Current Perspectives on Small Bowel Tumors: Overview of Prevalence, Clinical Manifestations, and Treatment Approaches

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ABSTRACT

Small bowel tumors (SBTs) constitute a rare yet increasingly recognized group of gastrointestinal neoplasms, accounting for less than 5% of all gastrointestinal cancers. Despite their infrequency, the incidence of SBTs has exhibited a notable upward trend, underscoring the importance of understanding these diverse and complex tumors. This review consolidates current knowledge on SBTs, encompassing epidemiology, risk factors, clinical manifestations, diagnostic advancements, and treatment modalities. Data from various sources are analyzed to present a comprehensive overview of the evolving landscape of SBTs. Our findings indicate that adenocarcinomas, carcinoid tumors, lymphomas, and gastrointestinal stromal tumors (GISTs) are the common SBTs. While adenocarcinoma and neuroendocrine tumors are the common types of SBTs in the West, GIST and lymphoma are more common in Asia. Common risk factors include genetic syndromes and inflammatory bowel diseases. There is variability in clinical presentations depending on the type of tumors. Although diagnostic challenges persist, advancements in imaging and endoscopic techniques have improved detection rates. Treatment strategies are evolving; surgical resection remains the mainstay for localized disease, augmented by systemic therapies and targeted agents for advanced stages. This review emphasizes the importance of early detection and individualized treatment approaches in improving outcomes for SBT patients. It addresses the need for ongoing research and innovation in managing these tumors.

Keywords: Small bowel tumors; adrenocarcinoma; gastrointestinal stromal tumors; neuroendocrine tumors; small bowel lymphoma (Siriraj Med J 2024; 76: 225-233)

INTRODUCTION

Small bowel tumors (SBT) are rare and have historically been responsible for less than 5% of gastrointestinal neoplasms. Nevertheless, the incidence of small intestinal cancer has increased over time and is associated with significant morbidity. Approximately 40 different histological types of tumors have been identified, and approximately two-thirds of those represent malignant diseases such as adenocarcinoma, carcinoid tumor, lymphoma, and gastrointestinal stromal tumor (GIST). This article aims to describe small bowel tumors, including epidemiology, risk factors, clinical manifestations, diagnosis, and treatment.

The rising incidence of small intestinal cancers and their varied histological presentation presents a complex challenge in clinical management and patient care, elevating the importance of understanding their epidemiology, risk factors, clinical manifestations, diagnosis, and treatment strategies. This surge reiterates the need for heightened awareness and advanced diagnostic approaches and calls for an in-depth exploration into the evolving dynamics

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of small bowel tumors. This article aims to address these critical aspects, offering a perspective on small bowel tumors to inform and guide clinical practice in this changing landscape.

Epidemiology and types of small bowel tumors

In the US, small bowel tumors account for 0.5% of all cancers. The estimated annual incidence of SBTs demonstrated 2.3 cases per 100,000 inhabitants and has increased over time.[1,2] The results from SEER-9 data, which includes 22,082 patients with small bowel cancers between 1976-2016, demonstrate that the incidence of small intestinal cancers more than doubled in the period from 12.1 to 27.9 per million. Most of this increase was neuroendocrine tumors, which increased from 3.7 to 14.6 per million.[3] In the UK, the overall small bowel tumor incidence rate also doubled from the early 1990s to 2014. The rate of new small bowel tumor cases has increased with an average of 1.9-2.4% per year over the last ten years.[4]

In symptomatic patients, small bowel tumors are important etiologies. It is the second leading cause in patients with obscure gastrointestinal (GI) bleeding (8.8%) and the fourth leading cause in those presenting with small bowel obstruction (5%).[5,6]

