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ORIGINAL ARTICLE

Clinical features and prognosis of malignant small bowel tumors: Experience from a university hospital in Chile

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KEYWORDS
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Abstract
Background: Small bowel tumors (SBT) are infrequent and represent a small proportion of digestive neoplasms. There is scarce information about SBT in Latin America.
Aim: To describe the epidemiology, clinical characteristics, diagnostic methods, and survival of malignant SBTs.
Methods: Retrospective observational study of adult patients with histopathological diagnosis of SBT between 2007 and 2021 in a university hospital in Chile.
Results: A total of 104 patients [51.9% men; mean age 57 years] with SBT. Histological type: neuroendocrine tumor (NET) (43.7%, $n = 38$), gastrointestinal stromal tumors (GIST) (21.8%, $n = 19$), lymphoma (17.2%, $n = 15$) and adenocarcinoma (AC) (11.5%, $n = 10$). GIST was more frequent in duodenum (50%; $n = 12$) and NET in the ileum (65.8%; $n = 25$). Metastasis was observed in 17 cases, most commonly from colon and melanoma. Nausea and vomiting were significantly more often observed in AC ($p = 0.035$), as well as gastrointestinal bleeding in GIST ($p = 0.007$).

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The most common diagnostic tools were CT and CT enteroclysis with an elevated diagnostic yield (86% and 94% respectively). The 5-year survival of GIST, NET, lymphoma and AC were 94.7% (95%CI: 68.1–99.2), 82.2% (95%CI: 57.6–93.3), 40.0% (95%CI: 16.5–82.8) and 25.9% (95%CI: 4.5–55.7%), respectively. NET (HR 6.1; 95%CI: 2.1–17.2) and GIST (HR 24.4; 95%CI: 3.0–19.8) were independently associated with higher survival compared to AC, adjusted for age and sex.
Conclusions: Malignant SBT are rare conditions and NETs are the most common histological subtype. Clinical presentation at diagnosis, location or complications may suggest a more probable diagnosis. GIST and NET are associated with better survival compared to other malignant subtypes.
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PALABRAS CLAVE
Adenocarcinoma de intestino delgado;
Tumores neuroendocrinos;
Tumores del estroma gastrointestinal;
Enteroclisis

Características clínicas y pronóstico de los tumores malignos de intestino delgado: experiencia en un hospital universitario de Chile

Resumen
Introducción: Los tumores del intestino delgado (TID) son infrecuentes y la información sobre ellos es escasa en Latinoamérica.
Objetivo: Describir la epidemiología, características clínicas, métodos diagnósticos y supervivencia de los TID malignos.
Métodos: Estudio observacional retrospectivo de pacientes adultos con diagnóstico histopatológico de TID entre 2007-2021 en un hospital universitario de Chile.
Resultados: Se observaron 104 pacientes (51,9% hombres; edad media 57 años) con TID. El tipo histológico fue tumor neuroendocrino (TNE) (43,7%, n = 38), tumor estromal gastrointestinal (GIST) (21,8%, n = 19), linfoma (17,2%, n = 15) y adenocarcinoma (AC) (11,5%, n = 10). Los GIST fueron más frecuentes en el duodeno (50%; n = 12) y los TNE en el íleon (65,8%; n = 25). Hubo 17 casos de metástasis, más comúnmente de colon y melanoma. Las náuseas y los vómitos se observaron con mayor frecuencia en AC (p = 0,035), así como el sangrado gastrointestinal en GIST (p = 0,007). Las herramientas de valoración más comunes fueron TC y enteroclisis por TC con un rendimiento diagnóstico alto (86% y 94%, respectivamente). La supervivencia a cinco años de los GIST, TNE, linfoma y AC fue 94,7% (intervalo de confianza [IC] 95%: 68,1-99,2), 82,2% (IC 95%: 57,6-93,3), 40,0% (IC 95%: 16,5-82,8) y 25,9% (IC 95%: 4,5-55,7), respectivamente. Los TNE (*hazard ratio* [HR] 6,1; IC 95%: 2,1-17,2) y GIST (HR 24,4; IC 95%: 3,0-19,8) se asociaron de forma independiente con una mayor supervivencia en comparación con AC, ajustado por edad y sexo.
Conclusiones: Los TID malignos son enfermedades poco frecuentes y los TNE son el subtipo histológico más común. La presentación clínica en el momento del diagnóstico, localización o complicaciones pueden sugerir un dictamen más probable. Los GIST y TNE se asocian a una mejor supervivencia en comparación con otros subtipos malignos.
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Introduction

