SMALL INTESTINAL TUMOURS: AN OVERVIEW ON CLASSIFICATION, DIAGNOSIS, AND TREATMENT

Chiara Notaristefano, *Pier Alberto Testoni

Division of Gastroenterology and Gastrointestinal Endoscopy, Vita-Salute San Raffaele University – Scientific Institute San Raffaele, Milan, Italy
**Correspondence to testoni.pieralberto@hsr.it*

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ABSTRACT

The small intestinal neoplasia group includes different types of lesions and are a relatively rare event, accounting for only 3-6% of all gastrointestinal (GI) neoplasms and 1-3% of all GI malignancies. These lesions can be classified as epithelial and mesenchymal, either benign or malignant. Mesenchymal tumours include stromal tumours (GIST) and other neoplasms that might arise from soft tissue throughout the rest of the body (lipomas, leiomyomas and leiomyosarcomas, fibromas, desmoid tumours, and schwannomas). Other lesions occurring in the small bowel are carcinoids, lymphomas, and melanomas. To date, carcinoids and GIST are reported as the most frequent malignant lesions occurring in the small bowel. Factors that predispose to the development of malignant lesions are different, and they may be hereditary (Peutz-Jeghers syndrome, familial adenomatous polyposis, hereditary non-polyposis colorectal cancer, neuroendocrine neoplasia Type 1, von Hippel-Lindau disease, and neurofibromatosis Type 1), acquired (sporadic colorectal cancer and small intestine adenomas, coeliac disease, Crohn's disease), or environmental (diet, tobacco, and obesity). Small bowel tumours present with different and sometimes nonspecific symptoms, and a prompt diagnosis is not always so easily performed. Diagnostic tools, that may be both radiological and endoscopic, possess specificity and sensitivity, as well as different roles depending on the type of lesion. Treatment of these lesions may be different and, in recent years, new therapies have enabled an improvement in life expectancy.

Keywords: Small intestinal neoplasia, hereditary syndromes, adenoma, adenocarcinoma, gastrointestinal stromal tumours, neuroendocrine tumours, melanoma, lymphoma.

INTRODUCTION

The small intestinal neoplasia group includes different types of lesions, either benign or malignant, accounting for only 3-6% of gastrointestinal (GI) neoplasms and 1-3% of all GI malignancies;[1-2] however, the incidence of small bowel primary malignant tumours is currently increasing year by year. Factors that predispose to the development of malignant lesions are different, and they may be hereditary, acquired, or environmental. Hereditary factors include: familial adenomatous polyposis (FAP), Peutz-Jeghers syndrome (PJS), hereditary non-polyposis colorectal cancer (HNPCC), multiple endocrine neoplasia Type 1 (MEN 1), von Hippel-Lindau (VHL) disease, and neurofibromatosis Type 1 (NF1). Acquired conditions associated with an increased risk of small bowel tumours are sporadic colorectal cancer and small intestinal adenomas, coeliac disease, and Crohn's disease. Environmental factors include diet, tobacco, and obesity; greater consumption of red meat, salt-cured and smoked foods, alcohol, and tobacco, and increased body mass index have been hypothesised to be predisposing factors for small intestinal cancer, but studies are still controversial.[3-9]

BENIGN LESIONS

There are different hereditary syndromes related to small bowel lesions:

- FAP: this autosomal dominant condition is caused by the mutation of *APC* gene on chromosome 5. 50% of individuals with FAP present adenomatous polyps of the duodenum, commonly found in the second and third portions. Duodenal adenocarcinoma is the second most common malignancy in FAP or attenuated FAP, with a lifetime risk of approximately 4–12%.