The prevalence of different histological subtypes varies across studies are presented in Fig 1. According to US data derived from the National Cancer Database from 1985-2005, the most common type of small bowel tumor is carcinoid tumor, which accounts for 37.4% of cases, followed by 36.9% for adenocarcinomas, 17.3% for lymphomas, and 8.4% for stromal tumors.[7] In the French cancer registry, adenocarcinoma is the most common histological type (38%), followed by neuroendocrine tumors (35%), lymphoma (15%), and sarcoma (12%).[8] Interestingly, GIST is more common in Asia than in the West and is the most common SBT in Thailand, accounting for 39.5% of cases, followed by adenocarcinoma (25.9%) and Lymphoma (24.3%).[9] Furthermore, a study from Taiwan also reports that GIST is common, accounting for 27.5% of small bowel tumors. The other common tumors are the same, including adenocarcinoma (26.1%) and lymphoma (29%).[10]

Risk factors of small bowel tumors

The risk factors for small bowel tumors are summarized in Table 1.[11-13]

Hereditary Mutations Linked to Small Bowel Tumors

1. Familial Adenomatous Polyposis (FAP): Characterized by a germline APC mutation, FAP significantly increases the risk of adenoma polyps growing and transforming into adenocarcinoma by the age of 40. The small intestine is notably the second most common site for adenocarcinoma in individuals with FAP, with a risk 330 times higher than the general population. Jagelman's study, which included 1255 FAP patients, found that 5% developed small bowel adenocarcinoma, predominantly in the duodenum.[2,12]

2. Lynch Syndrome: This hereditary defect in mismatch repair is known for increasing the risk of non-polyposis colorectal carcinoma. The relative risk for developing small bowel adenocarcinoma in those with Lynch syndrome, especially with the MLH1 mutation, ranges from 25 to 291 times that of the general population, though the lifetime risk remains low at about.[2,12]

3. Peutz-Jeghers Syndrome (PJS): Resulting from autosomal dominant inheritance involving a mutation

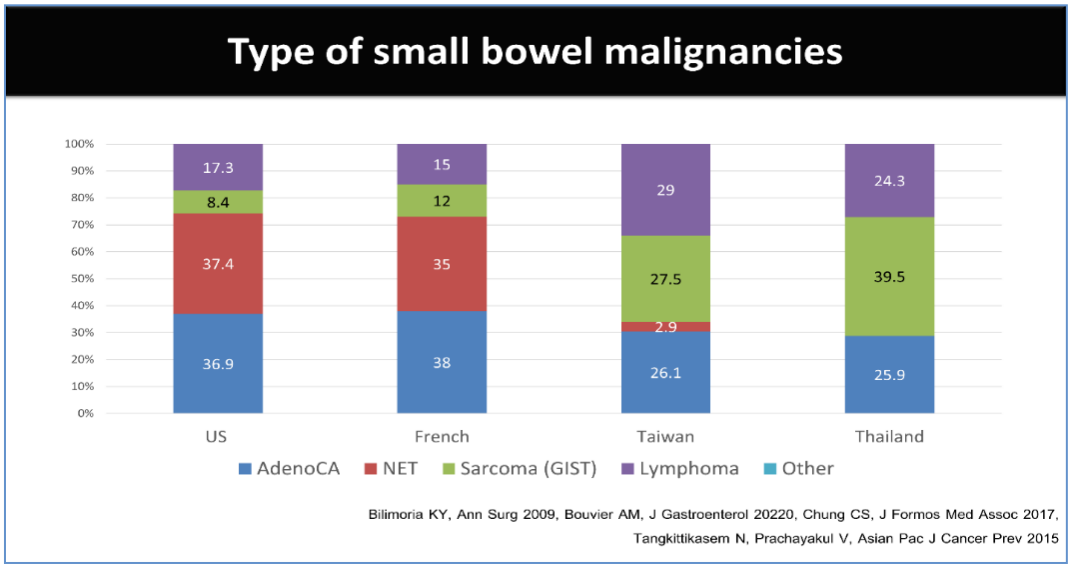

Fig 1. Types of small bowel tumors in different cohorts.