Small bowel tumors (SBT) are rare conditions, exhibiting a low global incidence estimated in about 2.4 cases per 100,000 habitants.[1] Although small bowel (SB) represents 90% of the surface of the gastrointestinal tract, SBT accounts for only 3–4% of all primary gastrointestinal tumors[1]. SBT incidence has increased throughout the last decades, especially due to a greater incidence of NET.[2] Also a greater incidence of SBT has been recently related to a higher human development index, gross domestic product, unhealthy lifestyle habits and metabolic disorders.[3] Most of these tumors are sporadic, however, associations with hereditary genetic syndromes and inherited conditions have been described, mostly with familial adenomatous polyposis, Lynch syndrome and Peutz-Jeghers syndrome. In addition, some immune mediated diseases, such as Crohn's disease or celiac disease, have been associated with an increased risk of developing small bowel adenocarcinomas and lymphomas.[4]

Among primary SBT, the most common subtypes are adenocarcinoma (AC), neuroendocrine tumors (NET), gastrointestinal stromal tumors (GIST) and lymphomas.[5] The most frequent primary malignant SBT are AC and NET.[2,6] It has been described a lower incidence of GIST and lymphomas compared to other SBT types, but they are usually observed among a younger population.[7] In contrast, SB metastasis are a very rare condition, most commonly originated from

the colon, melanoma, pancreas, lung and breast cancer.[5,8,9] However, limited studies have described the epidemiology and natural history of SBT in Latin America.[10–12] In Chile, there is no epidemiological published data regarding this type of malignant tumors.

Due to the low frequency of SBT, available data describing the clinical features and natural history of SBT are scarce. Currently, given the higher frequency of abdominal imaging diagnosis, SBT are commonly diagnosed in asymptomatic patients as an incidental finding.[13] However, when SBT presents with clinical symptoms, such as pain or gastrointestinal bleeding, usually are manifestations of a more advanced disease. Therefore, a high diagnostic suspicion is required for the recognition of malignant SBT.[9] The most common symptoms described in patients with malignant SBT are abdominal pain, gastrointestinal bleeding, bowel obstruction and weight loss.[13] A variety of endoscopic and imaging techniques are available for the diagnosis of SBT. Given the long extension of the SB, low diagnostic value has been given to esophagogastroduodenoscopy (EGD) and colonoscopy with ileoscopy.[14] In this context, video capsule endoscopy (VCE) allows a non-invasive complete examination of the SB. However, heterogeneous diagnostic yield has been described for VCE (30–80%), with a low risk of capsule retention due to the SBT.[15–17] This limited diagnostic yield may be related to low SB transit-time, an evaluation of the SB limited to the luminal side, presence of opaque debris and absence of intestinal mucosal disruption related to some SBT. Moreover, scarce data has been reported describing the diagnostic yield of device assisted enteroscopy (DAE). Despite the large anatomical extension that can be evaluated with this method, related procedural risks, limited availability, prolonged procedural time limits their routine application.[18,19] However, a great advantage of DAE is the possibility to collect biopsies for histopathological confirmation. On the other hand, imagine techniques have emerged as widely available noninvasive diagnostic tools for SBT diagnosis. Computed tomography (CT) and magnetic resonance imaging (MRI) enteroclysis have shown diagnostic yield over 84%,[20–23] with better diagnostic performance compared to CT or MRI without enteroclysis.[17]

In this context, the aim of this study was to describe the epidemiology, clinical features, diagnostic methods and prognosis of malignant SBT in a university hospital of Chile.

Patients and methods

Study design and patients

An observational, retrospective, and descriptive study was carried out in Pontificia Universidad Católica de Chile health care system (UC-Christus Health), Santiago, Chile. Patients over 18 years old with the histologic diagnosis of malignant SBT between March 2007 and November 2021 were included. Small bowel biopsies obtained from endoscopic techniques, or the surgical specimen were included. All biopsies were processed at one centralized pathology laboratory by two expert pathologists. Benign SBT and tumors originating from the Vater's ampulla were excluded because they were considered out of the scope of the study. Patients with extraintestinal abdominal malignancies extended locally to small bowel or peritoneal carcinomatosis, not originating from the SB, were also excluded. Demographic data, clinical charts, radiology reports and endoscopic reports were recorded. A computerized search was made in the biopsy and endoscopic database of the health care network using the keywords ''tumors'', ''neoplasm'', ''malignancy'', ''duodenum'', ''jejunum'', ''ileum'' and ''small bowel without specification'', which were chosen based on the database organization keywords. A total of 274 small bowel biopsies were obtained, each one was assessed by two independent reviewers. 170 biopsies were excluded for the absence of malignant SBT histology, which consisted of normal findings, ulcers, polyps, diverticulum, celiac disease, inflammatory bowel disease, intestinal tuberculosis, endometriosis, and Brunner's glands hyperplasia.

