoscopy and biopsy, intestinal contrast radiography, somatostatin receptors and I-131 meta-iodobenzylguanidine (MIBG) imaging (94), single-positron emission computed tomography (95), and OctreoScan imaging. Functional imaging uses radiolabeled somatostatin analogs, such as 111 Indium pentetreotide (OctreoScan) and $^{68}$Gallium DOTA PET-CT (DOTATATE, DOTATOC, or DOTANOC), which show the location of lesions by uptake of somatostatin analogues through cell-surface receptors (96). These studies are useful

for determining the extent of disease throughout the body and to confirm that lesions seen on anatomic imaging are NETs. Another functional imaging modality is PET imaging using $^{18}$fluoro-deoxy-glucose (FDG; a glucose analog), which is used to stage and monitor many types of cancers. FDG-PET takes advantage of the tendency of malignant tumors to accumulate more FDG compared to benign tissue. $^{70}$FDG-PET has limited value in NETs, as it has low sensitivity in well-differentiated, slower-growing NETs.[71] ,[72]FDG tends to be taken up by poorly-differentiated NETs with high proliferative activity, so FDG-PET may be useful in identifying poorly-differentiated, aggressive NETs associated with worse prognosis (97).

### 1.4.3. Prognosis

In cancer of the small intestine, colon and liver/gallbladder/pancreas, metastases were more common in patients with NET that in patients with adenocarcinoma. Only 3% of appendiceal NET developed metastases, whereas 41% of small intestinal NET developed metastases. Irrespective of the primary site, NETs show a relative preference toward the liver compared to adenocarcinoma. Although NET is currently relatively rare, it is frequently misdiagnosed, detected late and features increasing incidence. Increased awareness would be important because sensitive diagnostic tools are available, and therapy can be highly effective, if diagnosis of primary or recurrent NET is made early(98,99,100). Of note, specialized imaging such as for the somatostatin receptor should be employed to detect and stage NET, due to its high sensitivity and immediate predictive power for radioisotope therapy.

### 1.4.4. Treatment

Patients with small bowel NETs (localized or metastatic) have to be managed at experienced centers by a multidisciplinary team. Eligible patients should undergo surgical resection of primary and regional disease. Additionally, patients with metastatic disease should be evaluated on a case-by-case basis to evaluate surgical options that may mitigate bowel symptoms (i.e., pain, intestinal angina, obstruction) and carcinoid symptoms (flushing, diarrhea, hemodynamic instability) and prolong survival. Unlike other gastrointestinal malignancies, aggressive surgical management of these patients, even in the context of unresectable metastatic disease, can improve patients' symptoms and long-term survival (101).

# 2. AIM OF THE STUDY

The primary aim of this study was to assess the prognostic and clinical criteria to distinguish between adenocarcinoma, NET and GIST to create a possible algorithm for the diagnostic exams in patients with undefined small bowel neoplasm.

The secondary aim was to assess the burden of small bowel cancer (SBC) in patients with Crohn's disease (CD) and in those without IBD, and to identify possible factors associated with morbidity and with a poor prognosis.

# 3. MATERIALS AND METHODS

## 3.1. STUDY DESIGN

Data were collected from January 2010 to December 2022 from operating room lists of the "Azienda Ospedale-Università of Padova": ex-General Surgery Unit, ex-Surgery Clinic 1st Unit, current General Surgery 3, from January 2010 to December 2022. Clinical and diagnostic data were extracted from the patient's medical record on Galileo 1.4.3.13.107, DB.58.1 and collected in an anonymized database.

Notification to the ethics committee of the anonymized monocentric retrospective study according to the declaration of Helsinki of the World Medical Association was made.

### 3.1.1 Inclusion and Exclusion criteria

Patients with small bowel adenocarcinoma, GIST and NET were included. Ppatients with desmoids tumor, Non-Hodgkin Lymphoma and non-neoplastic phenotype were excluded.

## 3.2. DATA COLLECTION

The retrospective cohort data were collected using Microsoft Excel. The form used comprises several fields. Each record, corresponding to a single patient, had its single identification code (*patient ID*) and all data remained anonymous, in full respect of privacy. The forms were filled using information gathered, under permission, from the AOPD Galileo-1.4.3.13.107,DB:58.1 management application software , by consulting medical history forms and discharge letters regarding the single patient at the time of the small bowel surgery.

The retrospective cohort includes patients with surgically treated small bowel resection. Based on the histotype group it's possible to identify patients with adenocarcinoma, GIST, NET, desmoids tumor, Non-Hodgkin Lymphoma and non-neoplastic histology.

The evaluation fields include:

- anthropometric parameters of the patients: age of surgery, age of IBD diagnosis, BMI, weight loss, blood test (hemoglobin, lymphocytes, leucocytes, neutrophils, platelets, VES, PCR, albumin, NLR, PLR, PNI, oncological markers CEA and Ca 19,9);
- presentation symptoms diarrhea, abdominal pain, haemorrhage, anaemia, occlusion or sub-occlusion, stypsis;
- diagnostic exams: CT scan, MRI, Ultrasound, Enteroscopy,, PET, PET CT, entero MRI, thoraco-abdominal Rx;
- histopathologic characteristic of the tumor: site, histotypes, pT, pN, pM, positive node number, total node number, metastasis, grading, vascular invasion, perineural invasion, necrosis, lymphomonocites perineoplastic infiltration, DFS (disease free survival);
- treatment (chemotherapy, radiotherapy).

## 3.4. DIAGNOSIS

### 3.4.1 Adenocarcinoma

The basic assessment includes a contrast-enhanced thoraco-abdomino-pelvic CT scan to evaluate local and metastatic extension (16,44,45). Liver MRI may be useful in case of contra-indication for iodine contrast agent or if liver metastases are suspected on CT scan examination. Positron emission tomography (PET) scanning is not routinely indicated but may considered if there is doubt about metastasis on initial CT staging (46). A gastric endoscopy and colonoscopy looking for other tumors are indicated in case of suspicion of genetic predisposition. In case of duodenal adenocarcinoma, an endoscopic ultrasound is recommended to assess vascular invasion and discern duodenal lesions from ampullary, biliary or pancreatic primary (47).

Dosage of CEA and CA 19-9 is useful at the initial workup, particularly in the event of a metastatic tumor, due to their prognostic value (44).

In Crohn's disease, exploration of the entire intestine with MRI enterography or capsule endoscopy should be done to diagnose other synchronous tumor lesions. Systematic screening for microsatellite instability or loss of expression of one of the MMR proteins should be systematically carried out to screen for Lynch syndrome and, for it, prognostic and predictive value for immunotherapy (49).

The molecular abnormalities demonstrated in small bowel adenocarcinomas are common with those found in colonic adenocarcinomas but with different frequencies for some of them, which reflect a distinct carcinogenesis. Loss of expression of the adenomatous polyposis coli (APC) protein causes deregulation of β-catenin, which accumulates in the cytoplasm and then in the nucleus and acts as a transcription factor that stimulates the expression of genes involved in cell proliferation. Mutations in the *APC* gene are considered to be one of the major early events in colorectal carcinogenesis. The prevalence of *APC* mutations in small bowel adenocarcinoma is low, from 13 to 27%, depending on the series, (49, 102,103,104) unlike colorectal cancers where this mutation is found in nearly 80% of cases. It seems more common in tumors of the duodenum. A mutation in the *TP53* gene has been detected in 38% to 58% of tumors, less commonly in

duodenal tumors and in the case of DNA repair abnormality (dMMR phenotype). Mutation of *TP53* is associated with dismal prognosis (105). A *KRAS* mutation is found in 43% to 56% of cases. Other *RAS* mutations are present in less than 5% of tumors. Overexpression of the HER2 protein is observed more rarely, unlike in adenocarcinoma of the stomach. However, alteration or amplification of the *ERBB2* gene has been reported in 7% to 14% of tumors. A study reported an association of *ERBB2* mutation and duodenal location but this was not confirmed by other studies. One study reported an association with *ERBB2* mutation and dMMR tumors. Moreover, *ERBB2* mutation was associated with a dismal prognosis in one study but not in a larger study. The *BRAF* mutation frequency ranges from 4% to 11% but the majority of *BRAF* mutations were not the V600E, the most prevalent one in colorectal cancers. Mutation of *BRCA2* was reported in 5% of the tumors in one study. Overall, a potentially targetable alteration was reported in 90% of small bowel adenocarcinomas in one study. Nevertheless, a confirmation of the efficacy of targeted therapy remains to be demonstrated in small bowel adenocarcinoma treatment (103).

After diagnosis, follow-up with clinical examination, imaging and tumor marker dosage for a total duration of 5 years are recommended after a curative resection.

### 3.4.2 GIST

Endoscopic examination has an essential role in definitive diagnosis because it allows the direct visualization of the tumor, with the possibility of biopsies for pathological examination when it is locates in the duodenum. GISTs may emerge as tumors with smooth margins located in the submucosa, with a normal mucosa cover that bulges into the lumen of the digestive tract. In some cases, a central ulceration may be seen. Endoscopic ultrasonography (EUS) (106) permits the assessment of the invasion within the gastrointestinal wall and identification of the digestive tract layer as an origin for the GIST. Thus, most often, GISTs originate in the muscularis propria, and small lesions may also originate from the muscularis mucosa. Upon EUS, duodenal GISTs appear as a hypoechoic, homogeneous tumor, with clearly defined edges, rarely irregular and sometimes with associated ulcers. EUS also enables both guided biopsies and GIST differentiation to other

submucosal tumors (85).

Contrast-enhanced computed tomography (CT) is the imaging method of choice to identify and describe the neoplasms, as well as to assess their extension and the presence of metastatic disease (107). Thus, CT allows the identification of metastases, which are most commonly located in the liver, omentum and peritoneal cavity. It also allows differential diagnosis, assessment of response to treatment and identification of tumor recurrence.

Abdominal ultrasound, magnetic resonance imaging (MRI) and positron emission tomography (PET) are also useful in the evaluation of GISTs and in the detection of metastases (67). Although MRI has a diagnostic performance comparable to that of CT, CT scan remains the preferred initial imaging method used for staging the disease. There are some cases in which MRI may be a better imaging option, such as in GISTs found in specific locations (e.g., the rectum) or in evaluating the anatomical extension of surgery.

The definitive diagnosis is histopathological. Biological samples may be obtained during endoscopic exploration, laparoscopic excision or laparotomy. In the case of metastases, the samples for histopathological diagnosis can also be obtained by biopsy of the metastases. Depending on the tumor cell appearance after hematoxylin and eosin staining, three morphological types have been identified: spindle cell type, epithelioid type and mixed type (108,109).

Immunohistochemistry is essential for the diagnosis of GISTs. In over 95% of cases, GISTs are positive for CD117/c-Kit. Other markers used for the diagnosis of GISTs are DOG1, CD34, S-100 protein, SMA and Ki67 (110,111).

### 3.4.3 NET

The imaging studies such as a CT scan and/or a somatostatin receptor-based scan ($^{68}$Gallium PET DOTATATE preferred). A CT can suggest the presence of an SB NET based on the typical imaging findings of a mesenteric mass with typical characteristics including surrounding stranding/tethering, calcifications, and a spiculated appearance. Additional testing with a $^{68}$Gallium PET scan can be confirmatory of NET diagnosis based on lesion avidity.

The multiphasic CT scan (with coronal views and 3D reconstruction) will give important information about the exact location of the mass and its relation to the mesenteric vessels. The $^{68}$Gallium PET scan may identify other sites of disease (either within the bowel or mesentery and/or distant metastatic disease), as well as define the avidity of the tumor to somatostatin receptors, which can help guide subsequent therapies in the future.

Other means of establishing the diagnosis include a biopsy of the primary tumor via endoscopic approaches (colonoscopy with ileal intubation or double-balloon enteroscopy) or the mesenteric mass via a percutaneous approach. Specific neuroendocrine markers by immunohistochemistry including chromogranin A, synaptophysin and Ki-67 are employed to identify the phenotype using the MIB1 antibody and to stratify these lesions in a prognostic and predictive sense.

For neuroendocrine tumors, it is also important to define the tumor grading which is based on:

- degree of differentiation, which indicates how much the tumor resembles the tissue of origin (the tumor can be poorly or highly differentiated);

- proliferation index, determined in two ways: by mitotic index (number of mitoses per field) or by % positive immunohistochemical staining for Ki-67 (using the MIB1 antibody).

Positive immunohistochemical (IHC) staining for neuroendocrine markers synaptophysin and chromogranin will help confirm the diagnosis of a NET (119). Small bowel NETs tend to have a nested architecture and centrally located, oval nuclei with a “salt-and-pepper” appearance on H&E staining (120). Cells can have eosinophilic cytoplasmic granules, which represent intracellular serotonin.

Blood biomarkers are simpler for monitoring for disease progression or recurrence (96). One of the most consistently checked markers is chromogranin A (CgA), a protein of the granin family secreted by SBNETs with autocrine, paracrine, and endocrine activities (113). Chromogranin A remains the only tumor marker recommended by consensus guidelines (114,115), despite several shortcomings. It has a limited sensitivity and specificity of 71% and 50%, respectively, for identifying imaging-confirmed progression of well-differentiated

gastroenteropancreatic NETS. Some studies have found that CgA levels can correlate with hepatic tumor burden and a rise in CgA may correspond with tumor recurrence after surgical resection (116). However, CgA levels can be falsely elevated in renal dysfunction, inflammatory diseases like rheumatoid arthritis, and malignancies of the pancreas, lung, prostate, ovary, and breast (117,118). Notably, CgA levels can be falsely elevated due to the use of medications like proton pump inhibitors (PPIs) (114,117).

A 24-hour collection for urinary 5-hydroxyindoleacetic acid (5-HIAA) can confirm the diagnosis of carcinoid syndrome. 5-HIAA is a metabolite of serotonin and is measured as a proxy for serotonin. A 24-hour urinary 5-HIAA is more informative than a random measurement, as blood levels of serotonin change throughout the day. The test has a sensitivity of 85% and specificity of 90% for detecting carcinoid syndrome. However, it is difficult to collect, and levels can be affected by drugs and foods. A number of foods including avocados, pineapples, bananas, kiwi fruit, walnuts, and pecans can increase urinary 5-HIAA levels and should be avoided when levels are measured (112).

## 3.5. TREATMENT

### 3.5.1. Resection of small bowel for tumor

Skandalakis in Surgical Anatomy and Technique (121) illustrates the surgical technique of resection of small bowell for tumor.

**Step 1.** In the case of a small bowel tumor, proximal and distal margins of 10 cm are appropriate. Score the mesentery of the small bowel with the Bovie.

**Step 2.** Using a hemostat, ligate the vessels of the mesentery of the small bowel with 2–0 or 3–0 silk (Figs. 1 and 2 ).

**Step 3.** Using a 75-mm gastrointestinal anastomosis (GIA) stapler, transect the small bowel proximally and distally. When applying the GIA stapler, make sure that the stapled end is on the antimesenteric border of the small bowel (Fig. 2 ).

**Step 4.** Apply bowel bulldogs to the small bowel so that enteric contents do not spill.

**Step 5.** Align the two segments of the small bowel such that the antimesenteric borders about each other (Fig. 3). Using straight Mayo scissors transect the stapled corner of the small bowel at the antimesenteric border.