TABLE 1. Risk factors for small bowel tumors.

Type	Conditions	Risk
Adenocarcinoma	FAP	330x
	HNPCC (Lynch syndrome)	25-291x
	PJS	520x
	Crohn's disease	SIR 22x, prevalence 0.23%
		Most common at ileum
		0.2% after 10 y, 2.2% after 25 y
	Celiac disease	10-13x
NET	MEN1	5-10% of NET in GI tract
	NF-1	2-4x
Sarcoma(GIST)	NF-1	2-4x
Lymphoma	Celiac disease	

Abbreviations: FAP, familial adenomatous polyposis; GIST, gastrointestinal stromal tumor; HNPCC, hereditary nonpolyposis colorectal cancer; MEN1, multiple endocrine neoplasia syndrome type 1; NET, neuroendocrine tumor; NF-1, neurofibromatosis ype 1; PJS, Peutz-Jeghers Syndrome; SIR, standard incidence ratio

in the STK11 (SK11) gene, PJS increases the likelihood of individuals developing hamartomatous polyps within the gastrointestinal tract, with the relative risk of encountering small bowel tumors being 520 times greater than that observed in the general population.[2,12]

4. Multiple Endocrine Neoplasia Syndrome Type 1 (MEN1): Caused by an autosomal dominant defect in the MEN1 gene, this syndrome significantly predisposes individuals to neuroendocrine tumors (NETs) of the upper GI tract, representing 5-10% of all GI NETs.[12,14]

5. Neurofibromatosis Type 1 (NF1): An autosomal dominant defect in the NF1 gene, NF1 increases the risk of developing NET and sarcoma by 2-4 times in affected patients.[12,14]

6. Inflammatory Bowel Disease (Crohn's Disease): An autoimmune disorder causing widespread intestinal inflammation, most commonly in the ileum. Patients with Crohn's disease have a 17 to 41 times increased risk of developing small bowel adenocarcinoma, with a cumulative risk of 0.2% after 10 years and 2.2% after 25 years.[11,12]

Tumor characteristics

Adenocarcinomas are characterized by their proliferative nature, typically manifesting as mucosal lesions. These tumors measure an average of around 4 cm, with recorded sizes ranging from 1.4 to 14.5 cm. The duodenum is the most frequent location for these tumors, accounting for 56% of cases, with the jejunum and ileum following in prevalence.[7,9,15,16]

Neuroendocrine tumors present as subepithelial lesions and are generally smaller, averaging 1.6 cm, with a range between 1.0 to 2.5 cm. These tumors are notable for their potential to produce serotonin, leading to carcinoid syndrome. The ileum is their most common site, constituting over 70% of cases, with occurrences also noted in the duodenum and jejunum.[7,9,15,16]

Gastrointestinal Stromal Tumors (GISTs), the most common neoplasm of mesenchymal origin, are primarily caused by gain-of-function mutations in the oncogenic KIT or PDGFRA tyrosine kinase enzymes. GISTs emerge from the interstitial cells of Cajal within the muscular layers of the small intestine's wall, presenting as subepithelial lesions. Their median size lies between 6 and 7 cm, with a broader range observed from 1.5 to 18.5 cm. GISTs are unique in that they can develop anywhere along the small intestine.[7,9,15,16]

Lymphomas, while also subepithelial in nature, frequently involve the mucosal layer and can lead to lymphangiectasia. These tumors typically measure 6.7 cm in median size, spanning from 1.7 to 20 cm. The ileum is the most common site for lymphomas, hosting 30% of cases, followed by occurrences in the jejunum and duodenum.[7,9,15,16]