Demographic information, mainly age and year of diagnosis, personal history of neoplasia, familiar history of SBT, smoking, alcohol consumption and past medical history regarding arterial hypertension, metabolic conditions, inflammatory bowel disease and celiac disease was recorded. In addition, clinical symptoms reported by the treating physicians at the moment of diagnosis were recorded, such as abdominal pain, gastrointestinal bleeding, abdominal distention, bowel obstruction, bowel perforation, weight loss, diarrhea, vomiting and nauseas. Asymptomatic presentation was defined as the absence of any symptom reported by the treating physician at diagnosis. Diagnostic tests, such as EGD (proximal to angle of Treitz), colonoscopy, enteroscopy (including push enteroscopy beyond angle of Treitz and DAE), VCE, CT, CT enteroclysis, positron emission tomography (PET) and MRI, were reviewed from patient's clinical records. All diagnostic tools were evaluated at the time of SBT diagnosis. Diagnostic yield was defined as a positive finding independently in each diagnostic tool before histopathological confirmation of the SBT.

The present study was conducted according to the ethical standards established in the Declaration of Helsinki. Data obtained from patients were handled confidentially and anonymously by the researchers. The Ethical Committee of the Medical School at the Pontificia Universidad Católica of Chile approved the study protocol (ID 230518001).

Histopathological study

Histopathological samples of SBT tissue obtained through SB resections or endoscopic biopsy were analyzed. All the cases were analyzed to define the malignant SBT subtype (mainly AC, NET, GIST and lymphoma), tumor location (duodenum, jejunum and ileum), tissue infiltration and metastasis. AC, NET and GIST grading were classified according to the eight version of the American Joint Committee on Cancer (AJCC) Staging Manual, reporting tumor category of TNM system.[24] Also, NET grading was analyzed based on proliferative activity and Ki-67 and were classified according to the 2022 World Health Organization (WHO) Classification of Endocrine and Neuroendocrine Tumors.[25]

Table 1 Baseline patient's characteristics according to primary tumor subtype.

	Adenocarcinoma ($n=10$)	NET ($n=38$)	GIST ($n=19$)	Lymphoma ($n=15$)	p value[†]
Sex (male), n [%]	5 (50%)	23 (60.5%)	7 (36.8%)	9 (60%)	0.37
Age, mean [CI95%]	56.5 (46–61)	54 (41–63)	60 (51–69)	64 (51–73)	0.12
Smoking, n [%]					
Active smoking	2 (20%)	9 (23.7%)	2 (10.5%)	4 (26.7%)	0.63
Former smoker	1 (10%)	4 (10.5%)	12 (63.2%)	4 (26.7%)	0.31
Never smoker	7 (70%)	25 (65.8%)	5 (26.3%)	7 (46.7%)	0.57
Alcohol consumption, n [%]	1 (10%)	16 (42.1%)	7 (36.8%)	7 (46.7%)	0.25
Diabetes mellitus type 2, n [%]	0 (0%)	3 (7.9%)	4 (21.1%)	1 (6.7%)	0.25
Hypertension, n [%]	3 (30%)	14 (36.8%)	7 (36.8%)	6 (40%)	0.97
Coeliac disease, n [%]	1 (10%)	0 (0%)	0 (0%)	4 (26.7%)	**0.002**
Crohn disease, n [%]	1 (10%)	0 (0%)	0 (0%)	2 (13.3%)	0.06
Previous non-small bowel neoplasia, n [%]	3 (30%)	5 (13.2%)	4 (11.4%)	2 (13.3%)	0.58

[†] Chi square for categorical variables and Kruskal–Wallis for numerical variables. SBT: small bowel tumor; NET: neuroendocrine tumor; GIST: gastrointestinal stromal tumor.

Statistical analysis

Clinical and demographic data was described based on malignant SBT subtype. Numerical variables were reported in mean or median according to distribution analyzed by Kolmogorov–Smirnov method. Categorical variables were reported in percentages (%). Categorical variables were compared by Fisher exact test and numerical variables by *t*-test or Mann–Whitney according to distribution. Diagnostic yield of CT, MRI, CT enteroclysis, EC, EGD, colonoscopy and PET were assessed considering histology as the diagnostic standard. For survival analysis, time elapsed between diagnosis and death date was considered, using Kaplan–Meier curves and stratifying survival by tumor subtype using a Cox proportional hazard with AC and lymphomas as category reference, expressed as hazard ratios (HR). All models were adjusted by age and sex. Survival models were censored at loss of follow up or end of the study period (November 2021). As an exploratory analysis to evaluate the trend in frequency of SBT subtypes along the study period, time was divided in three-year intervals and SBT histological subtypes were analyzed by a multinomial regression adjusted for age and sex. An a priori alpha value of 0.05 was set. All analyses were performed with the STATA 17.0 version statistical package (Stata Corp, College Station, TX, USA).