**Step 6.** Insert each arm of the GIA stapler into the small bowel through the previously created opening and approximate the stapler such that the antimesenteric portions of the small bowel are in proximity to each other. Fire the stapler. Remove the stapler and briefly inspect the mucosal surface of the anastomosis for bleeding (Fig. 4).

**Step 7.** Using a 60 mm thoraco-abdominal (TA) stapler, close the resultant enterotomy.

**Step 8.** Close the mesentery of the small bowel with an interrupted 3–0 silk suture.

**Step 9.** Place a supporting 3–0 silk suture in the crotch of the anastomosis.

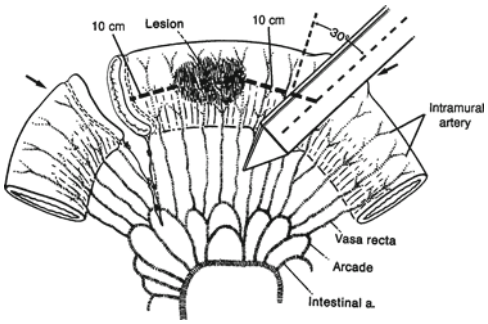


*Figure 1 Recommended position of non-crushing clamps for segmental re-section of the intestine (121)*

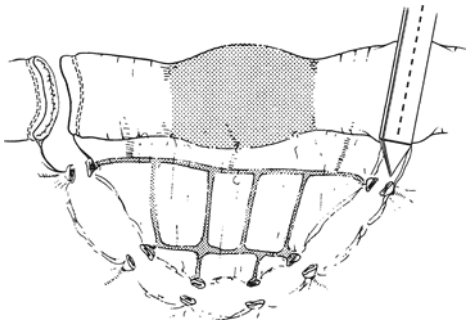

*Figure 2 Ligation of vessels (121)*

*Figure 3 Transection and sampling*

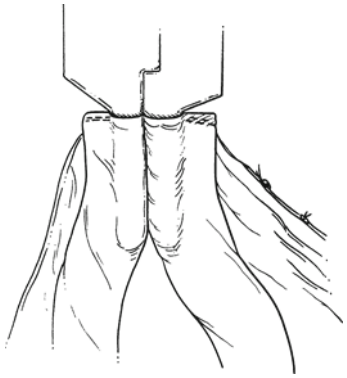

*Figure 4 Orientation of GIA stapler. (121)*

### 3.5.2. GIST surgery

The treatment for confirmed GISTs is surgery if the lesion is resectable with no metastases, or therapy with tyrosine kinase inhibitors if the lesion is unresectable, metastatic, or recurrent. The prognostic factors are tumor location, tumor size, mitotic index, and type of mutation. All surgical techniques can be performed laparoscopically using five trocars for wedge resection, subtotal gastrectomy or total gastrectomy based on tumor location(124). As GIST tends to arise from the organ of origin without diffuse infiltration, wedge resection of gastric and segmental resection of intestinal GIST are considered adequate therapy, while en bloc resection for omental or mesenteric tumors is usually recommended (125,126,127). Chemotherapy and irradiation appear to have no impact on the natural history of these tumors. GIST resistance to chemotherapy is pronounced, a phenomenon that has been linked to the higher expression of multidrug resistance proteins. Furthermore, the abdominal location of GISTs compromises the benefit of radiation therapy because of toxicity to adjacent structures.

### 3.5.3. NET surgery

The surgical approach has traditionally been through an open laparotomy (101), though there are increasing numbers of reports using minimally invasive—laparoscopic approaches (128,129).Both laparoscopic and robotic-based approaches are appropriate for different types of bowel resection including those for cancer (e.g., colorectal cancer); however, the important considerations unique to SB NET are outlined within this section on surgical principles. Whichever approach used must allow for complete and thorough evaluation of the entirety of the bowel and resection of the vascular pedicles proximal to the mesenteric mass involvement. These two goals are limited by laparoscopy as it does not allow for thorough evaluation and manual palpation of the whole bowel when looking for multifocal primary tumors in the small bowel the following steps should be applied after appropriate preoperative planning and thoughtful consideration of how these will align to the surgical principles outlined:

**Step 1**. Complete exploration of the abdomen focused on the entirety of the small bowel (palpation), liver, omentum, and pelvis. This includes localization of the

small bowel tumor(s) and the corresponding mesenteric mass(es).

**Step 2**. Complete mobilization of the involved mesentery off of the retroperitoneum to allow for increased length of the surgical field (mesentery) and releasing of the mesenteric mass from surrounding retroperitoneal structures (i.e., duodenum, pancreas). Commonly, this step includes a complete Cattell–Braasch maneuver. This should result in posterior and anterior control of the mesenteric disease to a level proximal to the disease.

**Step 3.** Incision of the peritoneum on the mesentery proximal to the area of involvement to release the desmoplastic fibrotic reaction and lengthen the mesentery releasing further the mass from the central vessels.

**Step 4.** Intramesenteric dissection to identify the vascular pedicles proximal to the mesenteric involvement and to allow understanding of the vascular anatomy spared and involved concerning the mesenteric mass.

**Step 5.** Assessment of the extent of small bowel resection required based on the planned vascular transection level. Often, this is straightforward if the transection is at the level of stage I–II lymph nodes; however, for those with stage III lymph nodes, this may require a more extensive intramesenteric and retroperitoneal dissection with the placement of bulldog clamps on vascular pedicles to assess the level of demarcation in the proximal and distal small bowel. The extent of the bowel to be resected and that remaining is measured.

**Step 6.** Isolation and transection of the vascular pedicle. We usually isolate the pedicle using a 0.5-in. penrose drain and transect it using a vascular stapler. Occasionally, the transection will need to be performed sharply on the vessel to allow a narrower dissection plane and to preserve nearby critical vessels.

**Step 7.** Transection of the more peripheral mesentery around the area of disease. This can be done sharply with ligatures or with the use of energy devices around the mass and towards the bowel wall on the proximal and distal side of the mesentery.

**Step 8.** Bowel resection and reconstruction. Given that SB NET are commonly located in the terminal ileum, the bowel resected follows the anatomy of a right

hemicolectomy, though with tumors located more proximally only small bowel is resected and the ileocecal valve can be preserved. It is paramount once the bowel is transected to revise hemostasis at the root of the mesenteric transection and to align the bowel anatomically to avoid twisting or internal hernias, before reconstruction.

Patients with stage III and IV lymph node disease present a real challenge for surgical management. These patients should be referred to high-volume centers with expertise in the treatment of SB NET, for comprehensive management and appropriate surgical decision-making. Surgical treatment is guided by the ability to accomplish a safe and complete resection while preserving enough small bowel to minimize the risk of the short-gut syndrome.

## 3.3. STATISTICS

Statistical analysis was performed using R 4.0 (R Foundation for Statistical Computing, Vienna, Austria) (R Core Team, 2020) [1921]. Set two-tailed alpha at 0.5 and beta at0.20at 0.20 and a standardized effect size at 1.1 2 the minimal sample size per group resulted to be 11 patients. Descriptive statistics were reported as median (Interquartile Range, IQR) for continuous variables and percentages (absolute numbers) for categorical variables. Fishers' test was used to compare dichotomous variables and the Mann-Whitney U test for comparisons of continuous variables. A p-value less than 0.05 was considered statistically significant.

# 4. RESULTS

The whole group includes fifty-five patients with surgically treated small bowel resection. Based on the histotype group it's possible to identify seventeen patients with adenocarcinoma, twenty patients with GIST, twelve patients with NET, two patients with desmoids tumor, three patients with Non-Hodgkin Lymphoma and one patient with non-neoplastic histology (figure 5). Patients with desmoids tumors, Non-Hodgkin Lymphomas and non-neoplastic histology were excluded.

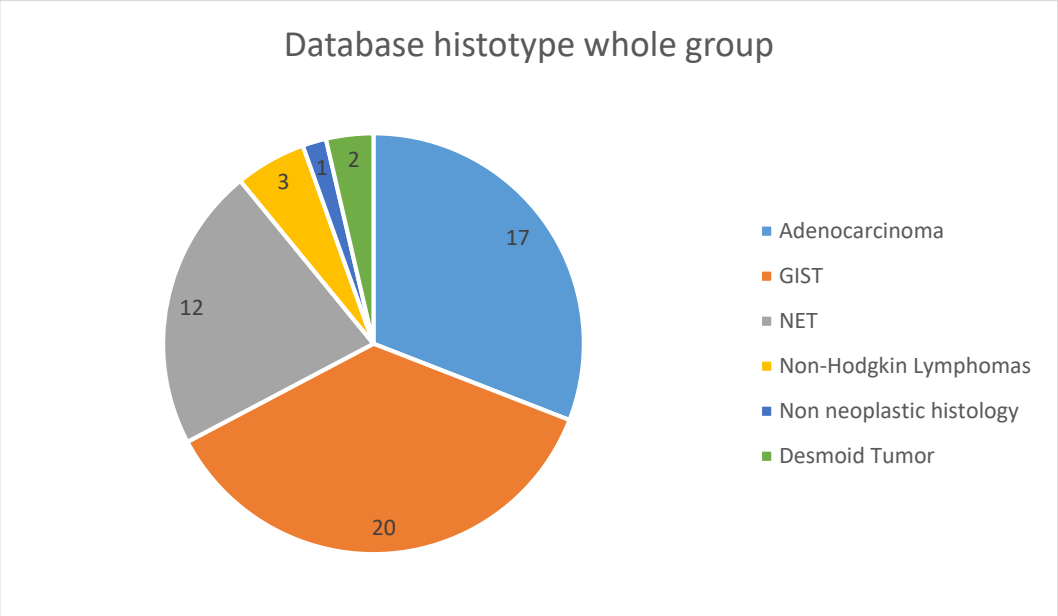


*Figure 5 Database histotype group*

To create the database, we searched the operating lists for all patients who had undergone small bowel resection (ileal, jejunal). The symptomatology leading up to the cause of the operation could be abdominal pain, the presence of a suspicious abdominal mass, occlusion, anemia, bleeding. Histological examination was made on abdominal masses and patients were divided in groups based on the results.

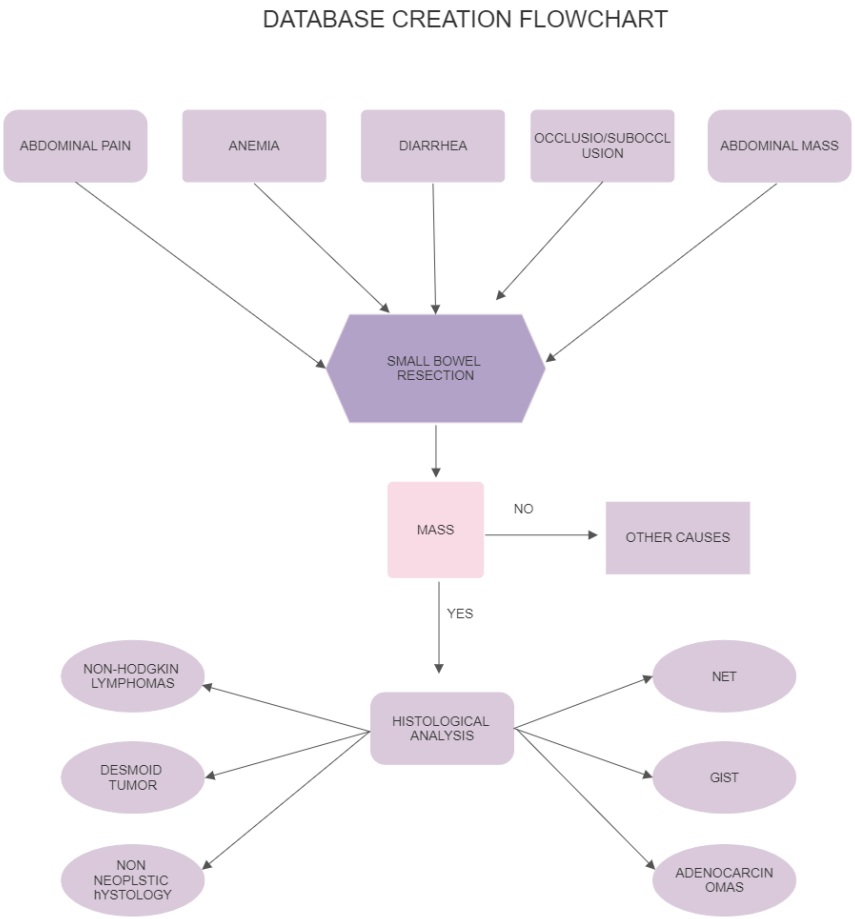


*Table 3 Database collection flowchart*

Based on the histological examination we collected seventeen patients with adenocarcinoma, 20 patients with GIST, twelve patients with NET, 3 patients with non-Hodgkin lymphoma, two patients with desmoid tumor and one patient with non neoplastic histology. We included in the study patients with adenocarcinoma, GIST, NETand we excluded patients with non-Hodgkin lymphoma, desmoid tumor and non-neoplastic histology (table 4).

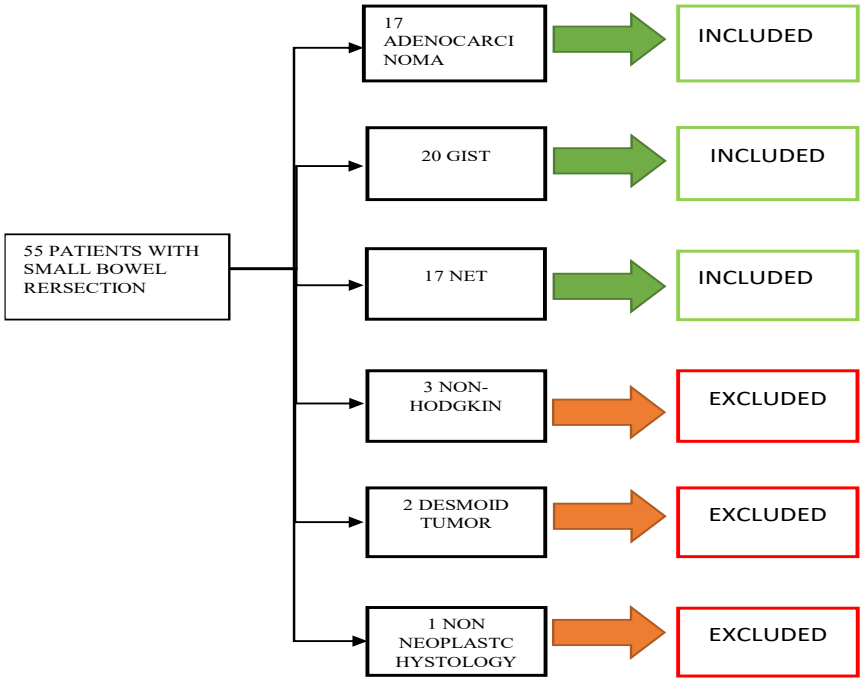


*Table 4 Flowchart of inclusion and exclusion patients*

## 4.1. PATIENT CHARACTERISTICS

In the whole group, 17 patients had adenocarcinoma and their median age of surgery was 62 years old, (IQR 48,25 -71,250). Only six of the patient with adenocarcinoma had concomitant IBD disease, the median age of diagnosis is 31 years old (IQR 23 – 40). Weight loss is known in five patients: median is 6 kg (IQR 2-9). BMI is known in eight patients: the median is 25,6 kg/m$^2$ (IQR 22,450-29,580). Hemoglobin concentration is known in every patient: the median is 11,1 g/dl, (IQR 9,875-12,075). Leucocytes number is known in all the seventeen patients: median 8226 U/uL (IQR 6585-9817,5). Platelets number is known in all patients: median 286000 (IQR 242500-35500). Diarrhea is known in three patients: median 1 (IQR 1-1). The number of positive nodes is known in fifteen patients: median 0 (IQR 0-1,5). The total number of nodes examined is known in fourteen patients: median 11,5 (IQR 9-20) (Table 3)

| | Adenocarcinoma | | |
|---|---|---|---|
| | N | Median | 25 - 75 P |
| AGE AT SURGERY | 17 | 62 | 48,250 - 71,250 |
| AGE AT IBD DIAGNOSIS | 6 | 31 | 23,000 - 40,000 |
| BMI | 8 | 25,6 | 22,450 - 29,580 |
| WEIGHT LOSS (Kg) | 5 | 6 | 2,000 - 9,000 |
| HEMOGLOBINE (g/dL) | 17 | 11,1 | 9,875 - 12,075 |
| LEUCOCYTES (U/uL) | 17 | 8226 | 6585,000 - 9817,500 |
| DIARRHEA | 3 | 1 | 1,000 - 1,000 |
| nr of POSITIVE NODES | 15 | 0 | 0,000 - 1,500 |
| nr of TOTAL NODES | 14 | 11,5 | 9,000 - 20,000 |
| PLATELETS | 17 | 286000 | 242500,000 - 355000,000 |