Clinical presentations

The overall average age of small bowel tumor patients is between 50 – 60 years old. The diagnosis of tumors is slightly more common in men than women, which accounts for of 52-58%.[9,10,17,18] Common symptoms include abdominal pain (39-63%), palpable mass (8-28%), overt bleeding (12-44%), occult bleeding (14-37%), and weight loss (25-44%). Diarrhea is not common and has only been reported in 3-20% of cases. Complications such as acute abdominal conditions, ileus, and obstruction, have also been reported from 10-20% of cases. Different tumors have different common presentations. Table 2 summarizes the clinical presentations of each tumor type.[9,17]

As shown in Table 2, in small bowel adenocarcinoma the most common presenting symptom is abdominal pain, which accounts for approximately 40-76% of patients, followed by overt bleeding at 21-24% and occult bleeding at 12-38%.[9,17]

In NET, the patients can be asymptomatic, have prolonged vague abdominal symptoms, or present with complications of local tumor progression or distant metastasis. Some patients develop carcinoid syndrome, which typically develops in those with distant metastasis, especially liver metastasis, which is reported in 24% of patients. Carcinoid syndrome manifests as flushing (94%), diarrhea (78%), generally voluminous watery, and abdominal cramps (50%). Furthermore, some patients are prone to have valvular heart disease, which occurs in 50% of patients which is mainly due to a deposit of fibrous tissue at the heart valve.[9,14,17]

GISTs often present with various symptoms, including GI bleeding, abdominal pain, palpable masses, and weight loss. The most common presentation is gastrointestinal bleeding, which has been reported in up to 80% of cases, higher than other types of small intestine tumors.[9,17]

Lymphoma often presents with abdominal pain in 60-84% of cases. Additionally, it can present with acute abdomen, which is observed in up to 40% of cases. Acute abdomen is caused by bowel obstruction and peritonitis, each accounting for 20% of cases.[9,17]

In summary, all types of small bowel tumors present with abdominal pain 40-70% except for NET, which accounts for 27%. A palpable mass is mostly present in patients with GIST, accounting for 40-48%. Overt and occult bleeding is found predominantly in patients with GIST, accounting for 25-88%. Gut obstruction is mostly present in patients with adenocarcinoma and lymphoma.

Diagnosis

Computed tomography

In cases of adenocarcinoma, CT scan results often show irregular thickening of the wall in a small segment. Additionally, it may present as either an ulcerated lesion or a ring-shaped "apple core" lesion with a narrowing of the passage. After contrast administration, CT scans usually show heterogeneous density lesions and moderate enhancement, and they may contain vascular invasion or

TABLE 2. Clinical presentations separated by each tumor type.

	Adenocarcinoma	NET	Sarcoma (GIST)	Lymphoma
Age (mean, years)	63.2		54.4	55.6
Male	54		44	62
Presenting duration (median, month)	2 (3-14)		6 (1-120)	3 (1-36)
Abdominal pain	40-76%	27%	34-70%	60-84%
Palpable mass	0-28%	8%	11-56%	16-28%
Overt bleeding	21-24%	5%	40-48%	15-32%
Occult bleeding/anemia	12-38%	16%	25-88%	11-16%
Diarrhea	12%	38%	8%	20%
Acute abdomen	19-33%	8%	11-28%	40-44%
Obstruction	29%		1.4%	24%
Peritonitis	4%		9.6%	20%
Weight loss	28-77%	22%	23-32%	58-76%

Abbreviations: GIST, gastrointestinal stromal tumor; NET, neuroendocrine tumor

metastatic features, such as lymphadenopathy, peritoneal or distant metastasis.[19]

A typical CT finding in neuroendocrine tumors, formerly known as carcinoids, illustrates a single enhanced mass within the mucosa of the small intestine. Unlike adenocarcinoma, it is uncommon for NET to be ulcerated. Following contrast administration, CT scans commonly show arterial enhancement with washout in the portovenous phase. This pattern is similar to a mural mass with contrast enhancement extending into the nearby mesentery, resulting in the formation of a soft tissue density mass during later stages. If the mass involves mesentery, It may feature calcifications, often with spiky borders due to the desmoplastic reaction. This can induce fibrotic responses in nearby tissues, resulting in bowel obstruction, ischemia, or vascular compromise. NET typically produces metastasis to lymph nodes and the liver, which may lead to carcinoid syndrome.[19] The CT findings of NET are shown in Fig 2.