Results

Patients and characteristics

One hundred and four malignant SBT were included in our study, 51.9% were male ($n=54$) with a mean age of 57 years-old (range 19–89). Baseline characteristics of the patients according to SBT type are described in Table 1. Out of all included cases, 93.3% ($n=97$) of the histologic analysis were obtained from surgical specimens. The remaining biopsies were obtained through endoscopic techniques, with complete endoscopic resection in 2 cases of early stage SBT. A representative case of a SBT with clinical presentation, diagnosis approach, surgical treatment and histological features is presented in Fig. 1.

Malignant small bowel tumor characteristics

Among malignant SBT, 83.7% ($n=87$) were primary SBT and 16.4% ($n=17$) were metastases from outside the SB. Histologic subtype of primary SBT were NET 43.7% ($n=38$), GIST 21.8% ($n=19$), lymphomas 17.2% ($n=15$), AC 11.5% ($n=10$), and 5.8% ($n=5$) other subtypes (i.e. leiomyosarcoma, liposarcoma). Tumoral stage (T) according to AJCC classification was reported in 90% ($n=9$), 92.1% ($n=35$) and 100% ($n=19$) for AC, NET and GIST, respectively. Among AC tumoral stages distribution at diagnosis was 0% ($n=0$) T1, 33% ($n=3$) T2, 33% ($n=3$) T3 and 33% ($n=3$) T4. Tumoral stage of NET were 15.8% ($n=6$) T1, 18.4% ($n=7$) T2, 26.3% ($n=10$) T3 and 31.6% ($n=12$) T4; WHO classification was reported in 81.6% ($n=31$) cases with grade 1 in 61.3% ($n=19$), grade 2 in 32.2% ($n=10$) and grade 3 in 6.5% ($n=2$). Meanwhile, GIST tumoral stages at diagnosis were 15.8% ($n=3$) T1, 57.9% ($n=11$) T2, 21% ($n=4$) T3 and 5.3% ($n=1$) T4. Tumoral stage was not significantly different among AC, NET and GIST ($p=0.072$).

Regarding anatomical location of SBT, 24.8% ($n=25$) were found in the duodenum, 28.9% ($n=30$) in the jejunum and 47.1% ($n=49$) in the ileum. In the duodenum the most common SBT subtype was GIST (50%; $n=12$) and NET was the most common SBT subtype in the jejunum (26.1%; $n=6$) and ileum (62.5%; ($n=25$). The description of SBT subtypes by anatomical location is presented in Table 2. SB metastases were localized in the ileum in 52.9% ($n=9$), jejunum in 41.2% ($n=7$) and duodenum in 5.9% ($n=1$) SB metastases were originated from melanoma (24%; $n=4$), colon (24%; $n=4$), cervix (12%; $n=2$) and lung (12%; $n=2$).

Small bowel tumor clinical features

Overall, 11.5% ($n=12$) of the malignant SBT presented asymptomatically as radiological or endoscopic finding,