*Table 3 Patient characteristics, adenocarcinoma*

In the whole group, twenty patients had GIST and their median age of surgery is 67,5 years old, (IQR 53-73). None has concomitant IBD or diarrhea. BMI is known in five patients: the median is 23,4 kg/m$^2$(IQR 23,1-25,550). Weight loss is known in only one patient: median 8 kg (IQR 8-8). Hemoglobin concentration is known in every patient: median 11,5 g/dl, (IQR 10,65-13,625). Leucocyte number is Known in every patient. Median 6170 U/uL (IQR 5377,5-7485,0). Platelets number is known in every patient: median 254000 (IQR 233000-2775000). None has a positive node. The total number of nodes is known in 4 patients: median 3,5 (IQR 2-6,5) (Table 4).

| | GIST | | |
|---|---|---|---|
| | N | Median | 25 - 75 P |
| AGE AT SURGERY | 20 | 67,5 | 53,000 - 73,000 |
| AGE AT IBD DIAGNOSIS | 0 | ? | ? - ? |
| BMI | 5 | 23,4 | 23,100 - 25,550 |
| WEIGHT LOSS (Kg) | 1 | 8 | 8,000 - 8,000 |
| HEMOGLOBINE (g/dL) | 19 | 11,5 | 10,650 - 13,625 |
| LEUCOCYTES (U/uL) | 19 | 6170 | 5377,500 - 7485,000 |
| DIARRHEA | 0 | ? | ? - ? |
| nr of POSITIVE NODES | 4 | 0 | 0,000 - 0,000 |
| nr of TOTAL NODES | 4 | 3,5 | 2,000 - 6,500 |
| PLATELETS | 19 | 254000 | 233000,000 - 277500,000 |

*Table 4 Patients Characteristics, GIST*

In the whole group, 12 patients had a NET and their median age of surgery is 70,5 years old, (IQR 61,5-78,5). None of them has concomitant IBD or diarrhea. BMI is known in 4 patients: median 26,45 kg/m$^2$ (IQR 23,4-30). Weight loss is known in three patients: the median is 7 kg (IQR 3,25-9,25). The hemoglobin concentration median is 13,05 g/dl (IQR 12,15-13,45). The leucocyte number median is 5400 U/uL (IQR 4755-10300). Platelet number median is 247500 (IQR 208000-279000). The positive node number is known in eight patients: median 3,5 (IQR 1,5-6). The total node number is known in eight patients: median 16,5 (IQR 13-23,5) (table 5).

| | NET | | |
|---|---|---|---|
| | N | Median | 25 - 75 P |
| AGE AT SURGERY | 12 | 70,5 | 61,500 - 78,500 |
| AGE AT IBD DIAGNOSIS | 0 | ? | ? - ? |
| BMI | 4 | 26,45 | 23,400 - 30,000 |
| WEIGHT LOSS (Kg) | 3 | 7 | 3,250 - 9,250 |
| HEMOGLOBINE (g/dL) | 12 | 13,05 | 12,150 - 13,450 |
| LEUCOCYTES (U/uL) | 12 | 5400 | 4755,000 - 10300,000 |
| DIARRHEA | 0 | ? | ? - ? |
| nr of POSITIVE NODES | 8 | 3,5 | 1,500 - 6,000 |
| nr of TOTAL NODES | 8 | 16,5 | 13,000 - 23,500 |
| PLATELETS | 12 | 247500 | 208000,000 - 279000,000 |

*Table 5 Patients characteristics, NET*

## 4.2. PATIENT CHARACTERISTICS ADENOCARCINOMA

We compared the characteristics of patients with sporadic and Crohn's disease-related adenocarcinoma (Table 6).

In our series, there are eleven patients with sporadic adenocarcinoma and six IBD-related adenocarcinoma. In patients with sporadic adenocarcinoma median age of surgery was 63 years old (IQR 57-70,75). BMI was known in 3 patients: median 30,45 kg/m$^2$ (IQR 20,89-31,015). Weight loss was known in five patients: median 6 kg (IQR 2-9). The hemoglobin concentration median is 10,4 g/dl (IQR 9,9-11,675). The leucocyte number median was 8226 U/uL, (IQR 6760-10072,5). Platelets number median was 330000 (IQR 271000-415000). The number of positive nodes is known for ten patients: the median is 0 (IQR 0-2). The total number of nodes is known for nine patients: median 11 (IQR 8,25-17-750. No diarrhea was recorded in patients with sporadic adenocarcinoma.

Six patients have IBD-related adenocarcinoma: the median age of surgery is 51 years old, and (IQR 46-71). The median age of IBD diagnosis is 31 years old, and (IQR 23-40). BMI is known for five patients: median 25,2 kg/m$^2$ (IQR 23-40). Weight loss is unknown for all patients. The hemoglobin concentration median is 12,6 g/dl (IQR 9,9-13,3). The leucocyte number median is 7850 U/uL (IQR 5790-8720). Platelets number median is 244500 (IQR 241000-251000). Record of diarrhea is known in three patients: median 1 (IQR 1-1). The number of positive nodes is known in five patients: median 0 (IQR 0-1,5). The total number of nodes is known in five patients: median 12, 25-758 P is 9,5-34,250.

| | Concomitant IBD | | | | | |
|---|---|---|---|---|---|---|
| | IBD | | | Sporadic | | |
| | N | Median | 25 - 75 P | N | Median | 25 - 75 P |
| AGE AT SURGERY | 6 | 51 | 46,000 - 71,000 | 11 | 63 | 57,000 - 70,750 |
| AGE AT IBD DIAGNOSIS | 6 | 31 | 23,000 - 40,000 | 0 | ? | ? - ? |
| BMI | 5 | 25,2 | 22,725 - 26,675 | 3 | 30,46 | 20,890 - 31,015 |
| WEIGHT LOSS (Kg) | 0 | ? | ? - ? | 5 | 6 | 2,000 - 9,000 |
| HEMOGLOBINE (g/dL) | 6 | 12,6 | 9,900 - 13,300 | 11 | 10,4 | 9,900 - 11,675 |
| LEUCOCYTES (U/uL) | 6 | 7850 | 5790,000 - 8720,000 | 11 | 8226 | 6760,000 - 10072,500 |
| DIARRHEA | 3 | 1 | 1,000 - 1,000 | 0 | ? | ? - ? |
| nr of POSITIVE NODES | 5 | 0 | 0,000 - 1,500 | 10 | 0 | 0,000 - 2,000 |
| nr of TOTAL NODES | 5 | 15 | 9,500 - 34,250 | 9 | 11 | 8,250 - 17,750 |
| PLATELETS | 6 | 244500 | 241000,000 - 251000,000 | 11 | 330000 | 271000,000 - 415000,000 |

*Table 6 Patients characteristics, Adenocarcinoma*

## 4.3. ADENOCARCINOMA VS GIST VS NET

### 4.3.1. Presentation of small bowel neoplasm

The different presentation of small bowel neoplasm in males and females. In our series, adenocarcinomas occurred more frequently in males, 82% vs 18% of cases, while in GIST it occurred in males in 40% vs 60% in females and in NET occurred in 16% occurred in males vs 84 % in females (fig. 6).

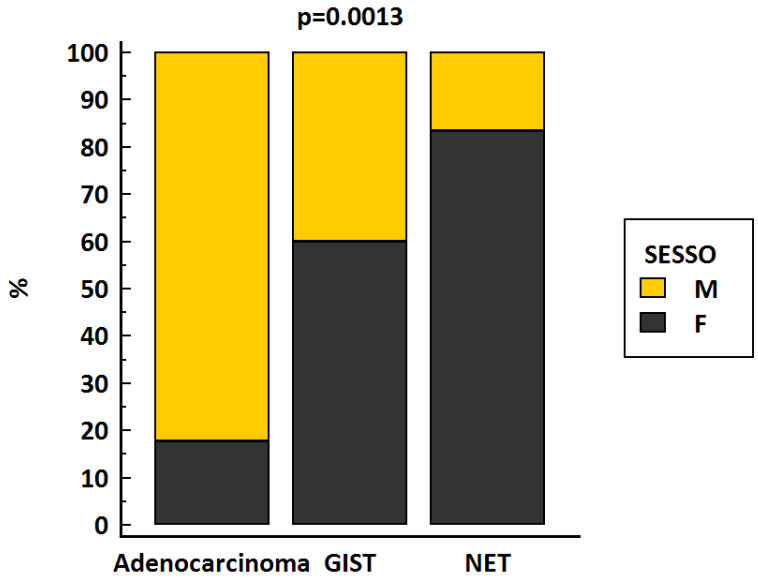


*Figure 6 Presentation of small bowel neoplasm*

The presentation symptoms of diarrhea had different distribution depending on the pathology: in Adenocarcinoma is present only in 6% of cases, in GIST is absent, in NET is present 25% (fig. 7).

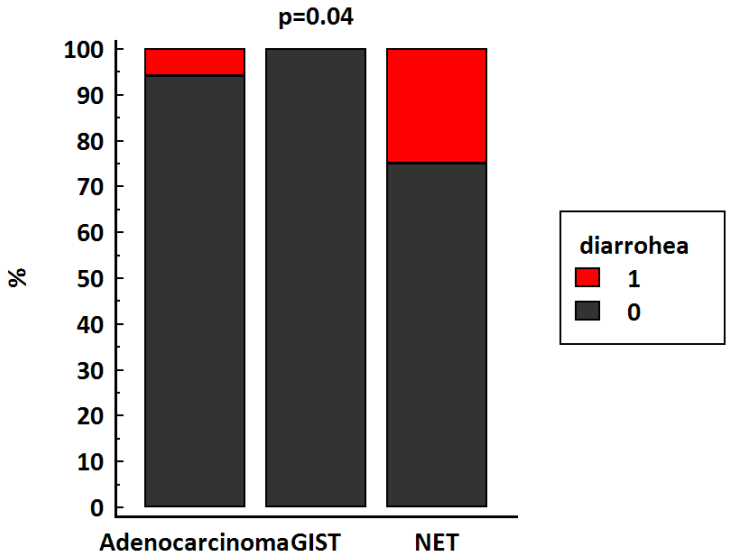


*Figure 7 Diarrhea in smal bowel neolasm*

Loss of Weight is present in 29,41% of patients with adenocarcinomas, 5% of patients with GIST and 25% of+ patients with NET. Pain is a common presentation in patients with small bowel neoplasm: in adenocarcinomas is present 17,04% of patients, in NETS in 58,3% of patients and in GISTS in 25% of patients. Subocclusion is a presentation symptom in 5,9 % of adenocarcinomas and in 25%

of NET.

### 4.3.2. Blood test in small bowel neoplasm

Hemoglobin concentration was higher in NET, lower in the adenocarcinoma and medium in GISTs in comparison to the other two (fig. 8).

In our series, NLR is higher in adenocarcinoma, medium in GIST and lower in NET (fig. 9).

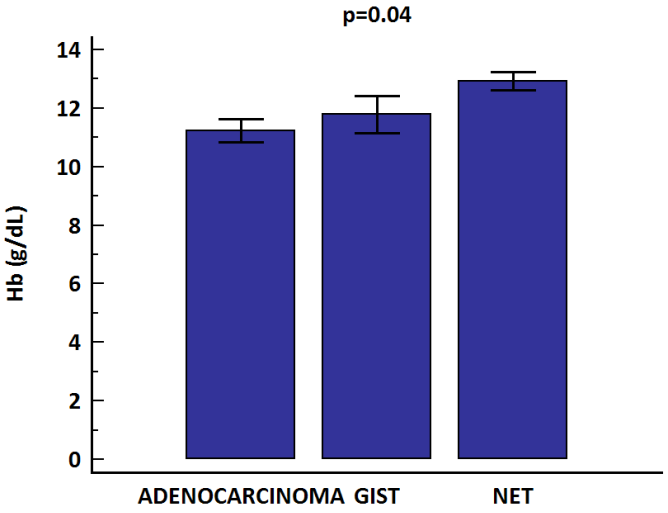


*Figure 8 Blood test Hemoglobin in small bowel neoplasm*

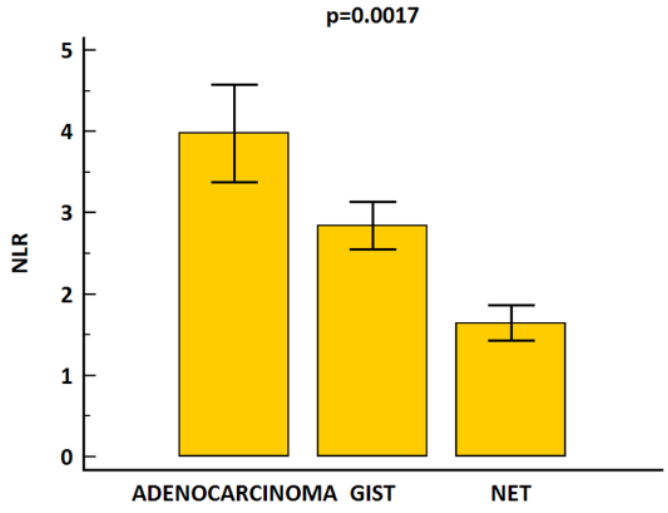


*Figure 9 Blood test NLR in small bowel neoplasm*

### 4.3.3. Histology in small bowel neoplasm

The number of positive nodes is very different between the three conditions: it was 1 in adenocarcinoma, 0 in Gist and 4 in NET (Figure 10).

In our series, patient with adenocarcinomas were pN0 in 75% of cases, pN1 in 5% of cases and pN2 in 20% of cases. In GIST patients, no nodal metastasis was observed. In NET patients, nodal metastasis were always present ( pN1 in 50% and pN2 in the other 50%) (fig 11).

