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Small Bowel Neoplasms and Polyps

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Abstract The small intestine is a relatively privileged organ that only rarely develops malignant or even benign tumors. Given this rarity, the relative inaccessibility of the organ during routine endoscopic procedures, and the typical absence or nonspecific nature of clinical manifestations, these tumors often go undiagnosed. Treatment and prognosis are tailored to each histological subtype of tumor. This chapter will discuss the epidemiology, presentation, diagnostics, and management for the most common small bowel tumors, and will highlight the importance of recognizing patients at higher risk of small bowel neoplasia.

Keywords Small bowel tumors · Adenocarcinoma · Carcinoid · Adenoma · Lynch syndrome · Familial adenomatous polyposis · Peutz-Jeghers syndrome · Crohn's disease

Introduction

Tumors of the small intestine, both benign and malignant, are decidedly rare in the general population. Even among tumors of the digestive tract, only 3 % occur in the small bowel despite the fact that the small intestine accounts for over 90 % of the gastrointestinal tract [1]. Because of their rarity, very little clinical attention is paid to these neoplasms, and in fact, most are detected coincidentally, only upon evaluating another disorder or unexplained symptoms. Of the several histological types, adenocarcinomas and carcinoids (neuroendocrine tumors) are the most common. In recent years, the advent of newer imaging techniques and a more clear understanding of certain high-risk conditions has provided better understanding as to which patients warrant heightened vigilance for the risk, or progression, of small bowel neoplasia.

Epidemiology

In the USA, small bowel tumors account for approximately 0.5 % of all cancers [1]. In 2015, the American Cancer Society estimated there would be over 9000 new cases and 1200 deaths from small bowel cancer annually [1]. In 1987, a population-based registry from the National Cancer Institute described that over the prior decade the distribution of malignant small bowel tumors was 45 % adenocarcinoma, 29 % carcinoid, 16 % lymphoma, and 10 % sarcoma [2]. In that study, incidence rates for all these tumors were higher in males and the incidence rate rose sharply after middle age. At the conclusion of the 10-year study, the incidence of malignant carcinoid tumors was 50 % higher than at the beginning. Indeed, in a subsequent study utilizing the US National Cancer Database (NCDB) in the year 2000, carcinoid tumors outnumbered adenocarcinoma [3], but currently they have roughly the same incidence [4]. The doubling of the overall incidence of small bowel cancers reported by the NCDB between 1973 and 2004 [4] is due, at least in part, to improved tumor detection with advanced radiographic and endoscopic techniques.

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Diagnosis

Diagnosing small bowel tumors can be challenging given the fact that patients are often asymptomatic, and when symptoms are present, they are usually nonspecific. Equally difficult is the fact that there is no standardized diagnostic approach to discovering these tumors. CT imaging has a respectable sensitivity rate of 80 % for small bowel tumors [5], but even better results (85–95 %) are obtained with CT and MR enterography [6, 7]. PET/CT may be useful in patients with adenocarcinoma or sarcomas, but its use in carcinoids is lacking given the fact that these tumors tend to be less FDG-avid. Somatostatin receptor scintigraphy (OctreoScan) is used as a complementary study to radiographic imaging for carcinoid tumors [8]. The added value of the OctreoScan is that this whole-body scan can also detect metastases outside the abdominal region [9]. As documented in a recent patient-based analysis, Octreoscan has a 88 % sensitivity and 97 % specificity for detecting neuroendocrine tumors [10].

Endoscopy is often a preferred modality given the ability to both detect and sample lesions. Capsule endoscopy has become increasingly used to assist with diagnosing small bowel tumors, and in a meta-analysis of 530 patients showed a lower small bowel tumor miss rate than push enteroscopy [11]. It has a higher sensitivity to detect polyps in patients with FAP as compared to radiographic studies [12•]. Push enteroscopy has a diagnostic yield of 6 % for small bowel tumors in patients who present with obscure gastrointestinal bleeding [13], with an inferior yield when compared to capsule endoscopy [14]. This limitation is at least in part due to the fact that push endoscopy cannot reliably evaluate lesions past the proximal jejunum [15]. The sensitivity for double balloon enteroscopy (DBE) in detecting small bowel tumors has been reported as 86 % [16]. There is no conclusive evidence favoring single balloon enteroscopy over DBE, and the decision to use either method is at the discretion of the operator [15]. The diagnostic yield for small bowel tumors with DBE appears to be comparable to capsule endoscopy [17]; however, capsule endoscopy is less invasive and is generally the initial approach and both are considered complementary to each other.