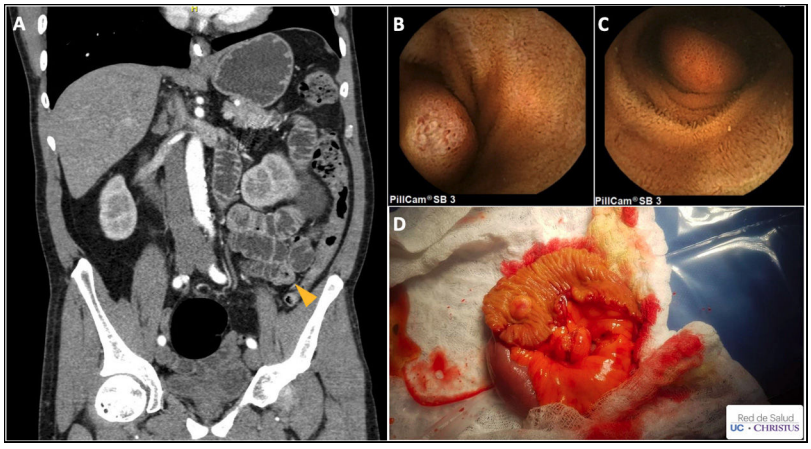


Figure 1 A 61-years-old male attended for 2 weeks of melena. Laboratory assay showed anemia (hemoglobin of 7.1 g/dl). Initially, esophagogastroduodenoscopy was performed, without signs of upper gastrointestinal bleeding. Colonoscopy showed a normal colon with blood coming from the terminal ileum, without identifying the origin of the bleeding. With the suspicion of small bowel bleeding, an endoscopic capsule (Pillcam SB 3®, Medtronic, USA) (panels B and C) was ingested, which showed the presence of a polypoid lesion of at least 20 mm in a distal segment of the jejunum. A computer tomography enteroclysis (panel A) was performed which showed a small bowel tumor without evidence of dissemination. The case was discussed in a multidisciplinary committee deciding a small bowel resection. Surgical small bowel piece is presented in panel D. The histological study of the surgical piece revealed the presence of a low grade (KI67: 1%), well differentiated neuroendocrine tumor. Patient presented favorable evolution and was discharged without recurrence during the follow up.

Table 2 Location and clinical manifestation of primary malignant small bowel tumors according to tumoral subtype.

	Adenocarcinoma ($n = 10$)	NET ($n = 38$)	GIST ($n = 19$)	Lymphoma ($n = 15$)	p value[†]
Location, n [%]					
Duodenum	4 (40%)	7 (18.4%)	12 (63.2%)	1 (6.7%)	**0.001**
Jejunum	5 (50%)	6 (15.8%)	5 (26.3%)	4 (26.7%)	0.137
Ileum	1 (10%)	25 (65.8%)	2 (10.5%)	10 (66.7%)	**<0.001**
Asymptomatic, n [%]	0 (0%)	8 (21.1%)	2 (10.5%)	0 (0%)	0.098
Symptoms, n [%]					
Abdominal pain	5 (50%)	20 (53.6%)	7 (36.8%)	10 (66.7%)	0.385
Low weigh	5 (50%)	6 (15.8%)	4 (21.1%)	6 (40%)	0.076
Nausea	3 (30%)	2 (5.3%)	0 (0%)	2 (13.3%)	**0.035**
Vomiting	5 (50%)	3 (7.9%)	1 (5.3%)	3 (20%)	**0.004**
Bloating	2 (20%)	4 (11%)	1 (5.3%)	1 (6.7%)	0.612
Diarrhea	0 (0%)	5 (13.2%)	3 (15.8%)	3 (20%)	0.531
Complications, n [%]					
Gastrointestinal bleeding	0 (0%)	5 (13.2%)	8 (42.1%)	1 (6.7%)	**0.007**
Intestinal obstruction	2 (20%)	3 (7.9%)	0 (0%)	1 (6.7%)	0.272
Intestinal perforation	0 (0%)	0 (0%)	0 (0%)	5 (33.3%)	**0.001**

[†] Fisher exact test. SBT: small bowel tumor; NET: neuroendocrine tumor; GIST: gastrointestinal stromal tumor.

without any symptoms or complications. The most common symptoms were abdominal pain (51.9%; $n = 54$), weight loss (23.1%; $n = 24$), diarrhea (14.4%; $n = 15$), vomiting (14.4%; $n = 15$), nausea (11.5%; $n = 11$) and abdominal bloating (8.7%; $n = 9$).

Respective of the SBT subtype, only higher frequencies of nausea (30%) and vomiting (50%) were observed in patients with AC contrasted to other SBT subtypes ($p = 0.035$ vs. $p = 0.004$). Clinical presentation according to malignant SBT subtype is detailed in Table 2.

Otherwise, some malignant SBT presented with complications at diagnosis. Gastrointestinal bleeding, intestinal obstruction and perforation were observed in 14.2% ($n = 15$), 15.1% ($n = 16$) and 7.6% ($n = 8$) of the patients at diagnosis, respectively. Gastrointestinal bleeding was significantly more commonly observed in patients with

Table 3 Diagnostic methods used in patients with small bowel tumors.

Diagnostic method	Frequency	Diagnostic yield[a]
First line endoscopic diagnostic methods, n [%]		
Esophagogastroduodenoscopy[b]	27 (26%)	11/27 (40.7%)
Ileoscopy during colonoscopy	19 (18.3%)	8/19 (42.1%)
Undirected to SB images, n [%]		
Computed tomography	71 (68.3%)	61/71 (85.9%)
Magnetic resonance imaging	12 (11.5%)	9/12 (75%)
Directed SB methods, n [%]		
Computed tomography enteroclysis	18 (17.3%)	17/18 (94.4%)
Video capsule endoscopy	3 (2.9%)	2/3 (66.7%)
Enteroscopy (including push enteroscopy and DAE)	10 (9.6%)	9/10 (90%)
Specific diagnostic methods, n [%]		
Positron emission tomography	22 (21.2%)	21/22 (95.5%)

[a] Defined as the proportions of positive exams for small bowel tumors among all the performed exams.
[b] Esophagogastroduodenoscopies proximal to angle of Treitz. DAE: device assisted enteroscopy.