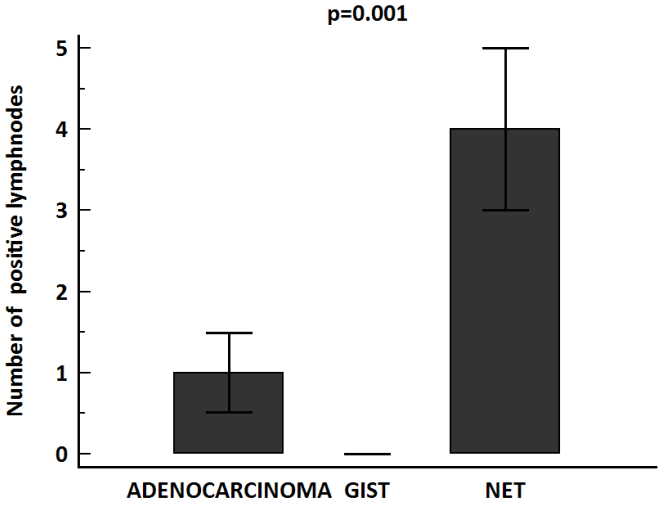


*Figure 10 Number of positive Lymphonodes*

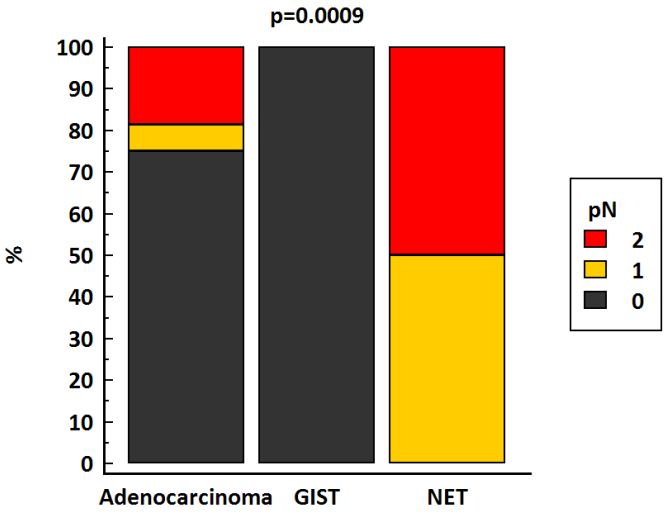


*Figure 11 pN in small bowel neoplasms*

In Adenocarcinoma patients, distant metastasis were present in 19% of cases. In GIST patients, distant metastasis were never observed. In NETs metastasis were present in 84% of cases (fig 12). LVI (Lymphovascular invasion) was present in 66% of the adenocarcinoma, 100% of the NET and 0% in the GIST (fig13).

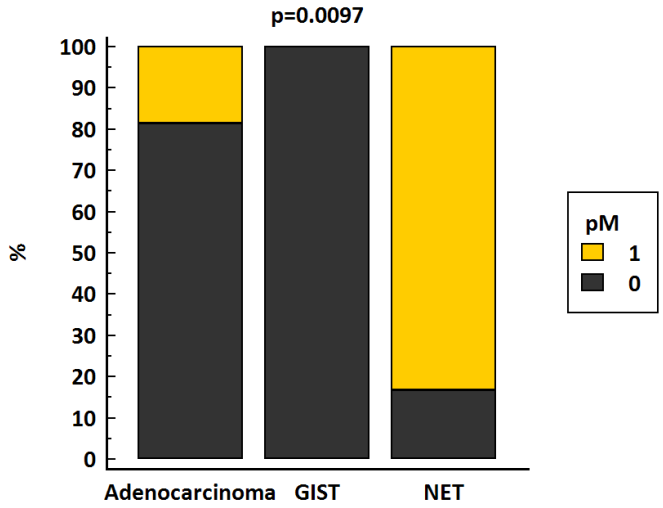


*Figure 12 pM in small bowel neoplasm*

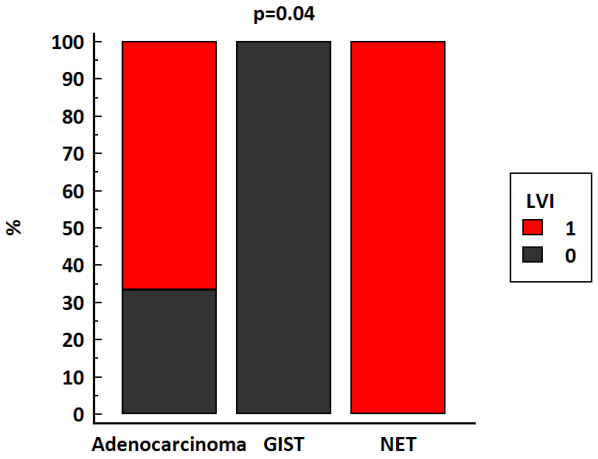


*Figure 13 LVI in small bowel neoplasm*

### 4.3.4. Survival in small bowel neoplasm

DFS (Disease free survival) after 60 months is 42% in adenocarcinoma, 52% in NET and 83% in GIST (figure 14).

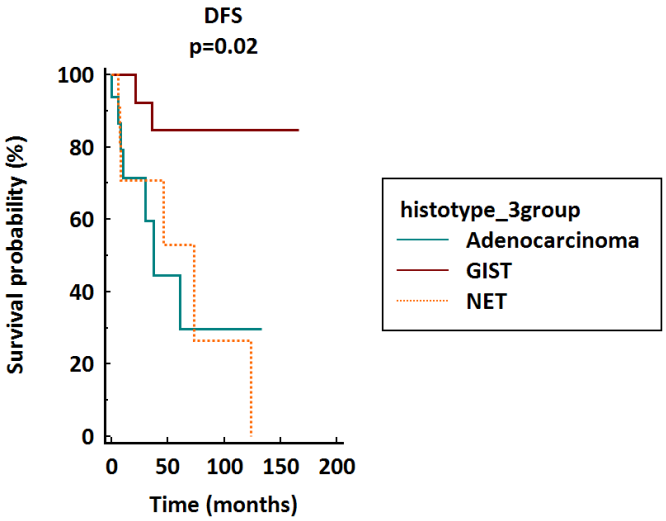


*Figure 14 DFS in small bowel neoplasm*

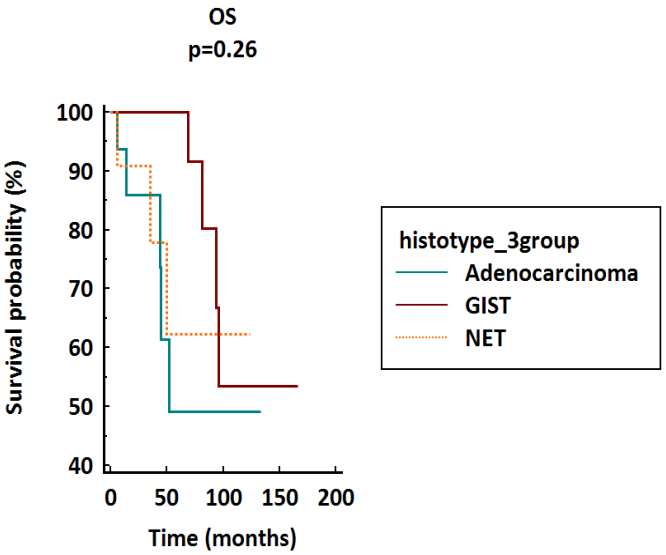


*Figure 15 OS in small bowel neoplasm*

OS (Overall survival) after 60 months is less than 50% in adenocarcinoma, 62% in NET and 100% in GIST.

Despite DFS is significant different between Adenocarcinomas, GISTs and NETs, OS after 120 months has no significant differences between the three histotype groups.

## 4.4. SPORADIC ADENOCARCINOMA VS CROHN'S DISEASE ADENOCARCINOMA

### 4.4.1. Oncological markers in IBD-related adenocarcinoma vs sporadic adenocarcinoma

The oncological marker concentration of Ca19,9 and CEA is very different between patients with sporadic adenocarcinoma (Ca 19,9 < 2 kU/L and CEA < 0.5ug/L) and in patients with IBD-related adenocarcinoma the median of Ca19,9 is 350 U/L and the median of CEA is 440 ug/L (figure 16-17).

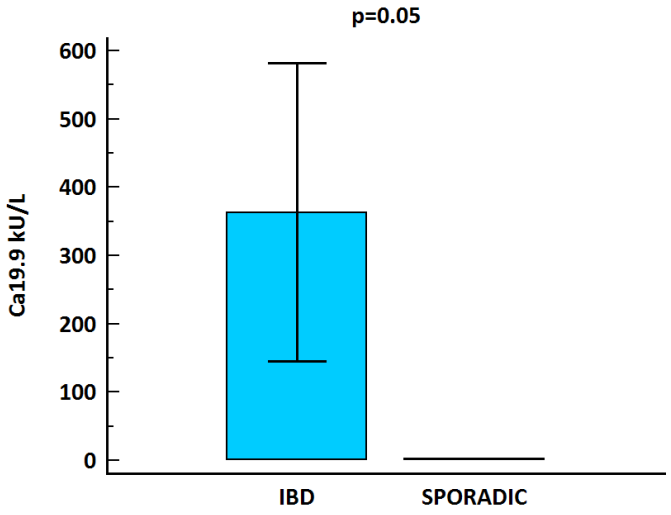


*Figure 16 Ca 19,9 in sporadic- vs IBD related adenocarcinomas*

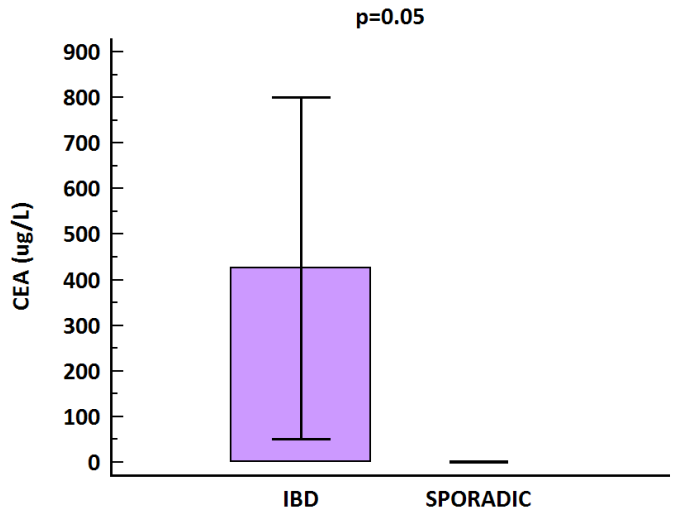


*Figure 17 CEA in sporadic- vs IBD related adenocarcinoma*

### 4.4.2. Survival in IBD-related adenocarcinoma vs sporadic adenocarcinoma

DFS (Disease free survival) is the same between sporadic adenocarcinoma and Crohn's disease related adenocarcinoma equal to respectively 32% and 0 % after 60 months (figure 18).

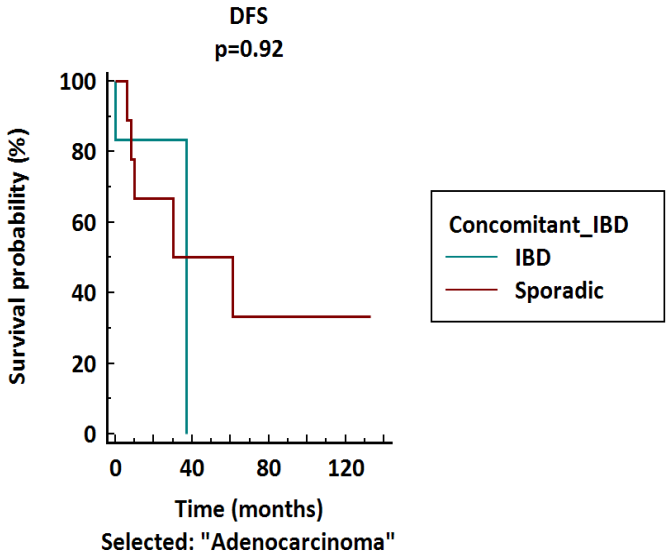


*Figure 18 DFS Sporadic vs concomitant IBD adenocarcinoma*

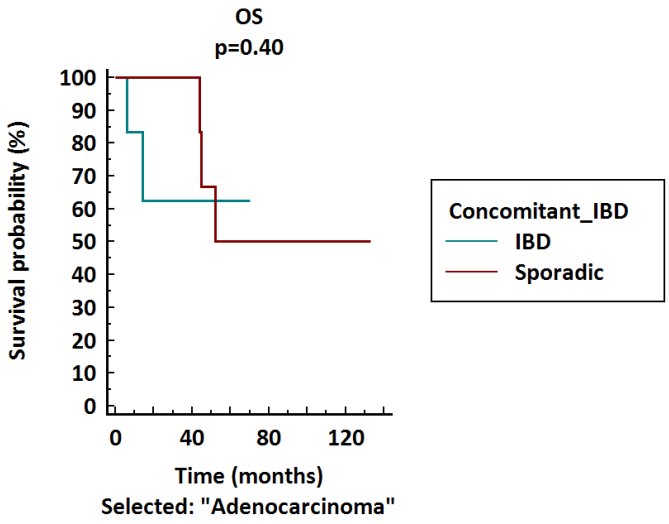


*Figure 19 OS Sporadic vs concomitant IBD adenocarcinoma*

OS (Overall survival) is not different in patients with sporadic and IBD-related

adenocarcinoma (figure 19).

# 5. DISCUSSION

Small bowel carcinomas are uncommon neoplasms, mostly sporadic. Small bowel neoplasm symptoms are very unspecific. Patients may present abdominal distension, pain, bleeding, diarrhea, occlusion or sub-occlusion, or anemia. A large number of small bowel neoplasms are discovered incidentally during imaging, endoscopy, or laparotomy for unrelated problems. Diagnostic is very poor. Based on the histologic type treatment and follow-up could be defined. Surgery is the mainstay of curative treatment for small bowel disease but the approach is different for different types of neoplasm (adenocarcinomas, GISTs, NETs). This study investigates presentation characteristics, and diagnostic features of adenocarcinomas, GISTs and NETs to build a diagnostic algorithm in patients with small bowel neoplasm. This study also aims to set if there are significant differences in presentation, prognosis and survival, between sporadic adenocarcinomas and Crohn's disease-related adenocarcinomas.

The analysis of the presentation of small bowel neoplasms in our series showed that gender predominance of male in of adenocarcinomas and GIST, according to Ocasio Quinones, et al (138), Qubaiah et al. (137). In accordance with what was observed by several investigators Debnath et al. (139),. On the other side Net is more frequent in our series in female patients, according to Scarpa et al. (86).

Analysis of presentation symptoms in our series showed the absence of diarrhea in the GIST tumor, probably because stromal tumors are mesenchymal tumor and may be related to the extraluminal growth of the tumor that does not affect the mucosa in agreement with Gheorghe et al. (85). On the other side in our series both NET and Adenocarcinoma present diarrhea. In adenocarcinomas, diarrhea is present in a few cases, which could be explained by the presence of sporadic adenocarcinomas and Crohn's disease-related adenocarcinomas. Diarrhea is one of the main symptoms of IBD. In NET diarrhea is one of the classic triad of carcinoid syndrome

(flushing ,diarrhea, and wheezing). This syndrome results from the tumor secretion of bioactive amines, such as serotonin, histamine, tachykinins, and prostaglandins. Serotonin increases gut motility, causing diarrhea, while other vasoactive substances cause flushing and wheezing through vasodilation and bronchoconstriction, respectively (136).