- PJS: is an autosomal dominant condition associated with a mutation of the *STK11* gene. The syndrome is characterised by the presence of small intestinal hamartomatous polyps, melanin spots on lips and buccal mucosa, and increased risk of developing different malignancies (breast, colon, pancreas, stomach, ovarian, lung, testicular, oesophagus). In these patients the cancer lifetime risk is about 13%.[10]

- HNPCC: Lynch syndrome depends on a germline mutation in a class of genes involved in DNA mismatch repair, including *hMSH2*, *hMLH1*, *hMSH6*, and *hPMS2*. Patients have an increased risk of developing different malignancies (colon, endometrium, stomach, ovarian, hepatobiliary tract, urinary tract, pancreas), with an overall cancer lifetime risk of about 1-4%.[11]

- Other familial syndromes are MEN1, VHL disease, and NF1, predisposing to increased risk of carcinoids.[12]

Adenomas

There are different types of adenomas: villous, tubular, and those arising from Brunner's gland. The first one occurs mostly in the duodenum (prevalence 0.4% during oesophagogastroduodenoscopy)[13,14] and has an increased potential for malignant transformation.[15,16] Adenomas arising around the ampulla of Vater represent about 10% of all duodenal adenomas, with a reported autopsy prevalence of 0.04–0.12% and a better prognosis compared with the other malignant ampullary neoplasms involving the pancreaticobiliary ductal system.[17] Ampullomas can be removed by endoscopic resection or surgery, when endoscopic removal is unfeasible (lesions already invasive). Adenomas located distal to the papilla are rare and most of them remain clinically silent until the advanced stages and have been discovered incidentally. Some of them occur in a familial polyposis setting: recent studies have revealed that up to 90% of patients with this hereditary syndrome have polyps in the jejunum and ileum.[18,19] Adenomas may present with anaemia, bleeding, obstruction, or, in case of ampulloma, with obstructive jaundice or pancreatitis.[20,21]

Leiomyomas, Lipomas, and Other

Leiomyomas are mesenchymal tumours arising from smooth muscle layer, usually small (<1 cm), well circumscribed, and submucosal. They are discovered incidentally and consist of bland spindle cells with low or moderate cellularity, mild or no cytological atypia, and rare mitoses.[2] Lipomas usually appear as submucosal, capsulated, yellowish masses protruding into the lumen, often single, and represent about 2.5% of non-malignant tumours of the intestinal tract.[21] Sometimes lesions are ulcerated. Lipomas are generally asymptomatic but melena, bloody stools, abdominal pain, or intestinal obstruction - secondary to intussusception - may occur.[22] Other rare benign lesions are the lymphangioma and haemangioma. Lymphangioma is a rare intra-abdominal tumour, usually identified in childhood; most intra-peritoneal lesions are found in the small bowel mesentery. Haemangiomas are rare lesions that usually present with bleeding.[23]

MALIGNANT LESIONS

The most frequent types of primary small bowel malignancies are adenocarcinoma, stromal tumours, sarcoma, carcinoid tumours, and lymphoma.[24] The incidence of all malignant lesions of small intestine ranges from 0.5-1.5/100,000 in males and 0.2-1.0/100,000 in females.[25] In general, the incidence of small intestine cancer is on the rise but, while in the 1980s the most frequent neoplasms were adenocarcinomas, between 1985 and 2005 the incidence of carcinoid tumours has increased significantly from 27.5-44.3%, while that of adenocarcinomas is slightly decreased from 42.1-32.6%. The proportion of patients with mesenchymal tumours or lymphoma remained almost unchanged. Also, the location of these tumours over these 20 years has changed. In fact, duodenal tumours increased (carcinoid 10.9–22.3%; adenocarcinoma 49.1–58.8%; stromal tumours 10.4–17.2%; lymphoma 10.2–21.7%; $p<0.0001$) with a concomitant decrease in jejunal and ileal malignancies.[26]

Adenocarcinoma

Adenocarcinoma represents about 30-40% of the cancers observed in the small intestine,[27] with the highest incidence in the duodenum, probably

reflecting the higher concentration of bile that increases the risk of adenocarcinoma.[28] The peak of presentation is at 58-70 years and is slightly superior in men than women (58% versus 42%).[24] Risk factors for developing adenocarcinomas are Crohn's disease and, in <10% of cases, inherited syndromes such as HNPCC and FAP.[29-31] The clinical presentation of adenocarcinoma might be non-specific, most frequently: abdominal pain (43%), nausea and vomiting (16%), anaemia (15%), overt GI bleeding (7%), jaundice (6%), and weight loss (3%). In about 10% of cases the neoplasia is asymptomatic.[32]

Neuroendocrine Tumours (NETs)