GIST (42%; $n = 8$) ($p = 0.007$). Perforation was only observed in patients with lymphoma, in 33.3% ($n = 5$) of the cases ($p < 0.001$). No significant differences were observed among intestinal obstruction between different SBT subtypes (Table 2).

Among the NETs observed in our study, 3% ($n = 1$) of them presented with a synchronous SB tumor in the ileum, corresponding to a second NET, this patient also presented an extraintestinal NET located in the pancreas. Moreover, 8% ($n = 3$) of patients with NET presented a metachronous NET during the follow up, located in the duodenum ($n = 1$) and ileum ($n = 2$).

Small bowel tumor diagnostic methods

Frequency and diagnostic yield of different diagnostic methods are described in Table 3. As a primary diagnostic approach, 18.3% ($n = 19$) of the SBT were initially diagnosed by an EGD or ileoscopy during a colonoscopy. When SBT was not diagnosed in either the EGD or colonoscopy ($n = 85$), the most frequent second diagnostic method were CT (74%; $n = 61$), CT enteroclysis (20%; $n = 17$), VCE (4%; $n = 3$) and DAE (10.6%; $n = 9$). In this context, positive SBT findings were observed in 85% ($n = 53/63$) of the CT, 94.1% (16/17) of the CT enteroclysis, 66.7% ($n = 2/3$) of the VCE and 100% ($n = 9/9$) of the DAE.

Trends in small bowel tumors subtype along the study period

During the study period an increase in the absolute frequency of overall SBT diagnosis was observed. Along all the evaluated study periods NETs were the most frequent SBT subtypes. There was a positive and significant trend in the frequency of NETs (OR 1.9; p-trend = 0.016), GIST (OR 2.3; p-trend = 0.007) and metastases (OR 2.1; p-trend = 0.014), contrasted with AC along the study period, evaluated in the multinomial regression adjusting for age and sex (Supplemental Table 1). Trends in frequency of diagnosis among SBT subtypes along the study period are presented in Fig. 2.

Small bowel tumor survival analysis

Overall, mean follow-up was 41.7 months (CI95%: 33.7–49.8). Five-year survival of GIST, NET, lymphoma, and AC were 94.7% (95%CI: 68.1–99.2), 82.2% (95%CI: 57.6–93.3), 40.0% (95%CI: 16.5–82.8) and 25.9% (95%CI: 4.5–55.7%), respectively (Fig. 3). There were no cases of reported survival at 5-year follow up of patients with SB metastases.

Based on the Cox regression analysis, SBT subtype was independently associated with survival ($p = 0.004$). NET and GIST histological subtypes demonstrated a significantly higher survival compared with AC with an HR of 6.1 (95%CI: 2.1–17.2) and 24.4 (95%CI: 3.0–19.8), respectively. Furthermore, NET and GIST demonstrated a significantly higher survival compared to lymphomas with adjusted HR of 5.0 (95%CI: 1.8–14.0) and 20.2 (95%CI: 2.5–16.1), respectively (Supplemental Table 2). Moreover, whereas sex was not independently associated to survival ($p = 0.46$), older ages demonstrated higher mortality among follow-up with HR 1.04 (95%CI: 1.01–1.07).

Discussion

Malignant SBT have a low incidence worldwide and they are considered rare conditions[1]. There is scarce information among these tumors in Latin America. Here we describe a comprehensive description of a series of malignant SBT evaluated at a tertiary university hospital in Chile between 2007 and 2021. Concordantly to international reports, NET has become the most common malignant SBT[2,6], specially located at the ileum. This histological subtype is related to a better prognosis contrasted to adenocarcinomas or lymphomas, but as much as 21% of NET may be asymptomatic, a low threshold of suspicion is required for the diagnosis.