The CT characteristics of GISTs may differ based on tumor size and aggressiveness. Typically, they appear

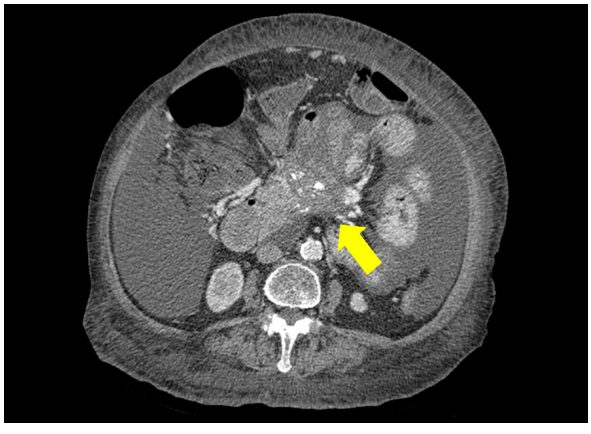

Fig 2. These features are typical of neuroendocrine tumors. A neuroendocrine tumor is characterized by a spiculated mass at the root of the mesentery with calcification and congestion of surrounding mesenteric vessels, which enhances in the post-contrast phase.

as large, prominently enhancing tumors visible on post-contrast imaging, although they may demonstrate hypo-enhancement and be situated within the lumen. GISTs typically exhibit significant enhancement during the arterial phase, followed by a decrease in enhancement during the venous phase. GISTs might display varied features because of necrosis or bleeding within the tumor and could lead to ulceration, formation of cavities, and connection with nearby structures through fistulas. Moreover, GISTs can induce obstruction in the small bowel either through direct pressure exerted by the mass or by causing the intestine to bend and compress. The bulky lymphadenopathy is uncommon in GISTs and is often found in other diagnoses rather than GISTs.[19] The CT findings of GISTs are shown in Fig 3.

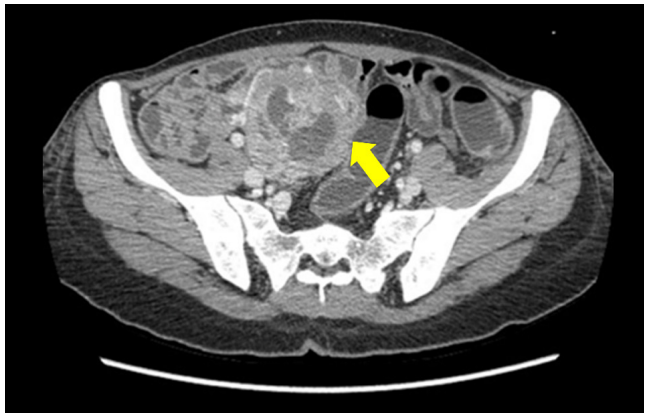

Fig 3. Computed topography in a 55-year-old female with gastrointestinal stromal tumor. The post-contrast phase of the CT scan reveals a large lobulated mass with internal necrosis, measuring 8.5x7.0 cm, located in the jejunoileal mesentery, abutting the walls of the jejunum and ileum.

The radiological presentation of lymphoma can vary significantly. In the initial stages, lymphoma might manifest as mucosal expansions resembling plaques. However, as the disease progresses, infiltrative lesions can lead to complete thickening of the wall and may even result in mucosal ulcers. Lymphomas are usually soft and preserve the lumen of the small intestine. Additionally, there may be dilation of the lumen (referred to as aneurysmal dilatation). Unlike adenocarcinoma, lymphomas can exhibit distinct CT scan characteristics, including prominent, uniform wall thickening (> 2 cm), eccentric stenosis, and concurrent lymph node enlargement. Additionally, they exhibit involvement at multiple sites compared to adenocarcinoma, often accompanied by distant lymph node enlargement and enlargement of the spleen. This can help distinguish lymphoma from other small bowel neoplasms.