Adenocarcinomas of the small bowel may have elevated levels of carcinoembryonic antigen (CEA), but its sensitivity and specificity for diagnosis is limited [18]. Biochemical testing with urinary 5-hydroxyindoleacetic acid (5-HIAA) and serum chromogranin-A (CgA) can be used in screening for carcinoid. An elevated urinary 5-HIAA, a breakdown product of serotonin, has a specificity of up to 100 % but a sensitivity reported between 35 and 70 % for neuroendocrine tumors, whereas CgA has a specificity and sensitivity reported as 86 and 68 %, respectively [9, 19]. Serum serotonin measurements are less sensitive and specific than both urinary 5-HIAA and CgA [9]. It is important to note that tryptophan-containing foods and certain medications can alter the results of urinary 5-HIAA, while a number of conditions and medications, most notably proton pump inhibitors, can alter the levels of CgA.

Small Intestinal Adenocarcinoma

Like the large bowel, most small bowel adenocarcinomas arise from adenomas, with adenoma size and histology playing a role in the progression to carcinoma [20].

Sporadic Small Intestinal Adenocarcinoma

Adenocarcinomas of the small bowel are located most often in the duodenum, with an incidence that progressively declines distally [21]. An important exception is Crohn's disease, where the ileum is the most frequent site given the tendency of this segment to develop chronic inflammation (see below). The pathogenesis of small bowel adenocarcinoma appears to show a common carcinogenesis pathway with colorectal cancer [4]. One of the largest studies assessing the clinical and biological characteristics of small bowel adenocarcinoma in 63 patients found low levels of HER2 overexpression, high levels of p53 overexpression, and high frequencies of KRAS mutations in the same range as colorectal carcinoma [22•].

In general, adenocarcinomas of the small bowel present with nonspecific symptoms, the most common being abdominal pain [21]. Nausea and vomiting can also occur, especially if there is gastric outlet obstruction from an obstructing duodenal mass. Because the symptoms are vague, greater than 50 % of patients will have stage III or IV disease at the time of diagnosis [23]. The 5-year survival rates are generally poor: 50–60 % for stage I, 49–55 % for stage II, 10–40 % for stage III, and 3–5 % for stage IV [22•].

Management of localized adenocarcinomas is surgical [24]. Lesions of the first and second portion of the duodenum necessitate pancreaticoduodenectomy [25]. Localized lesions in the third and fourth portion of the duodenum lend themselves to segmental resection. For jejunal and proximal ileal tumors, the surgical approach is a wide excision. For distal ileal tumors, right hemicolectomy is the surgical approach of choice.

There are no conclusive data on the role of adjuvant [21, 24] or neoadjuvant therapy. There are no prospective studies that have investigated the role of adjuvant therapy in small bowel tumors. The data for adjuvant chemotherapy has been extrapolated from node-positive colon cancer patients, where there is a survival benefit [26]. Therefore, it is reasonable to offer chemotherapy to patients who have node-positive small bowel adenocarcinoma. A NCDB population analysis in 2015 showed that patients with stage III disease had a higher median survival (42.4 vs 26.1 months) when given adjuvant chemotherapy as compared to surgical resection alone [27•]. The management of metastatic small bowel adenocarcinoma is

chemotherapy. Palliative maneuvers include radiation for bleeding tumors and endoscopic stenting for obstruction.

High-Risk Syndromes

Certain conditions are associated with an increased risk of small intestinal adenocarcinoma (Table 1). The inherited syndromes are important to recognize, because if an underlying germ line mutation can be identified in a patient, all at-risk relatives can be gene tested and if positive, offered appropriate screening for the cancers relevant to that syndrome, including small bowel adenocarcinoma [28].

FAP results from a mutation of the APC gene. While the predominant phenotype is colorectal adenomas, patients with FAP have a 50–90 % chance of having duodenal adenomas, and one in 20 progresses to a malignancy [29]. In fact, after colorectal carcinoma, duodenal adenocarcinoma is the second most common cause of cancer-associated mortality in patients with FAP. Studies using capsule endoscopy have shown that approximately 90 % of patients can develop jejunal and ileal polyps, though the clinical impact of small bowel surveillance has yet to be determined [29]. The descending duodenum is an area that is often poorly visualized by capsule endoscopy and since this area is prone to adenomas in patients with FAP, direct endoscopy is preferred for surveillance of the proximal duodenum. Patients with FAP can manifest extraintestinal tumors which may be helpful in recognizing the condition and hence the risk of small bowel neoplasia. These include osteomas (mandible, long bones, skull), thyroid cancer, adrenal adenoma/carcinoma, CNS tumors (especially medulloblastoma), and desmoid tumors.