NETs arise from the cells of the neuroendocrine system[33-35] and produce peptides, neuroamines, and vasoactive substances which lead to many clinical syndromes. 'Carcinoid tumours' originate from enterochromaffin cells of the aerodigestive tract and represent the majority of NETs; they are well differentiated lesions representing about 40% of small intestinal malignancies.[36] Lesions are classified into three groups according to their embryological origin, staining characteristics, and clinical behaviour: foregut (bronchial, gastric, and duodenal), midgut (jejunal, ileal, and caecal), and hindgut (distal colon and rectal) tumours.[36] NETs originate most commonly in the distal ileum, within 60 cm of ileocaecal valve,[37] and about 25% have synchronous lesions.[38] Symptoms are related to the enlarging of the lesion or secretion of vasoactive amines. The most common manifestations are vague abdominal pain (40% of cases)[30] and intermittent bowel obstruction, due to a mechanical obstruction or a desmoplastic reaction by mesenteric lymph-nodes, which, in turn, may lead also to mesenteric ischaemia.[38] Most NETS are indolent but some, even the smaller ones, can metastasise, mainly in the liver, mesentery, and peritoneum, producing the well-known 'carcinoid syndrome', characterised by cutaneous flushing, diarrhoea, bronchospasm, and right heart valvular disease, due to serotonin and other vasoactive substances (histamine, dopamine, hydroxytryptophan), tachykinins (kallikrein and substance P), and prostaglandins that are produced by liver metastases and released into the bloodstream without being inactivated.[39]

Gastrointestinal Stromal Tumours (GISTs)

GISTs arise either from the mesenchymal (non-epithelial) tissue of the GI tract (in the small intestine in 30-35% of cases[40]) or, rarely, from other intra-abdominal tissues.[41] These lesions represent 1-3% of all GI malignancies[42] and affect people between 40-60 years old, with a similar frequency in men and women.[43] In GIST patients, associated malignant lesions have been reported in 2.95% up to 43% of cases.[44,45] GISTs probably originate from, or have a stem cell in common with, the interstitial cell of Cajal.[46,47] GISTs may have different origins (myogenic, neural, bidirectional, or 'null phenotype') and differ from other lesions (such as leiomyomas) for the expression of the CD117 antigen,[48,49] part of the *KIT* transmembrane receptor tyrosine kinase (RTK) produced by the *KIT* proto-oncogene. The mutation of this proto-oncogene enables oncogenic signals in the cell in >80% of GISTs. However, some GISTs are *KIT* negative but may express a mutation in another RTK, the platelet-derived growth factor receptor alpha.[50,51]

Usually GISTs are sporadic lesions and do not have specific risk factors. GISTs may arise in the setting of specific tumour syndromes: familial GISTs (high-risk for developing one or more gastric or small bowel GISTs before 18-years of age); Carney's triad (association between GISTs, paraganglioma, and pulmonary chondroma occurring in young people of both sexes); Carney-Stratakis syndrome; NF1; or Recklinghausen's NF.[52] These lesions may be classified as spindle (70%), epithelioid (20%), and mixed type (10%),[53] and generally appear to arise from the muscularis propria of the bowel wall, with an intraluminal or extraluminal growth, with or without superficial ulcerations or extensive necrosis.[54] Patients may present with: bleeding into the bowel or abdominal cavity, anaemia, and abdominal pain, dyspepsia, nausea or vomiting, constipation or diarrhoea, frequent urination, and fatigue or a palpable mass. In about 25% of cases, GISTs are discovered incidentally during diagnostic imaging or surgery performed for other problems, and about 5% of GISTs are found at autopsy.[55-57]