In mesentery involvement, lymphoma does not incur vascular invasion compared with other types of small bowel tumors.[19]

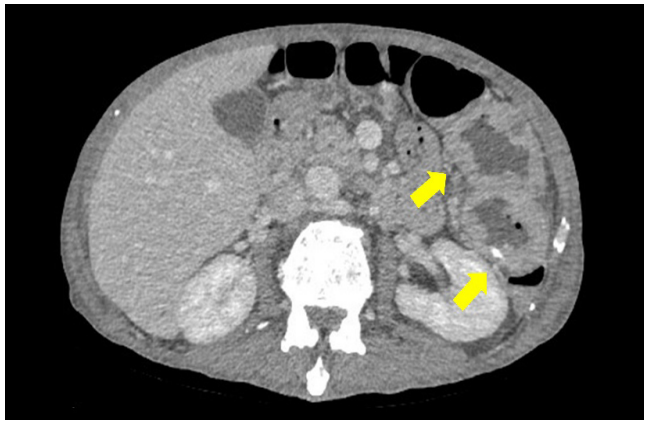

Fig 4. Small bowel lymphoma is demonstrated by marked asymmetrical bowel wall thickening with aneurysmal dilatation. However, it preserves the lumen of the intestine. Additionally, there are multiple lymphadenopathy. These features are typical of lymphoma.

Video capsule endoscopy

Video capsule endoscopy (VCE) can detect small bowel tumors in patients who have not had a tumor detected despite having undergone many investigations.[20,21] Fig 5 shows VCE findings of GIST. However, based on meta-analysis results comparing VCE to other diagnostic tools including push enteroscopy, small bowel follow through, and colonoscopy with ileoscopy, the VCE miss detection of neoplasms in 18.9% of all cases, which is higher than the miss rates of other lesions (4.7-8%).[22]

This is possible because of the unifocal nature of the tumor, and it is difficult to differentiate between a submucosal mass and an innocent bulge—a smooth protrusion of normal mucosa caused by loop bending or the pressure of an adjacent loop.[23] Compute tomography enterography can detect missed tumors by VCE[24], so the 2017 ASGE guidelines recommend performing CT enterography in patients with potential small bowel bleeding but negative VCE, or in patients suspected of having small bowel tumors.[25]

The endoscopic finding as described, Ulcerative masses were the most common morphological feature observed in lymphoma and adenocarcinoma cases, present in half of lymphoma patients (50%) and more than two-thirds of those with adenocarcinoma (72.2%). Additionally, a mucosal surface characterized by hyperemic nodularity was seen in 35% of lymphoma cases and 11.1% of adenocarcinoma cases. In patients with GIST, subepithelial tumors were the prevailing finding, occurring in nearly three-fifths of the cases (57.9%), while ulcerative masses were identified in over one-third of the cases (36.8%).[10]

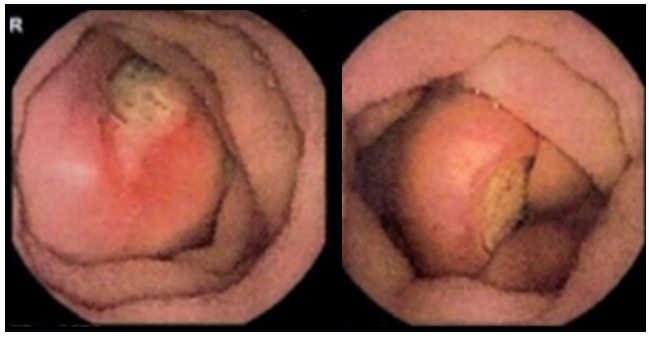

Fig 5. Imaging from video capsule endoscopy in a 55-year-old female with jejunal gastrointestinal stromal tumor shows an ulcerated subepithelial mass in the jejunum. The presence of an ulcerative lesion can be observed in over 30% of cases.