Peutz-Jeghers syndrome is an autosomal dominant disorder due to a mutation of STK11 tumor suppressor gene that results in hamartomas throughout the gastrointestinal tract [4]. Extraintestinal manifestations include pancreatic, breast, ovarian, and testicular tumors, as well as pigmented lesions of the mouth, hands, and feet. These patients have a relative risk of 520 of small bowel malignancy [30]. The hamartomas seen with this condition are replete with smooth muscle, making them firm and predisposing to intussusception. For this reason, clinical attention is often given to removing small intestinal hamartomas, mainly to prevent intussusception rather than progression to adenocarcinoma. Juvenile polyposis syndrome is another hamartomatous polyposis syndrome with a somewhat increased risk of small intestinal adenocarcinoma. Extra colonic manifestations include CNS tumors and cardiac malformations. Cowden's disease is characterized by hamartomas in the stomach, small intestine, and colon along with the characteristic extraintestinal manifestation of facial trichilemmomas.

Table 1 Conditions associated with increased risk for small intestinal adenocarcinoma

Inherited syndromes:
• Familial adenomatous polyposis
• Peutz-Jeghers syndrome
• Lynch syndrome
• Juvenile polyposis syndrome
• Cowden's syndrome
Crohn's disease
Celiac disease

Lynch syndrome is caused by a mutation in one of several DNA base mismatch repair genes. The more common cancers associated with Lynch syndrome are colorectal, endometrial, ovarian, brain, lung, and renal cancer. However, patients with Lynch syndrome have a 4 % lifetime risk of developing small bowel cancer, independent of a colorectal primary tumor [31], and small bowel adenocarcinoma can be the presenting cancer in a family. Patients with Lynch syndrome can develop these tumors up to 20 years earlier than the general population. Because of this, there is interest in using capsule endoscopy to screen for small bowel tumors in patients with Lynch syndrome [32]. A prospective study of capsule endoscopy in 200 asymptomatic patients with Lynch syndrome found 23 patients with a concerning lesion: two had neoplasia found in the duodenum (one adenocarcinoma, one adenoma) [12•]. Another patient had a missed duodenal adenocarcinoma on capsule endoscopy. The other 19 patients had either non-neoplastic lesions (Brunners' glands, lymphoid hyperplasia, heterotopic gastric mucosa) or no lesions identified on direct endoscopic exam. The positive predictive value of capsule endoscopy for small bowel tumors was 9 %, and negative predictive value was 99 %. There are no clear guidelines for small bowel imaging in Lynch syndrome, but it seems reasonable to pursue a baseline esophagogastroduodenoscopy, and reserve capsule endoscopy for patients with signs or symptoms such as unexplained anemia, weight loss, or abdominal symptoms, or those with a family history of small intestinal adenocarcinoma.

Small intestinal cancer risk is 20–30 times higher in patients with Crohn's disease than those without Crohn's disease [33]. The risk is directly related to the duration of disease and length of small bowel involvement [34]. Crohn's patients with small bowel carcinoma present at younger age and more often with diffuse involvement as compared to patients with de novo small bowel carcinoma [35]. Males are more commonly affected than females, and Crohn's patients with small bowel carcinoma have a worse prognosis than those with de novo carcinoma [35]. Small bowel adenocarcinomas are rarely diagnosed preoperatively in these patients, as they can present clinically like a stricture, a common complication of Crohn's disease [36].

The prevalence of small intestinal adenocarcinoma among patients with celiac disease may be as high as 8 % [37]. A Swedish registry found a relative risk of ten for small intestinal adenocarcinoma in celiac patients compared to the general population [38].

Carcinoid Tumors

Carcinoid tumors are the most common neuroendocrine tumors affecting the small bowel [39]. Small intestinal carcinoids grow indolently and are usually found incidentally as many patients are asymptomatic at presentation. If symptomatic, the most common complaint is nonspecific abdominal pain [40]. Carcinoid syndrome can occur when tumor products gain access to the systemic circulation, usually via metastasis to the liver, which causes watery diarrhea and flushing.

Unlike adenocarcinomas of the small bowel, the 10-year survival rates for locally advanced and metastatic carcinoids reach 40–70 % [41]. In 2006, a TNM staging system was developed to help classify small intestinal neuroendocrine tumors. However, due to overlap between staging groups, a more refined staging system was recently developed [41]. The treatment for localized disease is surgical excision [42]. In the patient with metastatic disease, surgical resection can be entertained, but carcinoid syndrome implies unresectable disease and surgery will likely only be offered in a palliative setting for symptomatic relief [43, 44]. Surgical palliation is often short-lived, and somatostatin analogues are typically used in metastatic carcinoid with greater long-term efficacy. These analogues, however, have limited effect on reducing tumor burden, and there is no conclusive evidence to support cytotoxic chemotherapy in the treatment of these tumors.