In our series, the full blood count showed the presence of anemia in the adenocarcinomas and in GISTs while in NET hemoglobin concentration values are in normal range in consideration of the mostly female gender presentation and the normal range of hemoglobin concentration. In Scarpa et al. at 9.2%, the pooled prevalence of gastrointestinal bleeding in patients with midgut NET was much lower than that reported by Sutton et al. and this clinical presentation seemed to be characteristic of the NETs of the duodenum. In GISTs anemia was caused by chronic occult bleeding and was note in several studies so it is expected also if GISTs are submucosal neoplasms, they should not theoretically bleed in the gut lumen. Instead, in at least a third, the neoplasm infiltrates and erodes, causing ischemia of the overlaying mucosa facing the alimentary tract lumen. This is in agreement with Scarpa et al *(*12) study on clinical presentation of GIST and Ruffolo et al study (22) on clinical presentation of adenocarcinoma in Crohn's disease.

NLR (Neutrophile Lymphocyte ratio) is a biomarker that conjugates the innate immune response, mainly due to neutrophils, and adaptive immunity, supported by lymphocytes (26). In our series patients with adenocarcinoma has high NLR, patients with NETs had a normal range of NLR. NLR in patients with GIST is in a grey zone between normal and pathological and may be as an early warning of pathological states or process such as cancer, atherosclerosis, infection, inflammation, psychiatric disorders and stress.

Concerning the pN stage in our study only patients with GISTs had no positive nodes (pN0), while a fourth of patients with adenocarcinomas had regional nodes metastasis at the diagnosis (pN1 or pN2). In NETs neoplasm nodes metastasis are always present both regional and distal, in according with the clinical presentation of the pathology as in Scarpa et al. (86)and in Burke et al. (131)in witch nodes metastasis was present in a  thirds of patients with NET. Presence of metastasis should be considered to discriminate between NETS and other neoplasms such GISTs and adenocarcinomas the diagnosis of small bowel neoplasm.  In case of

incidental abdominal mass, the presence of nodes metastasis may focus the diagnosis to NET rather than Adenocarcinomas or GIST tumors.

At the time of surgery metastasis were present in adenocarcinomas and in NETs, according to the clinical presentation in advanced stage of neoplasm due to the aspecifics symptoms, according to Scarpa et al. (86), Aparicio et al. (18), Aparicio et al. (42) , Wieghard et al. (133).

LVI (Lymphovascular invasion) is directly related and express the metastasis potential of the tumor. The presence of malignant cells within lymphovascular channels, is a crucial step in the invasion-metastasis cascade. LVI, when identified morphologically in the peritumoural area, is regarded as an indicator of metastatic potential and is strongly associated with a poor prognosis in many solid tumours (135). In our series LVI was maximum in NETS, witch presentation is very often in a advanced stage of disease. LVI was absent in GIST patients that had no metastasis in our series. Lastly in adenocarcinomas LVI was present in more than half of patient although metastasis occurred only in a fifth of them.

Comparison between sporadic adenocarcinomas and Crohn's disease relates adenocarcinomas shown the importance of oncological markers dosage to surveilling possible cancer insurgence in IBD related small bowel neoplasm. In addiction oncological markers as CEA and CA19,9 could be used to follow up the patients after surgical resection and treatment in agreement with Aparicio et al. (16) and Locher et al. (44) studies. The dosage of CEA and CA 19,9 is useful at the initial workup, particularly in the event of a metastatic tumor (44,141,142). Monitoring the concentration markers at the moment of the diagnosis allows to evaluate the subsequent changes of concentration after therapy to surveill the prognosis and progress of the neoplastic disease, particularly in case of metastatic progress or relapse of the disease (143). The not detectable concentration of markers is related to the remission of the tumor while the increase of the marker could indicate the presence of metastasis or relapse of disease (144). In our series, the increase of Ca 19,9 and CEA concentration in patients with IBD-related adenocarcinoma, is already present at the diagnosis of neoplasia. The concentration of these markers could therefore be used as a predictor of the onset of neoplastic disease in patients with IBD. Further studies should be performed on larger samples to evaluate the effective correlation and efficacy of the markers.

In our study disease free survival and overall survival analysis showed no difference in prognosis on sporadic cancer versus Crohn's disease related adenocarcinomas., In terms of overall survival, in Fields et al. (132) the 5-year survival was 36.5%, is similar to 43% reported by Wieghard et al. (133) for 179 patients with CD-associated SBA and 35% reported by Palascak-Juif et al. (134) The unadjusted survival in CD patients was not significantly different from that in sporadic patients. After adjusting for patient and tumour characteristics, CD patients had similar overall survival in all stages of disease. This is in agreement with two previous small cohort studies, which found no significant difference in overall survival between CD and sporadic SBA patient groups.

# 6. LIMITS

This work's main limit is the small number of patients recruited in the database. The quality of the research is influenced by the retrospective design, sometimes clinical records lack information that is impossible to integrate at present. The study's evaluation should consider these limits since these limitations have probably influenced final quality and accuracy. In our inclusion criteria, I considered the most important elements that influence the natural history of the disease, particularly the presentation symptoms of the neoplasm, modality of diagnosis, treatment and outcome.

This work's strength lies in the fact that it analysed a rare condition to emphasize the need to establish a diagnostic algorithm for these patients with small bowel neoplasm and to establish if adenocarcinoma in Crohn's disease has a different prognosis and outcome.

# 7. CONCLUSIONS

This study investigates presentation characteristics, and diagnostic features of adenocarcinomas, GISTs and NETs to address the diagnostic exams. In case of small bowel should value patients sex, hemoglobin concentration, presence of positive and metastasis. According to our study in case of absence of anaemia, diarrhea, nodes metastasis at the CT diagnostic, diagnosis should be address to GIST tumors and a PET with gallium should be done. In case of small mass and lymphonode involvement, Net should be suspected and $^{68}$Gallium PET should be done to investigate the presence of tumor.

This study also aimed to set if there are significant differences in presentation, prognosis and survival, between sporadic adenocarcinomas and Crohn's disease-related adenocarcinomas. Differential diagnosis remain difficult due to the aspecific symptoms like diarrhea, abdominal pain and anemia that are common presentation of IBD disease. Moreover survival analysis showed no difference in prognosis and overall survival between sporadic adenocarcinomas and concomitant OBD adenocarcinomas.

# BIBLIOGRAPHY


1. Raghav K, Overman MJ. Small bowel adenocarcinomas--existing evidence and evolving paradigms. Nat Rev Clin Oncol. 2013 Sep;10(9):534-44. doi: 10.1038/nrclinonc.2013.132. Epub 2013 Jul 30. PMID: 23897080; PMCID: PMC6076441
2. Giuffrida P, Vanoli A, Arpa G, Bonometti A, Luinetti O, Solcia E, Corazza GR, Paulli M, Di Sabatino A. Small Bowel Carcinomas Associated with Immune-Mediated Intestinal Disorders: The Current Knowledge. Cancers (Basel). 2018 Dec 29;11(1):31. doi: 10.3390/cancers11010031. PMID: 30597986; PMCID: PMC6356995
3. Dionigi chirurgia- Basi teoriche e Chirurgia generale, 4 edizione pag 778/783
4. Chow, J.S.; Chen, C.C.; Ahsan, H.; Neugut, A.I. A Population-Based Study of the Incidence of Malignant Small Bowel Tumours: SEER, 1973–1990. Int. J. Epidemiol. **1996**, 25, 722–728
5. Siegel, R.L.; Miller, K.D.; Jemal, A. Cancer Statistics, 2019. CA Cancer J. Clin. **2019**, 69, 7–34.
6. Lepage, C.; Bouvier, A.-M.; Manfredi, S.; Dancourt, V.; Faivre, J. Incidence and Management of Primary Malignant Small Bowel Cancers: A Well-Defined French Population Study. Am. J. Gastroenterol. **2006**, 101, 2826–2832.
7. Bouvier, A.-M.; Robaszkiewicz, M.; Jooste, V.; Cariou, M.; Drouillard, A.; Bouvier, V.; Nousbaum, J.-B.; French Network ofCancer Registries (FRANCIM). Trends in Incidence of Small Bowel Cancer According to Histology: A Population-Based Study.J. Gastroenterol. **2020**, 55, 181–188.
8. Legué, L.M.; Bernards, N.; Gerritse, S.L.; van Oudheusden, T.R.; de Hingh, I.H.J.T.; Creemers, G.-J.M.; Ten Tije, A.J.;Lemmens, V.E.P.P. Trends in Incidence, Treatment and Survival of Small Bowel Adenocarcinomas between 1999 and 2013: A Population-Based Study in The Netherlands. Acta Oncol. Stockh. Swed. **2016**, 55, 1183–1189.
9. Michael J Overman, MDHiroko Kunitake, Kenneth K Tanabe, Epidemiology, clinical features, and types of small bowel neoplasms EDITOR: Sonali Shah, MD

10. Bilimoria KY, Bentrem DJ, Wayne JD, Ko CY, Bennett CL, Talamonti MS. Small bowel cancer in the United States: changes in epidemiology, treatment, and survival over the last 20 years. Ann Surg. 2009 Jan;249(1):63-71. doi: 10.1097/SLA.0b013e31818e4641. PMID: 19106677.
11. Weiss NS, Yang CP. Incidence of histologic types of cancer of the small intestine. J Natl Cancer Inst. 1987 Apr;78(4):653-6. PMID: 3470541.
12. Hatzaras I, Palesty JA, Abir F, Sullivan P, Kozol RA, Dudrick SJ, Longo WE. Small-bowel tumors: epidemiologic and clinical characteristics of 1260 cases from the connecticut tumor registry. Arch Surg. 2007 Mar;142(3):229-35. doi: 10.1001/archsurg.142.3.229. PMID: 17372046.
13. McLaughlin PD, Maher MM. Primary malignant diseases of the small intestine. AJR Am J Roentgenol. 2013 Jul;201(1):W9-14. doi: 10.2214/AJR.12.8492. PMID: 23789703.
14. Di Sabatino A, Lenti MV, Giuffrida P, Vanoli A, Corazza GR. New insights into immune mechanisms underlying autoimmune diseases of the gastrointestinal tract. Autoimmun Rev. 2015 Dec;14(12):1161-9. doi: 10.1016/j.autrev.2015.08.004. Epub 2015 Aug 12. PMID: 26275585.
15. Legué LM, Bernards N, Gerritse SL, van Oudheusden TR, de Hingh IH, Creemers GM, Ten Tije AJ, Lemmens VE. Trends in incidence, treatment and survival of small bowel adenocarcinomas between 1999 and 2013: a population-based study in The Netherlands. Acta Oncol. 2016 Sep-Oct;55(9-10):1183-1189. doi: 10.1080/0284186X.2016.1182211. Epub 2016 May 12. PMID: 27170100.
16. Aparicio T, Pachev A, Laurent-Puig P, Svrcek M. Epidemiology, Risk Factors and Diagnosis of Small Bowel Adenocarcinoma. Cancers (Basel). 2022 May 2;14(9):2268. doi: 10.3390/cancers14092268. PMID: 35565398; PMCID: PMC9103761.
17. Bouvier AM, Robaszkiewicz M, Jooste V, Cariou M, Drouillard A, Bouvier V, Nousbaum JB; French Network of Cancer Registries (FRANCIM). Trends in incidence of small bowel cancer according to histology: a population-based study. J Gastroenterol. 2020 Feb;55(2):181-188. doi: 10.1007/s00535-019-01636-z. Epub 2019 Oct 19. PMID: 31630251.
18. Aparicio T, Zaanan A, Svrcek M, Laurent-Puig P, Carrere N, Manfredi S, Locher C, Afchain P. Small bowel adenocarcinoma: epidemiology, risk

factors, diagnosis and treatment. Dig Liver Dis. 2014 Feb;46(2):97-104. doi: 10.1016/j.dld.2013.04.013. Epub 2013 Jun 21. PMID: 23796552.

19. Faivre J, Trama A, De Angelis R, Elferink M, Siesling S, Audisio R, Bosset JF, Cervantes A, Lepage C; RARECARE Working Group. Incidence, prevalence and survival of patients with rare epithelial digestive cancers diagnosed in Europe in 1995-2002. Eur J Cancer. 2012 Jul;48(10):1417-24. doi: 10.1016/j.ejca.2011.10.038. Epub 2011 Dec 9. PMID: 22169462.
20. Hänninen UA, Katainen R, Tanskanen T, Plaketti RM, Laine R, Hamberg J, Ristimäki A, Pukkala E, Taipale M, Mecklin JP, Forsström LM, Pitkänen E, Palin K, Välimäki N, Mäkinen N, Aaltonen LA. Exome-wide somatic mutation characterization of small bowel adenocarcinoma. PLoS Genet. 2018 Mar 9;14(3):e1007200. doi: 10.1371/journal.pgen.1007200. PMID: 29522538; PMCID: PMC5871010.
21. Legué LM, Bernards N, Gerritse SL, van Oudheusden TR, de Hingh IH, Creemers GM, Ten Tije AJ, Lemmens VE. Trends in incidence, treatment and survival of small bowel adenocarcinomas between 1999 and 2013: a population-based study in The Netherlands. Acta Oncol. 2016 Sep-Oct;55(9-10):1183-1189. doi: 10.1080/0284186X.2016.1182211. Epub 2016 May 12. PMID: 27170100.
22. Cahill C, Gordon PH, Petrucci A, Boutros M. Small bowel adenocarcinoma and Crohn's disease: any further ahead than 50 years ago? World J Gastroenterol. 2014 Sep 7;20(33):11486-95. doi: 10.3748/wjg.v20.i33.11486. PMID: 25206256; PMCID: PMC4155342.
23. Palascak-Juif V, Bouvier AM, Cosnes J, Flourié B, Bouché O, Cadiot G, Lémann M, Bonaz B, Denet C, Marteau P, Gambiez L, Beaugerie L, Faivre J, Carbonnel F. Small bowel adenocarcinoma in patients with Crohn's disease compared with small bowel adenocarcinoma de novo. Inflamm Bowel Dis. 2005 Sep;11(9):828-32. doi: 10.1097/01.mib.0000179211.03650.b6. PMID: 16116317.
24. Piton G, Cosnes J, Monnet E, Beaugerie L, Seksik P, Savoye G, Cadiot G, Flourie B, Capelle P, Marteau P, Lemann M, Colombel JF, Khouri E, Bonaz B, Carbonnel F. Risk factors associated with small bowel adenocarcinoma in Crohn's disease: a case-control study. Am J Gastroenterol. 2008 Jul;103(7):1730-6. doi: 10.1111/j.1572-0241.2008.01847.x. Epub 2008 Jun

28. PMID: 18564124.

25. Vanoli A, Di Sabatino A, Furlan D, Klersy C, Grillo F, Fiocca R, Mescoli C, Rugge M, Nesi G, Fociani P, Sampietro G, Ardizzone S, Luinetti O, Calabrò A, Tonelli F, Volta U, Santini D, Caio G, Giuffrida P, Elli L, Ferrero S, Latella G, Ciardi A, Caronna R, Solina G, Rizzo A, Ciacci C, D'Armiento FP, Salemme M, Villanacci V, Cannizzaro R, Canzonieri V, Reggiani Bonetti L, Biancone L, Monteleone G, Orlandi A, Santeusanio G, Macciomei MC, D'Incà R, Perfetti V, Sandri G, Silano M, Florena AM, Giannone AG, Papi C, Coppola L, Usai P, Maccioni A, Astegiano M, Migliora P, Manca R, Martino M, Trapani D, Cerutti R, Alberizzi P, Riboni R, Sessa F, Paulli M, Solcia E, Corazza GR. Small Bowel Carcinomas in Coeliac or Crohn's Disease: Clinico-pathological, Molecular, and Prognostic Features. A Study From the Small Bowel Cancer Italian Consortium. J Crohns Colitis. 2017 Aug 1;11(8):942-953. doi: 10.1093/ecco-jcc/jjx031. PMID: 28333239.