Lymphoma

Lymphoma in the small intestine may be defined as primary when there are no peripheral or mediastinal lymphadenopathies, normal white and differential blood cell count, and no evidence of liver or spleen involvement, or it can be a component of systemic disease with GI involvement.[58] The primary intestinal lymphoma is the most common extranodal form, arising from the lymphoid aggregates in the submucosal layer; the ileum is the most common location. Risk factors for developing

small intestine lymphomas are coeliac disease, Crohn's disease, AIDS, Epstein-Barr virus infection, immunoproliferative small intestinal diseases (IPSID), long-term immunosuppressive therapy, and radiation and/or chemotherapy.[59,60] Lymphomas of the small intestine are generally divided into IPSID lymphomas, enteropathy-associated T cell lymphomas (EATLs), and other 'Western'-type non-IPSID lymphomas (e.g. diffuse large B cell lymphoma, mantle cell lymphoma, follicular lymphoma). Recently there was an increase in incidence of EATL in the US, maybe for the increasing seroprevalence of coeliac disease and better recognition of rare type of T cell lymphoma.[60] Principal symptoms in lymphomas are fever, weight loss, and drenching night sweats.[61]

Melanoma

Melanoma in the small intestine may be primary or a metastasis from a cutaneous primary lesion; sometimes it is impossible to establish whether the lesion is primary or secondary.[62] Primary intestinal melanoma is a rare carcinoma upon which different hypotheses are made of its origin, including that it is a metastasis of unknown origin.[62-68] Primary intestinal melanomas tend to be more aggressive and have a worse prognosis than cutaneous ones.[62] The neoplasia is more frequent in men, and occurs mainly in the ileum.[69,70] Metastatic intestinal melanomas are usually found in patients with a history of cutaneous, anal, or ocular melanoma; the frequency ranges from 35-70%[71-73] and may develop, either after some years from primary melanoma excision, or just 6 months after detection of a primary lesion.[67,75,76] Usually a metastatic melanoma presents with multiple polypoid masses that may be pigmented or not.[74,75] Symptoms are usually abdominal pain, intestinal obstruction, constipation, haematemesis, melena, anaemia, fatigue, weight loss, palpable abdominal mass, intestinal intussusception, and rarely, perforation.[74,77]

DIAGNOSIS

Small bowel tumours present with different and sometimes nonspecific symptoms, and a prompt diagnosis is not always so easily performed. The optimal diagnostic technique varies depending on the site and size of the tumour. In the past, the two most used diagnostic techniques were barium small bowel follow-through (SBFT) and enteroclysis; the former had a sensitivity of 30-44%[78] and was gradually abandoned for more sensitive technologies.[79] Enteroclysis utilises two different contrast techniques, thus enhancing the sensitivity up to 90%, compared to SBFT.[80] This technique can miss small lesions or lesions having continuous mucosal lining with adjacent mucosa, and causes discomfort to patients,[2] so it is now used less.

Computed tomography (CT) with the new technologies allows imaging of the entire abdomen in thin slices with lower artefacts than a conventional CT scan. Recently, CT enteroclysis plus enterography has been introduced; it permits an enhanced CT scanning and image processing after distension of the small bowel loops by using an orally administered high-volume contrast medium.[2] The combination of oral and intravenous enhancement permits a better recognition of hypervascular masses, as carcinoids or GISTs,[81,82] and enables an extraluminal visualisation, allowing a better tumour staging.[79] In a recent study, CT enterography showed an 84.7% sensitivity and 96.9% specificity in detecting tumours.[83] CT enterography has some limitations such as incomplete bowel distention, that can limit the interpretation of images in some patients because of a delayed contrast ingestion or scanning,[84] and radiation exposure.[85,86]

Magnetic resonance enterography obtains imaging similar to CT without radiation, but has some important limitations, such as higher costs, more variable image quality, and lower spatial resolution compared to CT scan,[87,88] although a recent study has shown a 95% overall diagnostic accuracy for small intestinal tumours.[89] Moreover, the technique is not always available in clinical practice.

Positron emission tomography (PET) with fluorodeoxyglucose may play a role in detecting adenocarcinomas, sarcomas, and some lymphomas, but it is not so useful for carcinoids. Recently, novel PET modalities with ^{18}F-dihydroxy-phenylalanine,[18] ^{11}C-5-hydroxytryptophan,[11] and ^{68}Ga-DOTATOC have been developed and seem to offer higher spatial resolution than conventional somatostatin-receptor scintigraphy, with improved sensitivity for detecting small lesions.[90,91]