Radionuclide scan

Somatostatin receptor-based imaging can be useful for identifying NET. The first widely utilized functional imaging modality is somatostatin receptor scintigraphy or Octreoscan, which adopts 111 Indium pentetreotide uptake to visualize NETs. Somatostatin-receptor for functional PET imaging, using gallium Ga-68 DOTATATE (Ga-68 DOTATATE), gallium Ga-68 DOTATOC (Ga-68 DOTATOC), or gallium Ga-68 DOTANOC are approved in the US for usage in conjunction with integrated PET/CT for diagnostic imaging of NETs. These PET modalities can more sensitively detect NETs and have the potential to provide improved spatial resolution.[26]

Tumor markers

Tumor markers are helpful in the diagnosis of NET. The tumor is able to secrete both nonhormonal and hormonal tumor markers. 5-Hydroxyindoleacetic acid (5-HIAA) serves as a serotonin byproduct and is utilized as an indicator for serotonin levels. Conducting a 24-hour urine collection for 5-HIAA can confirm the presence of carcinoid syndrome. The test exhibits an overall sensitivity of 70% and specificity of 90% for diagnosing carcinoid syndrome. However, the accuracy of the results can be influenced by various drugs and food items, such as avocados, pineapples, bananas, kiwi fruit, walnuts, and pecans, which have been found to elevate urinary 5-HIAA levels. It's recommended to avoid consuming these items when undergoing testing for accurate results.[26-28]

Chromogranin A (CgA) is an acid glycoprotein with 439 amino acids present in most neuroendocrine cells' secretory dense core granules. It is acknowledged as a prevalent serum marker due to its secretion alongside the amines and peptides found in neurosecretory granules within tumors. Its sensitivity for accurately identifying the progression of well-differentiated gastroenteropancreatic NETs confirmed by imaging is modest, at 60%, while its specificity remains high at 90%.[26-28] Nevertheless, false-positive elevation of chromogranin can occur in certain conditions, such as chronic kidney disease, Parkinson's disease, untreated hypertension, pregnancy, steroid treatment or glucocorticoid excess, chronic atrophic gastritis or treatment with acid suppressant medications, especially Proton-pump inhibitors.[26,27]

Treatment

Adenocarcinoma

Surgery - Localized invasive adenocarcinomas of the small bowel can be best optimized by surgical resection. Furthermore, surgery can be performed in patients presenting with obstructive symptoms for palliative surgery.

Medical treatment – In metastatic disease, systemic chemotherapy is the mainstay of treatment in these settings. Several drugs have shown effectiveness in treating metastatic small bowel adenocarcinomas, such

as Capecitabine, 5-fluorouracil, Cisplatin, 5-fluorouracil, Gemcitabine, and Irinotecan, with varying response rates. An oxaliplatin-based chemotherapy regimen is considered to be a first-line regimen. The role of targeted therapy in expressing both VEGF with 91% and EGFR with 71% is highly illustrated in small bowel adenocarcinomas and KRAS mutations. Patients with genomic expression are considered for targeted agents such as bevacizumab, regorafenib, or anti-EGFR monoclonal antibodies.[29]

Nowaday, Immune checkpoint inhibitors, such as Pembrolizumab, which is a programmed death receptor 1 inhibitor (PD-1 inhibitor), play a role in the treatment of some metastatic small bowel adenocarcinomas with deficient mismatch repair (dMMR). Some studies have demonstrated the benefits of Pembrolizumab in the treatment of small bowel adenocarcinoma. In the United States, Pembrolizumab is approved for the treatment of various advanced solid tumors, including small bowel adenocarcinomas that exhibit microsatellite instability-high (MSI-H) or dMMR and have progressed after prior treatment. This approval represents a significant milestone as it is the first approval of a tissue-agnostic anticancer treatment when no satisfactory alternative treatment options are available.[30,31]