26. Svrcek M, Piton G, Cosnes J, Beaugerie L, Vermeire S, Geboes K, Lemoine A, Cervera P, El-Murr N, Dumont S, Scriva A, Lascols O, Ardizzone S, Fociani P, Savoye G, Le Pessot F, Novacek G, Wrba F, Colombel JF, Leteurtre E, Bouhnik Y, Cazals-Hatem D, Cadiot G, Diebold MD, Rahier JF, Delos M, Fléjou JF, Carbonnel F. Small bowel adenocarcinomas complicating Crohn's disease are associated with dysplasia: a pathological and molecular study. Inflamm Bowel Dis. 2014 Sep;20(9):1584-92. doi: 10.1097/MIB.0000000000000112. PMID: 25029614.

27. Grolleau C, Pote NM, Guedj NS, Zappa M, Theou-Anton N, Bouhnik Y, Panis Y, Cazals-Hatem DL. Small bowel adenocarcinoma complicating Crohn's disease: a single-centre experience emphasizing the importance of screening for dysplasia. Virchows Arch. 2017 Nov;471(5):611-617. doi: 10.1007/s00428-017-2125-z. Epub 2017 Apr 18. PMID: 28421339.

28. Bojesen RD, Riis LB, Høgdall E, Nielsen OH, Jess T. Inflammatory Bowel Disease and Small Bowel Cancer Risk, Clinical Characteristics, and Histopathology: A Population-Based Study. Clin Gastroenterol Hepatol. 2017 Dec;15(12):1900-1907.e2. doi: 10.1016/j.cgh.2017.06.051. Epub 2017 Jul 8. PMID: 28694132.

29. Michelassi F., Testa G., Pomidor W.J., Lashner B.A., Block G.E. Adenocarcinoma complicating Crohn's disease. *Dis. Colon Rectum.* 1993;36:654–661. doi: 10.1007/BF02238592.
30. Sigel J.E., Petras R.E., Lashner B.A., Fazio V.W., Goldblum J.R. Intestinal adenocarcinoma in Crohn's disease: A report of 30 cases with a focus on coexisting dysplasia. *Am. J. Surg. Pathol.* 1999;23:651–655. doi: 10.1097/00000478-199906000-00003.
31. Palascak-Juif V., Bouvier A.M., Cosnes J., Flourié B., Bouché O., Cadiot G., Lémann M., Bonaz B., Denet C., Marteau P., et al. Small bowel adenocarcinoma in patients with Crohn's disease compared with small bowel adenocarcinoma de novo. *Inflamm. Bowel Dis.* 2005;11:828-832.doi: 10.1097/01.mib.0000179211.03650.b6.
32. Piton G., Cosnes J., Monnet E., Beaugerie L., Seksik P., Savoye G., Cadiot G., Flourie B., Capelle P., Marteau P., et al. Risk factors associated with small bowel adenocarcinoma in Crohn's disease: A case-control study. *Am. J. Gastroenterol.* 2008;103:1730–1736. doi: 10.1111/j.1572-0241.2008.01847.x.
33. Widmar M., Greenstein A.J., Sachar D.B., Harpaz N., Bauer J.J., Greenstein A.J. Small bowel adenocarcinoma in Crohn's disease. *J. Gastrointest. Surg.* 2011;15:797–802. doi: 10.1007/s11605-011-1441-x.
34. Whitcomb E., Liu X., Xiao S.Y. Crohn enteritis-associated small bowel adenocarcinomas exhibit gastric differentiation. *Hum. Pathol.* 2014;45:359–367. doi: 10.1016/j.humpath.2013.09.014.
35. Weber N.K., Fletcher J.G., Fidler J.L., Barlow J.M., Pruthi S., Loftus E.V., Jr., Pardi D.S., Smyrk T.C., Becker B.D., Pasha S.F., et al. Clinical characteristics and imaging features of small bowel adenocarcinomas in Crohn's disease. *Abdom. Imaging.* 2015;40:1060–1067. doi: 10.1007/s00261-014-0144-7.
36. Wieghard N., Mongoue-Tchokote S., Young J.I., Sheppard B.C., Tsikitis V.L. Prognosis of small bowel adenocarcinoma in Crohn's disease compares favourably with de novo small bowel adenocarcinoma. *Colorectal. Dis.* 2017;19:446–455. doi: 10.1111/codi.13531.
37. Wikipedia https://en.wikipedia.org/wiki/Crohn%27s_disease

38. Molodecky NA, Soon IS, Rabi DM, Ghali WA, Ferris M, Chernoff G, Benchimol EI, Panaccione R, Ghosh S, Barkema HW, Kaplan GG. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology. 2012 Jan;142(1):46-54.e42; quiz e30. doi: 10.1053/j.gastro.2011.10.001. Epub 2011 Oct 14. PMID: 22001864.
39. Michael J Overman, MDHiroko Kunitake, Kenneth K Tanabe, Epidemiology, clinical features, and types of small bowel neoplasms EDITOR: Sonali Shah, MD
40. Dabaja BS, Suki D, Pro B, Bonnen M, Ajani J. Adenocarcinoma of the small bowel: presentation, prognostic factors, and outcome of 217 patients. Cancer. 2004 Aug 1;101(3):518-26. doi: 10.1002/cncr.20404. PMID: 15274064.
41. Sakae H, Kanzaki H, Nasu J, Akimoto Y, Matsueda K, Yoshioka M, Nakagawa M, Hori S, Inoue M, Inaba T, Imagawa A, Takatani M, Takenaka R, Suzuki S, Fujiwara T, Okada H. The characteristics and outcomes of small bowel adenocarcinoma: a multicentre retrospective observational study. Br J Cancer. 2017 Nov 21;117(11):1607-1613. doi: 10.1038/bjc.2017.338. Epub 2017 Oct 5. PMID: 28982111; PMCID: PMC5729438.
42. Aparicio T, Henriques J, Manfredi S, Tougeron D, Bouché O, Pezet D, Piessen G, Coriat R, Zaanan A, Legoux JL, Terrebone E, Pocard M, Gornet JM, Lecomte T, Lombard-Bohas C, Perrier H, Lecaille C, Lavau-Denes S, Vernerey D, Afchain P; NADEGE Investigators. Small bowel adenocarcinoma: Results from a nationwide prospective ARCAD-NADEGE cohort study of 347 patients. Int J Cancer. 2020 Aug 15;147(4):967-977. doi: 10.1002/ijc.32860. Epub 2020 Jan 22. PMID: 31912484.
43. Masselli G, Di Tola M, Casciani E, Polettini E, Laghi F, Monti R, Bernieri MG, Gualdi G. Diagnosis of Small-Bowel Diseases: Prospective Comparison of Multi-Detector Row CT Enterography with MR Enterography. Radiology. 2016 May;279(2):420-31. doi: 10.1148/radiol.2015150263. Epub 2015 Nov 24. PMID: 26599801.
44. Locher C, Batumona B, Afchain P, Carrère N, Samalin E, Cellier C, Aparicio T, Becouarn Y, Bedenne L, Michel P, Parc Y, Pocard M, Chibaudel B, Bouché O; Thésaurus National de Cancérologie Digestive (TNCD). Small bowel adenocarcinoma: French intergroup clinical practice guidelines for diagnosis, treatments and follow-up (SNFGE, FFCD, GERCOR, UNICANCER, SFCD,

SFED, SFRO). Dig Liver Dis. 2018 Jan;50(1):15-19. doi: 10.1016/j.dld.2017.09.123. Epub 2017 Oct 6. PMID: 29174568.

45. Benson AB, Venook AP, Al-Hawary MM, Arain MA, Chen YJ, Ciombor KK, Cohen SA, Cooper HS, Deming DA, Garrido-Laguna I, Grem JL, Hoffe SE, Hubbard J, Hunt S, Kamel A, Kirilcuk N, Krishnamurthi S, Messersmith WA, Meyerhardt J, Miller ED, Mulcahy MF, Nurkin S, Overman MJ, Parikh A, Patel H, Pedersen KS, Saltz LB, Schneider C, Shibata D, Skibber JM, Sofocleous CT, Stoffel EM, Stotsky-Himelfarb E, Willett CG, Johnson-Chilla A, Gregory KM, Gurski LA. Small Bowel Adenocarcinoma, Version 1.2020, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2019 Sep 1;17(9):1109-1133. doi: 10.6004/jnccn.2019.0043. PMID: 31487687; PMCID: PMC10191182.
46. Cronin CG, Lohan DG, Browne AM, Roche C, Murphy JM. Magnetic resonance enterography in the evaluation of the small bowel. Semin Roentgenol. 2009 Oct;44(4):237-43. doi:
47. Nylund K, Ødegaard S, Hausken T, Folvik G, Lied GA, Viola I, Hauser H, Gilja OH. Sonography of the small intestine. World J Gastroenterol. 2009 Mar 21;15(11):1319-30. doi: 10.3748/wjg.15.1319. PMID: 19294761; PMCID: PMC2658828.
48. AJCC Cancer Staging Manual. 8th ed. Springer; Berlin/Heidelberg, Germany: 2017. Small Intestine; pp. 221–234.
49. Aparicio T, Svrcek M, Henriques J, Afchain P, Lièvre A, Tougeron D, Gagniere J, Terrebonne E, Piessen G, Legoux JL, Lecaille C, Pocard M, Gornet JM, Zaanan A, Lavau-Denes S, Lecomte T, Deutsch D, Vernerey D, Puig PL. Panel gene profiling of small bowel adenocarcinoma: Results from the NADEGE prospective cohort. Int J Cancer. 2021 Apr 1;148(7):1731-1742. doi: 10.1002/ijc.33392. Epub 2021 Jan 4. PMID: 33186471.
50. Overman MJ, Hu CY, Kopetz S, Abbruzzese JL, Wolff RA, Chang GJ. A population-based comparison of adenocarcinoma of the large and small intestine: insights into a rare disease. Ann Surg Oncol. 2012 May;19(5):1439-45. doi: 10.1245/s10434-011-2173-6. Epub 2011 Dec 21. PMID: 22187121; PMCID: PMC3342860.

51. Michelassi F, Testa G, Pomidor WJ, Lashner BA, Block GE. Adenocarcinoma complicating Crohn's disease. Dis Colon Rectum. 1993 Jul;36(7):654-61. doi: 10.1007/BF02238592. PMID: 8348849.
52. Halfdanarson TR, McWilliams RR, Donohue JH, Quevedo JF. A single-institution experience with 491 cases of small bowel adenocarcinoma. Am J Surg. 2010 Jun;199(6):797-803. doi: 10.1016/j.amjsurg.2009.05.037. PMID: 20609724.
53. Overman MJ, Hu CY, Wolff RA, Chang GJ. Prognostic value of lymph node evaluation in small bowel adenocarcinoma: analysis of the surveillance, epidemiology, and end results database. Cancer. 2010 Dec 1;116(23):5374-82. doi: 10.1002/cncr.25324. Epub 2010 Aug 16. PMID: 20715162.
54. Potter DD, Murray JA, Donohue JH, Burgart LJ, Nagorney DM, van Heerden JA, Plevak MF, Zinsmeister AR, Thibodeau SN. The role of defective mismatch repair in small bowel adenocarcinoma in celiac disease. Cancer Res. 2004 Oct 1;64(19):7073-7. doi: 10.1158/0008-5472.CAN-04-1096. PMID: 15466202.
55. Vanoli A, Di Sabatino A, Martino M, Klersy C, Grillo F, Mescoli C, Nesi G, Volta U, Fornino D, Luinetti O, Fociani P, Villanacci V, D'Armiento FP, Cannizzaro R, Latella G, Ciacci C, Biancone L, Paulli M, Sessa F, Rugge M, Fiocca R, Corazza GR, Solcia E. Small bowel carcinomas in celiac or Crohn's disease: distinctive histophenotypic, molecular and histogenetic patterns. Mod Pathol. 2017 Oct;30(10):1453-1466. doi: 10.1038/modpathol.2017.40. Epub 2017 Jun 30. PMID: 28664941.
56. Brcic I, Cathomas G, Vanoli A, Jilek K, Giuffrida P, Langner C. Medullary carcinoma of the small bowel. Histopathology. 2016 Jul;69(1):136-40. doi: 10.1111/his.12908. Epub 2016 Jan 13. PMID: 26599717.
57. Vanoli A, Di Sabatino A, Biancone L, Martino M, Macciomei MC, Zorzi F, Pallone F, Solcia E, Corazza GR. Small bowel Epstein-Barr virus-positive lympho-epithelioma-like carcinoma in Crohn's disease. Histopathology. 2017 Apr;70(5):837-839. doi: 10.1111/his.13133. Epub 2017 Jan 18. PMID: 27891660.
58. Vanoli A, Di Sabatino A, Martino M, Dallera E, Furlan D, Mescoli C, Macciomei MC, Biancone L, Neri B, Grillo F, Biletta E, Rugge M, Sessa F, Paulli M, Corazza GR, Solcia E. Epstein-Barr virus-positive ileal carcinomas

associated with Crohn's disease. Virchows Arch. 2017 Oct;471(4):549-552. doi: 10.1007/s00428-017-2209-9. Epub 2017 Jul 27. PMID: 28752215.

59. Santini D, Fratto ME, Spoto C, Russo A, Galluzzo S, Zoccoli A, Vincenzi B, Tonini G. Cetuximab in small bowel adenocarcinoma: a new friend? Br J Cancer. 2010 Oct 12;103(8):1305; author reply 1306. doi: 10.1038/sj.bjc.6605898. Epub 2010 Sep 14. PMID: 20842127; PMCID: PMC2967067.
60. Falcone R, Roberto M, Filetti M, Anselmi E, Marchetti P. Anti epidermal growth factor receptor therapy in small bowel adenocarcinoma: Case report and literature review. Medicine (Baltimore). 2018 Jan;97(3):e9672. doi: 10.1097/MD.0000000000009672. PMID: 29505011; PMCID: PMC5779780.
61. Le DT, Durham JN, Smith KN, Wang H, Bartlett BR, Aulakh LK, Lu S, Kemberling H, Wilt C, Luber BS, Wong F, Azad NS, Rucki AA, Laheru D, Donehower R, Zaheer A, Fisher GA, Crocenzi TS, Lee JJ, Greten TF, Duffy AG, Ciombor KK, Eyring AD, Lam BH, Joe A, Kang SP, Holdhoff M, Danilova L, Cope L, Meyer C, Zhou S, Goldberg RM, Armstrong DK, Bever KM, Fader AN, Taube J, Housseau F, Spetzler D, Xiao N, Pardoll DM, Papadopoulos N, Kinzler KW, Eshleman JR, Vogelstein B, Anders RA, Diaz LA Jr. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science. 2017 Jul 28;357(6349):409-413. doi: 10.1126/science.aan6733. Epub 2017 Jun 8. PMID: 28596308; PMCID: PMC5576142.
62. Zakaria AH, Daradkeh S. Jejunojejunal intussusception induced by a gastrointestinal stromal tumor. Case Rep Surg. 2012;2012:173680. doi: 10.1155/2012/173680. Epub 2012 Nov 19. PMID: 23213593; PMCID: PMC3506898.
63. Sankey RE, Maatouk M, Mahmood A, Raja M. Case Report: Jejunal gastrointestinal stromal tumour, a rare tumour, with a challenging diagnosis and a successful treatment. J Surg Case Rep. 2015 May 1;2015(5):rjv050. doi: 10.1093/jscr/rjv050. PMID: 25935905; PMCID: PMC4417130.
64. Patel N, Benipal B. Incidence of Gastrointestinal Stromal Tumors in the United States from 2001-2015: A United States Cancer Statistics Analysis of 50 States. Cureus. 2019 Feb 22;11(2):e4120. doi: 10.7759/cureus.4120. PMID: 31037234; PMCID: PMC6478492.