Octreoscan™ uses a radiolabelled form of somatostatin to detect NET metastases outside the abdominopelvic region. It is also able to offer functional information regarding somatostatin receptor expression in order to predict the response to treatment.[92] Recent advances in digestive endoscopy allow an accurate diagnosis of lesions in the small intestine and, with the exclusion of capsule

endoscopy, attainment of a histology specimen or to perform therapeutic procedures. Upper GI endoscopy and colonoscopy permit identification and management of lesions proximal to ligament of Treitz or in distal ileum and rectum.[2]

Push enteroscopy (PE) enables detection of lesions until proximal jejunum because push video enteroscopes are 200-250 cm long (depending on type and manufacturer).[2,93] PE is easy to perform, the overtube is reusable, and there is no need to set up a special system (e.g. a pump control system), so procedure-related costs are low.[94] Complications occur in <1% of cases and are duodenal mucosal stripping or perforation, pancreatitis, or Mallory–Weiss tear.[93]

Double balloon enteroscopy (DBE) was introduced in 2004 and was the first therapeutic deep enteroscopy. DBE may be performed by the oral (antegrade) or aboral (retrograde) route, under different sedation on the basis of the approach. Usually it is a 'targeted procedure' in which lesions have been previously identified on prior capsule endoscopy or radiological imaging. The diagnostic yield of DBE ranges from 43-80%.[95-97] Like PE, DBE is associated to some complications (perforations, bleeding, and pancreatitis) ranging from 0.8% for diagnostic, to 4% for therapeutic procedures. Pancreatitis was reported in 0.2-0.3% of cases but its incidence appears to have decreased over time.[95] The German double-balloon registry reported a 0.005% mortality rate related to post-polypectomy perforation and subsequent post-surgical pancreatitis.[98]

Single balloon enteroscopy (SBE), introduced in 2007, has one balloon at the distal end of the overtube. The success rate of total enteroscopy ranges from 15-25%; the diagnostic yield of SBE ranges from 47-60%. The complication rate of 1% includes perforation and pancreatitis.[96]

Spiral enteroscopy (SE) by the Endo-Ease Discovery is performed using a spiral overtube made of polyvinyl chloride. The main difference between balloon-assisted enteroscopy and SE is that the latter uses a continuous pleating of the small bowel by a clockwise rotation of the overtube, rather than the push-pull technique.[79,93] Its diagnostic role has not yet been established and additional studies are necessary.[79]

Capsule endoscopy (CE) consents to obtain a direct visualisation of mucosa of the entire intestinal lumen, and is safe and less invasive than other endoscopic procedures, with a very low risk of retention. It has a high detection rate (65.8%) for small bowel tumours, compared with other radiological techniques,[99] determines the extension of tumour involvement, and assesses the response to treatment.[100] CE has some limitations too; the exact location of the lesion is difficult to establish and there are false positive or false negative findings because the capsule flows into the small intestine in absence of endoluminal insufflation. Small bowel preparation, peristalsis, or incomplete examination may also affect the diagnostic accuracy.[79]

Endoscopic ultrasonography (EUS) is the most accurate technique for distinguishing leiomyomas from other submucosal lesions because the leiomyoma arises from the muscularis propria (the fourth hypoechoic layer of the intestinal wall). EUS is able to differentiate benign from malignant lesions; features of malignancy are the disruption of tissue layers, the changes in vascularisation and tissue stiffness, and the presence of enlarged lymph nodes. EUS features have a positive predictive value of 100% for a malignant or borderline GIST. The diagnosis of GIST may be further improved by the combined use of cytologic analysis and immunohistochemistry for *KIT* mutations by EUS-guided fine needle aspiration.

TREATMENT

Adenocarcinoma

Currently, the only option available to treat small bowel adenocarcinoma with a curative intent is surgical resection. The type of resection differs, according to the location of the tumour: jejunal and ileal lesions require wide resection, removing both the mesentery and lymphatics up to the superior mesenteric vessels.[101] If tumour is located near the ileocaecal valve, the ileocolic or right colon resection is recommended. In duodenal tumours early lesion can be resected by endoscopy or push enteroscopy,[102] while surgical laparotomy or laparoscopy is required for endoscopically unreachable lesions. Lesions of proximal duodenum require pancreaticoduodenectomy, while more distant lesions can be amenable to pancreas sparing duodenectomy.[103] Relapse mostly occurs in the form of local recurrence and peritoneal carcinomatosis. There is no evidence of a significant benefit in survival with adjuvant chemotherapy after surgery, but chemotherapy is frequently used because these lesions tend to recur.[12,104]