Neuroendocrine tumors

Surgery – Resection of the tumor is pragmatic for locoregional and resection of liver metastasis to improve overall survival.[14,26]

Medical treatment – In systemic therapy, somatostatin analogs are beneficial due to the high expression of somatostatin receptors in NETs. Activation of these receptors by synthetic somatostatin peptide mimetics helps inhibit cell proliferation pathways and decrease hormone secretion. Numerous clinical trials have shown that somatostatin analogs are highly effective as initial medical treatment, preventing tumor progression and managing symptoms of carcinoid syndrome in advanced gastroenteropancreatic NETs.[14,26] Everolimus actions by blocking the mammalian target of rapamycin (mTOR) protein, which activates a kinase downstream of the phosphoinositide 3-kinase/Akt pathway, supporting tumor cell survival, angiogenesis, and growth. Everolimus may play a role in additional treatments of small bowel neuroendocrine tumors.[14,26]

Gastrointesinal stromal tumor

Surgical resection is favorable for potentially resectable tumors.

Medical treatment – The treatment of Gastrointestinal Stromal Tumors (GISTs) underwent a significant transformation when it was discovered that mutations in the KIT or PDGFRA genes could activate the growth of these cancer cells. This discovery led to the development of effective systemic therapies in the form of small molecule inhibitors that target these receptor tyrosine kinases. Imatinib is an effective inhibitor when there is abnormal tyrosine kinase activity due to molecular rearrangements.

TABLE 3. Summary of treatment options for small bowel tumors.

	Surgery	Medical treatment
Adenocarcinoma	Resection Hepatic resection in liver metastasis	Oxaliplatin-containing regimen Fluoropyrimdine-base chemoradiotherapy VEGF-A inhibitor: bevacizumab EGFR inhibitor: cetuximab Immune checkpoint inhibitor
NET	Resection Radioembolization in liver metastasis	Somatostatin analogs mTOR inhibitor: everolimus, VEGF-A inhibitor: bevacizumab Interferon Cytotoxic therapy: poor response
Sarcoma (GIST)	Resection	Tyrosine kinase inhibitor
Lymphoma	Resection in cases with complications (obstruction/perforation)	Standard CMT for lymphoma

Abbreviations: GIST, gastrointestinal stromal tumor; NET, neuroendocrine tumor

Subsequently, it became clear that targeted therapy with imatinib provided remarkable, fast, and long-lasting clinical benefits in GISTs.

There is a trend in the use of TKIs for GISTs that do not respond well to initial treatment, particularly in advanced gastrointestinal stromal tumor patients. This includes medications like Sunitinib, which is approved in the United States for treating advanced GISTs that do not respond adequately to imatinib or are intolerant to it.[32-34]

Regorafenib, a multikinase inhibitor with activity against KIT, PDGFR, VEGFR, and others), is indicated for patients who do not respond to imatinib and sunitinib. Furthermore, Ripretinib is also approved by the US Food and Drug Administration (FDA) for advanced GIST patients who have previously received three or more TKIs, including imatinib.[32,35] However, some GIST patients, particularly those without KIT or PDGFRA mutations, do not experience significant benefits from initial TKI treatment with imatinib. Therefore, further research will be required in the future.

CONCLUSION

This review highlights the increasing incidence and complex heterogeneity of small bowel tumors (SBTs), which pose significant diagnostic and therapeutic challenges. Future research should focus on comprehensive epidemiological data to further understand the global burden of SBTs and the impact of environmental and genetic factors on their incidence. Furthermore, the development of biomarkers for early detection, longitudinal studies to elucidate the long-term efficacy of new treatment modalities, and the implementation of precision oncology to tailor therapies based on individual genetic profiles are warranted.

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