Although clinical presentation is not specific for any histological subtype of SBT, some useful clinical data can be

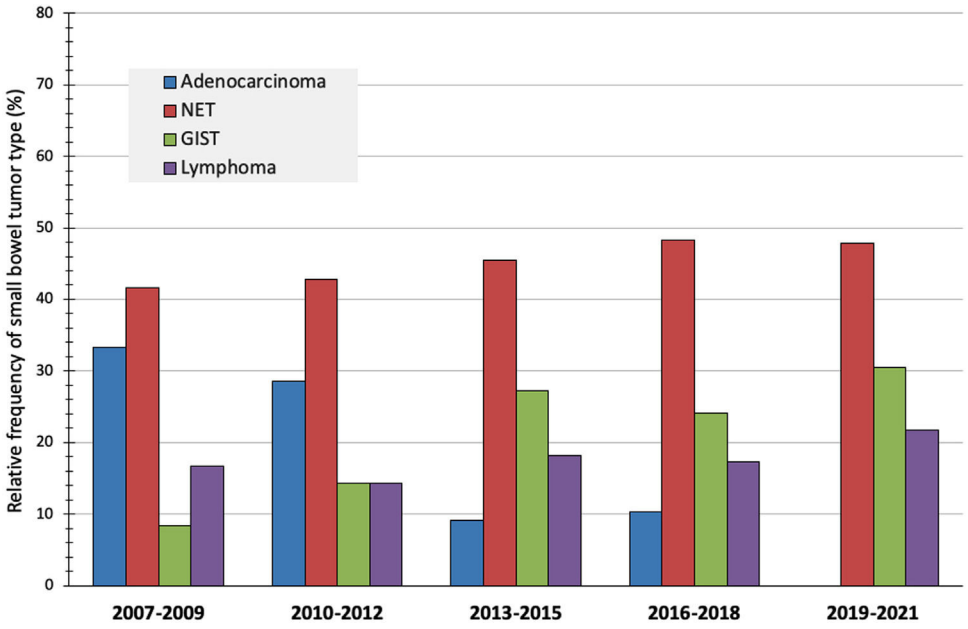
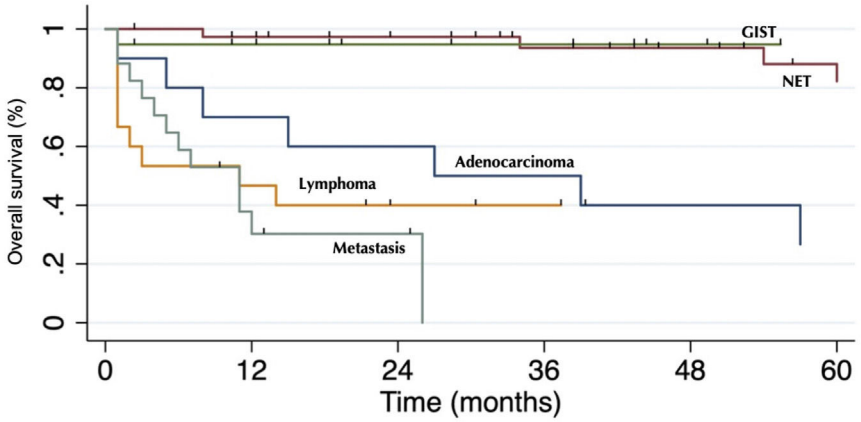


Figure 2 Trends in the relative frequency of malignant small bowel tumors subtype along the study period.



Adenocarcinoma	10	(3)	7	(1)	6	(1)	5	(1)	3	(1)	2
NET	38	(1)	35	(0)	31	(1)	25	(0)	20	(1)	15
GIST	19	(1)	16	(0)	13	(0)	12	(0)	8	(0)	6
Lymphoma	15	(8)	7	(1)	4	(0)	3	(0)	2	(0)	2
Metastasis	17	(10)	5	(1)	3	(2)	0	(0)	0	(0)	2

Figure 3 Kaplan–Meier survival function of malignant small bowel tumors according to histological subtype. Survival at risk table is presented before the graph with total sample by each histopathological subtype along the follow up and deaths per period in parenthesis.

obtained from our results. First, in our study we did not observe important differences by sex or age at diagnosis among different histological subtypes. As is expected, clinical history of celiac disease should suggest the diagnosis of a lymphoma when a SBT is diagnosed, especially in a refractory celiac disease. Nonetheless, a higher risk of adenocarcinoma has been reported among celiac disease[26] and one case of adenocarcinoma was observed in this condition in our study. Second, most of the symptoms at diagnosis are not specific, but nausea and vomiting were more often observed among AC compromising the duodenum. Also, complications may suggest a more probable histology, bleeding from small bowel was more commonly observed in GIST and NET and not observed in any case of AC. On the other hand, intestinal perforations were observed exclusively in lymphomas. Third, location may strongly suggest histological subtype of a malignant SBT,[6] AC and GIST are much more commonly observed in the proximal SB, especially the duodenum, in contrast to NET and lymphomas that are more commonly observed in the ileum.