Neoadjuvant therapy should be used for unresectable lesions and seems to improve survival; however, data are available only for a small number of patients.[105,106] Another possible targeted treatment is the use of biological agents, in particular, the vascular endothelial growth factor inhibitor bevacizumab.[107] The role of more radical resection, or metastasectomy, for advanced lesions is not clear, but some reports refer a role for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy.[108,109] Palliative approaches consist of resectional or bypass procedures. In the case of obstruction by lesions accessible by endoscopy, self-expandable metal stent placement is the best option.[110] Palliative radiotherapy may have a role in duodenal tumours.

NETs

Surgical resection is usually the option for NETs of any size and should include resection of adjacent mesentery and lymph nodes. Patients with lesions near the ileocaecal valve require right hemicolectomy. Partial small bowel resection could be performed for more proximal tumours. Superficial tumours, accessible by endoscopy, may be resected endoscopically.[98,111] In metastatic liver disease, resection of hepatic metastases prolongs the disease-free survival; non-surgical ablation (cryo/alcohol/radiofrequency ablation) and hepatic transarterial embolisation (TAE) or chemoembolisation (TACE) should also be options in these cases.[5] Some patients with isolated liver metastasis may benefit from orthotopic transplantation.[112,113] Surgery is not possible in most patients with carcinoid-syndrome but a debulking surgery could give a short-term relief to patients.[5] Metastatic NETs are generally managed with the somatostatin analogues octreotide and lanreotide.[98] Octreotide can also be administered in the perioperative period to mitigate the risk of precipitating carcinoid symptoms while mobilising the tumours during surgery. Systemic traditional chemotherapy is not usually undertaken because NETs are particularly resistant.[5]