65. DeMatteo RP, Lewis JJ, Leung D, Mudan SS, Woodruff JM, Brennan MF. Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. Ann Surg. 2000 Jan;231(1):51-8. doi: 10.1097/00000658-200001000-00008. PMID: 10636102; PMCID: PMC1420965.
66. Fletcher CD, Berman JJ, Corless C, Gorstein F, Lasota J, Longley BJ, Miettinen M, O'Leary TJ, Remotti H, Rubin BP, Shmookler B, Sobin LH, Weiss SW. Diagnosis of gastrointestinal stromal tumors: A consensus approach. Hum Pathol. 2002 May;33(5):459-65. doi: 10.1053/hupa.2002.123545. PMID: 12094370.
67. Scarpa M, Bertin M, Ruffolo C, Polese L, D'Amico DF, Angriman I. A systematic review on the clinical diagnosis of gastrointestinal stromal tumors. J Surg Oncol. 2008 Oct 1;98(5):384-92. doi: 10.1002/jso.21120. PMID: 18668671.
68. ESMO Guidelines Working Group; Blay JY, Le Cesne A. Gastrointestinal stromal tumors: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol. 2007 Apr;18 Suppl 2:ii27-9. doi: 10.1093/annonc/mdm024. Erratum in: Ann Oncol. 2008 May;19(5):1027-9. PMID: 17491033.
69. Nilsson B, Bümming P, Meis-Kindblom JM, Odén A, Dortok A, Gustavsson B, Sablinska K, Kindblom LG. Gastrointestinal stromal tumors: the incidence, prevalence, clinical course, and prognostication in the preimatinib mesylate era--a population-based study in western Sweden. Cancer. 2005 Feb 15;103(4):821-9. doi: 10.1002/cncr.20862. PMID: 15648083.
70. Beghini A, Tibiletti MG, Roversi G, Chiaravalli AM, Serio G, Capella C, Larizza L. Germline mutation in the juxtamembrane domain of the kit gene in a family with gastrointestinal stromal tumors and urticaria pigmentosa. Cancer. 2001 Aug 1;92(3):657-62. doi: 10.1002/1097-0142(20010801)92:3<657::aid-cncr1367>3.0.co;2-d. PMID: 11505412.
71. Robson ME, Glogowski E, Sommer G, Antonescu CR, Nafa K, Maki RG, Ellis N, Besmer P, Brennan M, Offit K. Pleomorphic characteristics of a germ-line KIT mutation in a large kindred with gastrointestinal stromal tumors, hyperpigmentation, and dysphagia. Clin Cancer Res. 2004 Feb 15;10(4):1250-4. doi: 10.1158/1078-0432.ccr-03-0110. PMID: 14977822.

72. Mantese G. Gastrointestinal stromal tumor: epidemiology, diagnosis, and treatment. Curr Opin Gastroenterol. 2019 Nov;35(6):555-559. doi: 10.1097/MOG.0000000000000584. PMID: 31577561.

73. An W, Sun PB, Gao J, Jiang F, Liu F, Chen J, Wang D, Li ZS, Shi XG. Endoscopic submucosal dissection for gastric gastrointestinal stromal tumors: a retrospective cohort study. Surg Endosc. 2017 Nov;31(11):4522-4531. doi: 10.1007/s00464-017-5511-3. Epub 2017 Apr 3. PMID: 28374257.

74. Nikfarjam M, Kimchi E, Shereef S, Gusani NJ, Jiang Y, Liang J, Sehmbey M, Staveley-O'Carroll KF. Surgical outcomes of patients with gastrointestinal stromal tumors in the era of targeted drug therapy. J Gastrointest Surg. 2008 Nov;12(11):2023-31. doi: 10.1007/s11605-008-0561-4. Epub 2008 Jun 11. PMID: 18546049.

75. Casali PG, Abecassis N, Aro HT, Bauer S, Biagini R, Bielack S, Bonvalot S, Boukovinas I, Bovee JVMG, Brodowicz T, Broto JM, Buonadonna A, De Álava E, Dei Tos AP, Del Muro XG, Dileo P, Eriksson M, Fedenko A, Ferraresi V, Ferrari A, Ferrari S, Frezza AM, Gasperoni S, Gelderblom H, Gil T, Grignani G, Gronchi A, Haas RL, Hassan B, Hohenberger P, Issels R, Joensuu H, Jones RL, Judson I, Jutte P, Kaal S, Kasper B, Kopeckova K, Krákorová DA, Le Cesne A, Lugowska I, Merimsky O, Montemurro M, Pantaleo MA, Piana R, Picci P, Piperno-Neumann S, Pousa AL, Reichardt P, Robinson MH, Rutkowski P, Safwat AA, Schöffski P, Sleijfer S, Stacchiotti S, Sundby Hall K, Unk M, Van Coevorden F, van der Graaf WTA, Whelan J, Wardelmann E, Zaikova O, Blay JY; ESMO Guidelines Committee and EURACAN. Gastrointestinal stromal tumours: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018 Oct 1;29(Suppl 4):iv68-iv78. doi: 10.1093/annonc/mdy095. Erratum in: Ann Oncol. 2018 Oct 1;29(Suppl 4):iv267. PMID: 29846513.

76. Koo DH, Ryu MH, Kim KM, Yang HK, Sawaki A, Hirota S, Zheng J, Zhang B, Tzen CY, Yeh CN, Nishida T, Shen L, Chen LT, Kang YK. Asian Consensus Guidelines for the Diagnosis and Management of Gastrointestinal Stromal Tumor. Cancer Res Treat. 2016 Oct;48(4):1155-1166. doi: 10.4143/crt.2016.187. Epub 2016 Jun 24. PMID: 27384163; PMCID: PMC5080813.

77. Alberini JL, Al Nakib M, Wartski M, Gontier E, Cvitkovic F, Rixe O, Rougier P, Pecking AP. Place de l'imagerie par Tomographie par Emission de Positons pour les tumeurs stromales gastro-intestinales [The role of PET scan in gastrointestinal stromal tumors]. Gastroenterol Clin Biol. 2007 Jun-Jul;31(6-7):585-93. French. doi: 10.1016/s0399-8320(07)89435-8. PMID: 17646785.
78. Yang Z, Wang F, Liu S, Guan W. Comparative clinical features and short-term outcomes of gastric and small intestinal gastrointestinal stromal tumours: a retrospective study. Sci Rep. 2019 Jul 11;9(1):10033. doi: 10.1038/s41598-019-46520-1. PMID: 31296939; PMCID: PMC6624285.
79. Emory TS, Sobin LH, Lukes L, Lee DH, O'Leary TJ. Prognosis of gastrointestinal smooth-muscle (stromal) tumors: dependence on anatomic site. Am J Surg Pathol. 1999 Jan;23(1):82-7. doi: 10.1097/00000478-199901000-00009. PMID: 9888707.
80. Rossi CR, Mocellin S, Mencarelli R, Foletto M, Pilati P, Nitti D, Lise M. Gastrointestinal stromal tumors: from a surgical to a molecular approach. Int J Cancer. 2003 Nov 1;107(2):171-6. doi: 10.1002/ijc.11374. PMID: 12949790.
81. McGrath PC, Neifeld JP, Lawrence W Jr, Kay S, Horsley JS 3rd, Parker GA. Gastrointestinal sarcomas. Analysis of prognostic factors. Ann Surg. 1987 Dec;206(6):706-10. doi: 10.1097/00000658-198712000-00004. PMID: 3689007; PMCID: PMC1493319.
82. Pidhorecky I, Cheney RT, Kraybill WG, Gibbs JF. Gastrointestinal stromal tumors: current diagnosis, biologic behavior, and management. Ann Surg Oncol. 2000 Oct;7(9):705-12. doi: 10.1007/s10434-000-0705-6. PMID: 11034250.
83. Pierie JP, Choudry U, Muzikansky A, Yeap BY, Souba WW, Ott MJ. The effect of surgery and grade on outcome of gastrointestinal stromal tumors. Arch Surg. 2001 Apr;136(4):383-9. doi: 10.1001/archsurg.136.4.383. PMID: 11296107.
84. Plaat BE, Hollema H, Molenaar WM, Torn Broers GH, Pijpe J, Mastik MF, Hoekstra HJ, van den Berg E, Scheper RJ, van der Graaf WT. Soft tissue leiomyosarcomas and malignant gastrointestinal stromal tumors: differences in clinical outcome and expression of multidrug resistance proteins. J Clin

Oncol. 2000 Sep 15;18(18):3211-20. doi: 10.1200/JCO.2000.18.18.3211. PMID: 10986053.

85. Gheorghe G, Bacalbasa N, Ceobanu G, Ilie M, Enache V, Constantinescu G, Bungau S, Diaconu CC. Gastrointestinal Stromal Tumors-A Mini Review. J Pers Med. 2021 Jul 22;11(8):694. doi: 10.3390/jpm11080694. PMID: 34442339; PMCID: PMC8400825.
86. Scarpa M, Prando D, Pozza A, Esposti ED, Castoro C, Angriman I. A systematic review of diagnostic procedures to detect midgut neuroendocrine tumors. J Surg Oncol. 2010 Dec 1;102(7):877-88. doi: 10.1002/jso.21708. PMID: 20812262.
87. WILLIAMS ED, SANDLER M. The classification of carcinoid tum ours. Lancet. 1963 Feb 2;1(7275):238-9. doi: 10.1016/s0140-6736(63)90951-6. PMID: 14000847.
88. Newton JN, Swerdlow AJ, dos Santos Silva IM, Vessey MP, Grahame-Smith DG, Primatesta P, Reynolds DJ. The epidemiology of carcinoid tumours in England and Scotland. Br J Cancer. 1994 Nov;70(5):939-42. doi: 10.1038/bjc.1994.424. PMID: 7947101; PMCID: PMC2033547.
89. Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. Cancer. 2003 Feb 15;97(4):934-59. doi: 10.1002/cncr.11105. PMID: 12569593.
90. Hemminki K, Li X. Incidence trends and risk factors of carcinoid tumors: a nationwide epidemiologic study from Sweden. Cancer. 2001 Oct 15;92(8):2204-10. doi: 10.1002/1097-0142(20011015)92:8<2204::aid-cncr1564>3.0.co;2-r. PMID: 11596039.
91. Sutton R, Doran HE, Williams EM, Vora J, Vinjamuri S, Evans J, Campbell F, Raraty MG, Ghaneh P, Hartley M, Poston GJ, Neoptolemos JP. Surgery for midgut carcinoid. Endocr Relat Cancer. 2003 Dec;10(4):469-81. doi: 10.1677/erc.0.0100469. PMID: 14713260.
92. Shebani KO, Souba WW, Finkelstein DM, Stark PC, Elgadi KM, Tanabe KK, Ott MJ. Prognosis and survival in patients with gastrointestinal tract carcinoid tumors. Ann Surg. 1999 Jun;229(6):815-21; discussion 822-3. doi: 10.1097/00000658-199906000-00008. PMID: 10363895; PMCID: PMC1420828.

93. Eckhauser FE, Argenta LC, Strodel WE, Wheeler RH, Bull FE, Appelman HD, Thompson NW. Mesenteric angiopathy, intestinal gangrene, and midgut carcinoids. Surgery. 1981 Oct;90(4):720-8. PMID: 7281010.
94. Kaltsas GA, Mukherjee JJ, Grossman AB. The value of radiolabelled MIBG and octreotide in the diagnosis and management of neuroendocrine tumours. Ann Oncol. 2001;12 Suppl 2:S47-50. doi: 10.1093/annonc/12.suppl_2.s47. PMID: 11762352.
95. Orlefors H, Sundin A, Ahlström H, Bjurling P, Bergström M, Lilja A, Långström B, Oberg K, Eriksson B. Positron emission tomography with 5-hydroxytryprophan in neuroendocrine tumors. J Clin Oncol. 1998 Jul;16(7):2534-41. doi: 10.1200/JCO.1998.16.7.2534. PMID: 9667275.
96. Tran CG, Sherman SK, Howe JR. Small Bowel Neuroendocrine Tumors. Curr Probl Surg. 2020 Dec;57(12):100823. doi: 10.1016/j.cpsurg.2020.100823. Epub 2020 May 15. PMID: 33234227; PMCID: PMC7722476.
97. Maxwell JE, Howe JR. Imaging in neuroendocrine tumors: an update for the clinician. Int J Endocr Oncol. 2015;2(2):159-168. doi: 10.2217/ije.14.40. PMID: 26257863; PMCID: PMC4526141.
98. Riihimäki M, Hemminki A, Sundquist K, Sundquist J, Hemminki K. The epidemiology of metastases in neuroendocrine tumors. Int J Cancer. 2016 Dec 15;139(12):2679-2686. doi: 10.1002/ijc.30400. Epub 2016 Sep 9. PMID: 27553864.
99. Polish A, Vergo MT, Agulnik M. Management of neuroendocrine tumors of unknown origin. J Natl Compr Canc Netw. 2011 Dec;9(12):1397-402; quiz 1403. doi: 10.6004/jnccn.2011.0118. PMID: 22157557.
100. Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, Abdalla EK, Fleming JB, Vauthey JN, Rashid A, Evans DB. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol. 2008 Jun 20;26(18):3063-72. doi: 10.1200/JCO.2007.15.4377. PMID: 18565894.
101. Gangi A, Anaya DA. Surgical Principles in the Management of Small Bowel Neuroendocrine Tumors. Curr Treat Options Oncol. 2020 Aug 29;21(11):88. doi: 10.1007/s11864-020-00784-2. PMID: 32862334.
102. Hänninen UA, Katainen R, Tanskanen T, Plaketti RM, Laine R, Hamberg J, Ristimäki A, Pukkala E, Taipale M, Mecklin JP, Forsström LM, Pitkänen E,

Palin K, Välimäki N, Mäkinen N, Aaltonen LA. Exome-wide somatic mutation characterization of small bowel adenocarcinoma. PLoS Genet. 2018 Mar 9;14(3):e1007200. doi: 10.1371/journal.pgen.1007200. PMID: 29522538; PMCID: PMC5871010.