Several diagnostic tools are available for the study of patients with a suspected malignant tumor of the SB and

the best workup strategy should be individualized to each patient considering the clinical presentation and risk factors. In our series the most common diagnostic tool was CT and CT enteroclysis with elevated diagnostic yield (86% and 94% respectively). These diagnostic techniques offer a widely available, fast, and non-invasive and accurate diagnostic approach in many cases, and they should be considered especially in health care centers where more advanced diagnostic techniques are not available. Also, these imaging techniques allowed to establish the stage of the disease when a malignant SBT is diagnosed.[9] We observe a relatively low number of VCE applied for the diagnosis of malignant SBT in our study. After a negative EGD and colonoscopy, VCE is a useful noninvasive diagnostic tool for the diagnosis of SBT, particularly in the setting of a SB bleeding.[27] The diagnostic yield of VCE in our study is comparable to what has been reported by other series,[15,16] and although VCE retention may be a concern in these patients, we did not observe any cases of VCE retention in our study.

DAE was commonly applied as a diagnostic technique for SBT in our study. A major advantage over other diagnostic methods is the capability to obtain histological samples or manage complications such as bleeding. It also allows tattooing to facilitate surgical excision. Most of the DAEs performed in our study were done in the older years of the series, suggesting the replacement of invasive techniques by less invasive imaging techniques throughout the study period. Finally, PET galio-dotatate was used in several cases for the suspicion of a NET with very high diagnostic yield (96%). Future studies may address the design and validation of diagnosis algorithms for malignant SBT considering the wide variety of diagnostic tools available.

NETs are becoming the most common type of SBT.[2,6,28] In our study, NETs were the most frequent subtype of SBT and we observed along the study period a positive trend in their frequency contrasted with AC. As we illustrated in the clinical case (Fig. 1), these kind of SBT can be very challenging with a heterogeneous clinical presentation, sometimes life-threatening complications, they might be multifocal, and usually require a multidisciplinary approach for their diagnosis and treatment including gastroenterologist, digestive surgeons, oncologist, radiologist, pathologist, among others. Diagnostic tools available for NETs from the SB have diversified with the availability of PET gallium-dotatate. This nuclear medicine technique allows the assessment of the expression of somatostatin receptors, distinctive of NETs, with a highly accurate anatomical resolution obtained from the CT scan phase.[29] We evaluated 23 patients with this diagnostic technique, and 96% ($n = 22/23$) were correctly classified, illustrating its high diagnostic performance.

A less common subtype of malignant SBT are solid malignant tumor metastases. It has been described that a vast variety of solid tumors may present metastasis to the SB. In our study we observed an elevated proportion of SB metastasis, representing 16.4% of all observed malignant SBT. Presentation of metastatic disease was more commonly located in the ileum and colon and melanoma were the most common origins of this disease, with poor prognosis contrasted with other SBT types.

Defining the histological subtype of a malignant SBT is crucial in terms of the treatment but also to define the prognosis. It has been reported that some specific subtypes of SBT are related to a better prognosis, especially when they are confined to the SB.[30] We observed a better prognosis with a higher 5-year survival among GIST and NET contrasted to adenocarcinomas, lymphomas or metastasis. Considering the design of our study we did not assess features of each histological subtype related to a better prognosis. Most heterogeneous prognosis was observed among AC, and it has been reported that the staged of the disease at diagnosis, especially the lymph node involvement, are fundamental for defining the prognosis.[31]

Our study has some strengths and limitations. A well characterized series of malignant SBT with survival follow up was attained in Latin America. We conducted a retrospective, single center study of the malignant SBT observed at our university hospital, therefore our observations must be validated or contrasted with other regional or international experiences. Given the low frequency of these kinds of tumors, a low sample size was attained, this impeded us to perform more detailed subgroups analysis. Nevertheless, the sample size obtained is comparable to other series. Moreover, malignant SBT are a very heterogeneous group of pathologies, therefore future studies may focus on the characterization of a specific histologic subtype with a multicenter design. Finally, the retrospective design of our study impeded us to further assess and compare different diagnosis techniques and only the diagnostic yield was reported.

In conclusion, malignant SBT are rare conditions and NET are the most common histological subtype. Although the clinical presentation is not specific for any histological subtype, symptoms at diagnosis, location or complications may suggest a more probable diagnosis and may help to orientate the best diagnostic approach. Defining the histological subtypes through the variety of available diagnostic methods is essential considering the important differences observed in the prognosis.

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Conflicts of interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.gastrohep.2024.01.013.

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