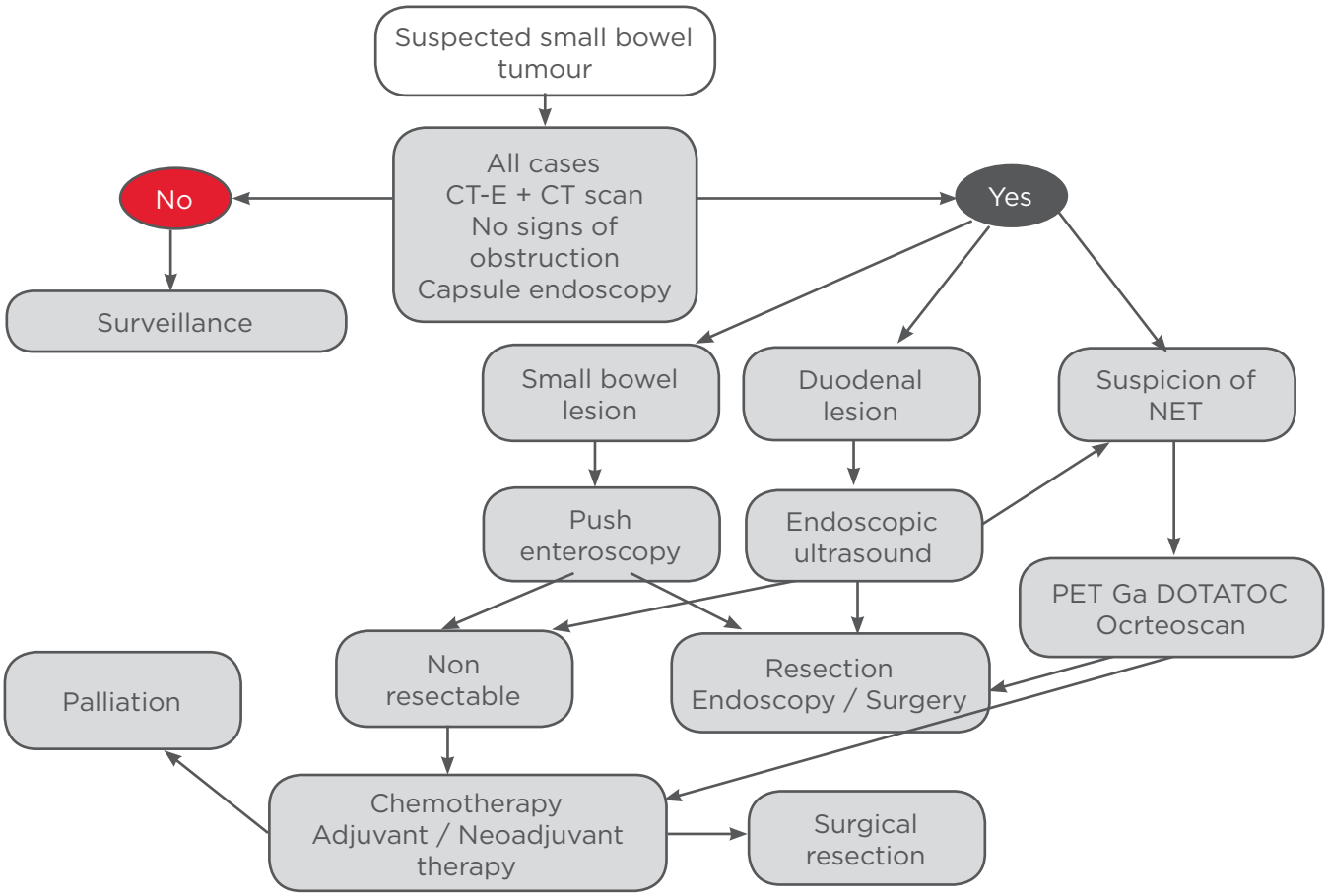

Figure 1: Simplified algorithm of diagnosis and treatment of small bowel neoplasms.
CT-E: computed tomography enterography; NET: neuroendocrine tumour; PET: positron emission tomography.

GISTs

Surgery is the treatment of choice for GISTs. Small gastric GISTs can be excised at laparoscopy;[52] local recurrence is generally due to an incomplete resection.[114] Survival after complete resection ranges from 48-80% at 5 years; in incomplete resection, only 9% of patients survive for an average of 12 months.[115,116] Patients with lesions >3 cm or with malignant metastatic disease (10-20% of cases[111,112]) can be treated with a tyrosine-kinase inhibitor, imatinib. Imatinib can also be used as neoadjuvant therapy. If the tumour becomes resistant to imatinib, it could be treated with a broader spectrum tyrosine kinase inhibitor, sutinib.[12] Surgery is not recommended for GIST progressing at several sites, except to relieve severe symptoms such as bowel obstruction or bleeding.[52] In patients with metastatic disease, radiotherapy is used to control abdominal metastases and relieve symptoms,[113] while palliation is done by hepatic TAE or TACE, and radiofrequency ablation.[117-119]

Lymphoma

The gold standard in treatment of lymphoma is chemotherapy. Resection should be an option in case of bleeding, obstruction, or perforation.[120] In patients with Helicobacter pylori or Campylobacter jejuni infection, the eradication of the infection results in regression of early stage immunoproliferative small intestinal disease; however, most patients relapse with high-grade disease. In these cases, radiotherapy and chemotherapy are the mainstay of treatment.[121-123] EATL is treated with combination chemotherapy using anthracyclines such as epirubicin.[12]

Melanoma

Primary intestinal metastatic melanoma requires surgery.[124] Metastasectomy should be done in patients for whom complete removal of lesions is not possible because in these cases, surgery is the only palliative therapy.[66] Chemotherapy, immunotherapy, and biochemotherapy are included in the treatment of metastatic disease as adjuvant and neoadjuvant treatment.[24,125]

An algorithm of diagnosis and treatment of small bowel neoplasms is reported in Figure 1.

CONCLUSIONS

Small bowel tumours include a large group of lesions with increasing incidence, particularly for NETs. Unfortunately, given the absence or non-specificity of symptoms, the majority of lesions are diagnosed late and have a poor prognosis. In recent years, diagnostic technology and new therapies have led to improved life expectancy. A better understanding of the aetiopathogenesis and risk factors will very likely result in earlier diagnosis and a more effective treatment of these tumours.

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