103. Schrock AB, Devoe CE, McWilliams R, Sun J, Aparicio T, Stephens PJ, Ross JS, Wilson R, Miller VA, Ali SM, Overman MJ. Genomic Profiling of Small-Bowel Adenocarcinoma. JAMA Oncol. 2017 Nov 1;3(11):1546-1553. doi: 10.1001/jamaoncol.2017.1051. PMID: 28617917; PMCID: PMC5710195.
104. Laforest A, Aparicio T, Zaanan A, Silva FP, Didelot A, Desbeaux A, Le Corre D, Benhaim L, Pallier K, Aust D, Pistorius S, Blons H, Svrcek M, Laurent-Puig P. ERBB2 gene as a potential therapeutic target in small bowel adenocarcinoma. Eur J Cancer. 2014 Jul;50(10):1740-1746. doi: 10.1016/j.ejca.2014.04.007. Epub 2014 May 2. PMID: 24797764.
105. Alvi MA, McArt DG, Kelly P, Fuchs MA, Alderdice M, McCabe CM, Bingham V, McGready C, Tripathi S, Emmert-Streib F, Loughrey MB, McQuaid S, Maxwell P, Hamilton PW, Turkington R, James JA, Wilson RH, Salto-Tellez M. Comprehensive molecular pathology analysis of small bowel adenocarcinoma reveals novel targets with potential for clinical utility. Oncotarget. 2015 Aug 28;6(25):20863-74. doi: 10.18632/oncotarget.4576. PMID: 26315110; PMCID: PMC4673235.
106. Watson RR, Binmoeller KF, Hamerski CM, Shergill AK, Shaw RE, Jaffee IM, Stewart L, Shah JN. Yield and performance characteristics of endoscopic ultrasound-guided fine needle aspiration for diagnosing upper GI tract stromal tumors. Dig Dis Sci. 2011 Jun;56(6):1757-62. doi: 10.1007/s10620-011-1646-6. Epub 2011 Mar 1. PMID: 21360279.
107. Bratu O.G., Cherciu A.I., Bumbu A., Lupu S., Marcu D.R., Ionita R.F., Manea M., Furam C., Diaconu C.C., Mischianu D.L.D. Retroperitoneal tumors—Treatment and prognosis of tumor recurrence. *Rev. Chim.* 2019;70:191–194. doi: 10.37358/RC.19.1.6879.
108. Gerrish ST, Smith JW. Gastrointestinal stromal tumors-diagnosis and management: a brief review. Ochsner J. 2008 Winter;8(4):197-204. PMID: 21603502; PMCID: PMC3096364.
109. Kapatia G, Gupta N, Saikia UN, Gupta P, Rohilla M, Gupta O, Srinivasan R, Rajwanshi A, Dey P. Fine needle aspiration cytology of primary and

metastatic gastrointestinal stromal tumour. Cytopathology. 2020 Mar;31(2):136-143. doi: 10.1111/cyt.12785. Epub 2020 Jan 8. PMID: 31698512.

110. Pallag A, Roşca E, ţiŢ DM, MuŢiu G, Bungău SG, Pop OL. Monitoring the effects of treatment in colon cancer cells using immunohistochemical and histoenzymatic techniques. Rom J Morphol Embryol. 2015;56(3):1103-9. PMID: 26662146.
111. Miettinen M, Lasota J. Histopathology of gastrointestinal stromal tumor. J Surg Oncol. 2011 Dec;104(8):865-73. doi: 10.1002/jso.21945. PMID: 22069171; PMCID: PMC7384443.
112. Feldman JM, Lee EM. Serotonin content of foods: effect on urinary excretion of 5-hydroxyindoleacetic acid. Am J Clin Nutr. 1985 Oct;42(4):639-43. doi: 10.1093/ajcn/42.4.639. PMID: 2413754.
113. Taupenot L, Harper KL, O'Connor DT. The chromogranin-secretogranin family. N Engl J Med. 2003 Mar 20;348(12):1134-49. doi: 10.1056/NEJMra021405. PMID: 12646671.
114. Shah MH, Goldner WS, Halfdanarson TR, Bergsland E, Berlin JD, Halperin D, Chan J, Kulke MH, Benson AB, Blaszkowsky LS, Eads J, Engstrom PF, Fanta P, Giordano T, He J, Heslin MJ, Kalemkerian GP, Kandeel F, Khan SA, Kidwai WZ, Kunz PL, Kuvshinoff BW, Lieu C, Pillarisetty VG, Saltz L, Sosa JA, Strosberg JR, Sussman CA, Trikalinos NA, Uboha NA, Whisenant J, Wong T, Yao JC, Burns JL, Ogba N, Zuccarino-Catania G. NCCN Guidelines Insights: Neuroendocrine and Adrenal Tumors, Version 2.2018. J Natl Compr Canc Netw. 2018 Jun;16(6):693-702. doi: 10.6004/jnccn.2018.0056. PMID: 29891520.
115. Strosberg JR, Halfdanarson TR, Bellizzi AM, Chan JA, Dillon JS, Heaney AP, Kunz PL, O'Dorisio TM, Salem R, Segelov E, Howe JR, Pommier RF, Brendtro K, Bashir MA, Singh S, Soulen MC, Tang L, Zacks JS, Yao JC, Bergsland EK. The North American Neuroendocrine Tumor Society Consensus Guidelines for Surveillance and Medical Management of Midgut Neuroendocrine Tumors. Pancreas. 2017 Jul;46(6):707-714. doi: 10.1097/MPA.0000000000000850. PMID: 28609356; PMCID: PMC5642985.

116. Welin S, Stridsberg M, Cunningham J, Granberg D, Skogseid B, Oberg K, Eriksson B, Janson ET. Elevated plasma chromogranin A is the first indication of recurrence in radically operated midgut carcinoid tumors. Neuroendocrinology. 2009;89(3):302-7. doi: 10.1159/000179900. Epub 2009 Jan 29. PMID: 19176944.

117. Hsiao RJ, Mezger MS, O'Connor DT. Chromogranin A in uremia: progressive retention of immunoreactive fragments. Kidney Int. 1990 Mar;37(3):955-64. doi: 10.1038/ki.1990.71. PMID: 2313983.

118. Modlin IM, Bodei L, Kidd M. Neuroendocrine tumor biomarkers: From monoanalytes to transcripts and algorithms. Best Pract Res Clin Endocrinol Metab. 2016 Jan;30(1):59-77. doi: 10.1016/j.beem.2016.01.002. Epub 2016 Jan 18. PMID: 26971844.

119. Klimstra DS, Modlin IR, Adsay NV, Chetty R, Deshpande V, Gönen M, Jensen RT, Kidd M, Kulke MH, Lloyd RV, Moran C, Moss SF, Oberg K, O'Toole D, Rindi G, Robert ME, Suster S, Tang LH, Tzen CY, Washington MK, Wiedenmann B, Yao J. Pathology reporting of neuroendocrine tumors: application of the Delphic consensus process to the development of a minimum pathology data set. Am J Surg Pathol. 2010 Mar;34(3):300-13. doi: 10.1097/PAS.0b013e3181ce1447. PMID: 20118772.

120. Bellizzi AM. Immunohistochemistry in the diagnosis and classification of neuroendocrine neoplasms: what can brown do for you? Hum Pathol. 2020 Feb;96:8-33. doi: 10.1016/j.humpath.2019.12.002. Epub 2019 Dec 17. PMID: 31857137; PMCID: PMC7177196.

121. Skandalakis, Surgical Anatomy and Technique_ A Pocket Manual (2014, Springer-Verlag New York, pages 412-414

122. Gangi A, Anaya DA. Surgical Principles in the Management of Small Bowel Neuroendocrine Tumors. Curr Treat Options Oncol. 2020 Aug 29;21(11):88. doi: 10.1007/s11864-020-00784-2. PMID: 32862334.

123. Ruffolo C, Scarpa M, Polese L, D'Amico FE, Boetto R, Pozza A, D'Incà R, Checchin D, Sturniolo GC, Bassi N, Angriman I. Clinical presentation and diagnosis of intestinal adenocarcinoma in Crohn's disease: analysis of clinical predictors and of the life-time risk. J Gastrointest Surg. 2010 Nov;14(11):1746-51. doi: 10.1007/s11605-010-1265-0. Epub 2010 Jul 14. PMID: 20628906.

124. Iorio N, Sawaya RA, Friedenberg FK. Review article: the biology, diagnosis and management of gastrointestinal stromal tumours. Aliment Pharmacol Ther. 2014 Jun;39(12):1376-86. doi: 10.1111/apt.12761. Epub 2014 Apr 20. PMID: 24749828.

125. Miettinen M, Sarlomo-Rikala M, Lasota J. Gastrointestinal stromal tumors: recent advances in understanding of their biology. Hum Pathol. 1999 Oct;30(10):1213-20. doi: 10.1016/s0046-8177(99)90040-0. PMID: 10534170.

126. Nishida T, Hirota S, Taniguchi M, Hashimoto K, Isozaki K, Nakamura H, Kanakura Y, Tanaka T, Takabayashi A, Matsuda H, Kitamura Y. Familial gastrointestinal stromal tumours with germline mutation of the KIT gene. Nat Genet. 1998 Aug;19(4):323-4. doi: 10.1038/1209. PMID: 9697690.

127. Crosby JA, Catton CN, Davis A, Couture J, O'Sullivan B, Kandel R, Swallow CJ. Malignant gastrointestinal stromal tumors of the small intestine: a review of 50 cases from a prospective database. Ann Surg Oncol. 2001 Jan-Feb;8(1):50-9. doi: 10.1007/s10434-001-0050-4. PMID: 11206225.

128. Massimino KP, Han E, Pommier SJ, Pommier RF. Laparoscopic surgical exploration is an effective strategy for locating occult primary neuroendocrine tumors. Am J Surg. 2012 May;203(5):628-631. doi: 10.1016/j.amjsurg.2011.12.010. Epub 2012 Mar 27. PMID: 22459446.

129. Figueiredo MN, Maggiori L, Gaujoux S, Couvelard A, Guedj N, Ruszniewski P, Panis Y. Surgery for small-bowel neuroendocrine tumors: is there any benefit of the laparoscopic approach? Surg Endosc. 2014 May;28(5):1720-6. doi: 10.1007/s00464-013-3381-x. Epub 2014 Jan 1. PMID: 24380996.

130. Zahorec R. Neutrophil-to-lymphocyte ratio, past, present and future perspectives. Bratisl Lek Listy. 2021;122(7):474-488. doi: 10.4149/BLL_2021_078. PMID: 34161115.

131. Burke AP, Thomas RM, Elsayed AM, Sobin LH. Carcinoids of the jejunum and ileum: an immunohistochemical and clinicopathologic study of 167 cases. Cancer. 1997 Mar 15;79(6):1086-93. PMID: 9070484.

132. Fields AC, Hu FY, Lu P, Irani J, Bleday R, Goldberg JE, Melnitchouk N. Small Bowel Adenocarcinoma: Is There a Difference in Survival for Crohn's Versus Sporadic Cases? J Crohns Colitis. 2020 Mar 13;14(3):303-308. doi: 10.1093/ecco-jcc/jjz157. PMID: 31541248.

133. Wieghard N, Mongoue-Tchokote S, Young JI, Sheppard BC, Tsikitis VL. Prognosis of small bowel adenocarcinoma in Crohn's disease compares favourably with de novo small bowel adenocarcinoma. Colorectal Dis. 2017 May;19(5):446-455. doi: 10.1111/codi.13531. PMID: 27659145.

134. Palascak-Juif V, Bouvier AM, Cosnes J, Flourié B, Bouché O, Cadiot G, Lémann M, Bonaz B, Denet C, Marteau P, Gambiez L, Beaugerie L, Faivre J, Carbonnel F. Small bowel adenocarcinoma in patients with Crohn's disease compared with small bowel adenocarcinoma de novo. Inflamm Bowel Dis. 2005 Sep;11(9):828-32. doi: 10.1097/01.mib.0000179211.03650.b6. PMID: 16116317.

135. Mohammed A. Aleskandarany, Sultan N. Sonbul, Abhik Mukherjee, Emad A. Rakha; Molecular Mechanisms Underlying Lymphovascular Invasion in Invasive Breast Cancer. *Pathobiology* 1 September 2015; 82 (3-4): 113–123. https://doi.org/10.1159/000433583

136. Yu J, Refsum E, Perrin V, Helsingen LM, Wieszczy P, Løberg M, Bretthauer M, Adami HO, Ye W, Blom J, Kalager M. Inflammatory bowel disease and risk of adenocarcinoma and neuroendocrine tumors in the small bowel. Ann Oncol. 2022 Jun;33(6):649-656. doi: 10.1016/j.annonc.2022.02.226. Epub 2022 Mar 8. PMID: 35276334.

137. Qubaiah O, Devesa SS, Platz CE, Huycke MM, Dores GM. Small intestinal cancer: a population-based study of incidence and survival patterns in the United States, 1992 to 2006. Cancer Epidemiol Biomarkers Prev. 2010 Aug;19(8):1908-18. doi: 10.1158/1055-9965.EPI-10-0328. Epub 2010 Jul 20. PMID: 20647399; PMCID: PMC2919612.

138. Ocasio Quinones GA, Khan Suheb MZ, Woolf A. Small Bowel Cancer. 2023 Jun 1. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan–. PMID: 32809560.

139. Debnath D, Rees J, Myint F. Are we missing diagnostic opportunities in cases of carcinoid tumours of the appendix? Surgeon. 2008 Oct;6(5):266-72. doi: 10.1016/s1479-666x(08)80049-2. PMID: 18939372.

140. Catassi C, Verdu EF, Bai JC, Lionetti E. Coeliac disease. Lancet. 2022 Jun 25;399(10344):2413-2426. doi: 10.1016/S0140-6736(22)00794-2. Epub 2022 Jun 9. PMID: 35691302.

141. Matsui S, Yamamoto Y, Okamura Y, Ito T, Ashida R, Ohgi K, Yamada M, Otsuka S, Uesaka K, Sugiura T. The Prognostic Relevance of Preoperative CEA and CA19-9 for Ampulla of Vater Carcinoma. Anticancer Res. 2022 Jun;42(6):3169-3176. doi: 10.21873/anticanres.15806. PMID: 35641260.
142. Kau SY, Shyr YM, Su CH, Wu CW, Lui WY. Diagnostic and prognostic values of CA 19-9 and CEA in periampullary cancers. J Am Coll Surg. 1999 Apr;188(4):415-20. doi: 10.1016/s1072-7515(98)00326-3. PMID: 10195726.
143. Zaanan A, Costes L, Gauthier M, Malka D, Locher C, Mitry E, Tougeron D, Lecomte T, Gornet JM, Sobhani I, Moulin V, Afchain P, Taïeb J, Bonnetain F, Aparicio T. Chemotherapy of advanced small-bowel adenocarcinoma: a multicenter AGEO study. Ann Oncol. 2010 Sep;21(9):1786-1793. doi: 10.1093/annonc/mdq038. Epub 2010 Mar 11. PMID: 20223786.
144. Shah KJ, Malleo G, Low J, Skordilis K, Makin AJ, Siriwardena AK. Duodenal duplication cyst with profound elevation of intracystic carbohydrate antigen (CA 19-9) and carcinoembryonic antigen (CEA): a rare but important differential in the diagnosis of cystic tumours of the pancreas. JOP. 2006 Mar 9;7(2):200-4. PMID: 16525204.