Primary Lymphoma

Primary gastrointestinal lymphoma is the most common extranodal manifestation of lymphoma, with the most common site being the stomach in majority of patients, followed by the small bowel [45]. They can be T or B cell in origin, and high or low grade [46]. These include mucosa-associated lymphoid tissue (MALT) lymphomas, diffuse large B cell lymphomas, Burkitt lymphomas, and mantle cell lymphomas. The management of these tumors generally follows the same treatment schemes as the tumors that arise outside the small bowel. Celiac disease can be associated with a rapidly fatal intestinal T cell non-Hodgkin lymphoma, which does not have a standardized treatment protocol [47].

Mesenchymal Tumors

Gastrointestinal stromal tumors (GIST) are the most common mesenchymal tumor, followed by leiomyosarcomas [48], and up to 30 % of GISTs occur in the small intestine. GISTs are defined by their positivity for the CD117 antigen and expression of the c-kit receptor tyrosine kinase [49]. Most GISTs are benign, but the risk of malignancy is higher for those tumors that are larger than 5 cm, have more mitoses, presence of necrosis, and *c-kit* exon 11 deletion [50]. Treatment of mesenchymal tumors is primarily surgical, and for GISTs includes the use of imatinib, a selective tyrosine kinase inhibitor. This is typically used as adjuvant therapy [51] or monotherapy in advanced, unresectable disease [52].

Benign Tumors

The major types of benign tumors of the small bowel include adenomas, leiomyomas, and lipomas. These increase in frequency moving distally within the small bowel [53]. Adenomas can be villous or tubular. One major risk factor is FAP, where 80 % of patients develop duodenal adenomas [54]. There are no strict guidelines to management, but in general adenomas are removed endoscopically if they are amenable, and larger lesions should be considered for surgical removal [55]. Patients with duodenal adenomas should be screened for colorectal cancer as they are at increased risk [56]. The Spigelman classification categorizes duodenal cancer risk based on the number, size and histology of duodenal adenomas, and is used to help make endoscopic and surgical management decisions [54].

Conclusions

Small bowel tumors have been increasing in incidence over the past several years, likely due to technological advancements in our ability to detect them. Despite this, several studies have cited the relative difficulty with diagnosing early stage small bowel tumors. Treatment of small bowel tumors remains largely surgical across the histological subtypes, and in general the data for adjuvant and neoadjuvant therapy is fairly limited or extrapolated. Given the relative occult and indolent nature of these tumors, many present at an advanced stage, which makes treatment more difficult. Further investigative efforts into diagnostic modalities that allow for sensitive and specific screening testing may improve patient outcomes via earlier detection. Genetic markers to risk stratify patients for screening, outside of the known heritable cancer syndromes, may prove to be a useful adjunct.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin. 2015;65(1):5.
2. Weiss NS, Yang CP. Incidence of histologic types of cancer of the small intestine. J Natl Cancer Inst. 1987;78(4):653.
3. Bilimoria KY, Bentrem DJ, Wayne JD, et al. Small bowel cancer in the United States: changes in epidemiology, treatment, and survival over the last 20 years. Ann Surg. 2009;249(1):63.
4. Aparicio T, Zaanan A, Svrcek M, et al. Small bowel adenocarcinoma: epidemiology, risk factors, diagnosis and treatment. Dig Liver Dis. 2014;46:97–104.
5. Laurent F, Raynaud M, Biset JM, et al. Diagnosis and categorization of small bowel neoplasms: role of computed tomography. Gastrointest Radiol. 1991;16(2):115.
6. Pilleul F, Penigaud M, Milot L, et al. Possible small-bowel neoplasms: contrast-enhanced and water-enhanced multidetector CT enteroclysis. Radiology. 2006;241(3):796.
7. Pappalardo G, Gualdi G, Nunziale A, et al. Impact of magnetic resonance in the preoperative staging and the surgical planning for treating small bowel neoplasms. Surg Today. 2013;43(6):613–9.
8. Kunz PL, Reidy-Lagunes D, Anthony LB, et al. Consensus guidelines for the management and treatment of neuroendocrine tumors. Pancreas. 2013;42(4):557–77.
9. Pape UF, Perren A, Niederle B, et al. ENETS consensus guidelines for the management of patients with neuroendocrine neoplasms from the jejuno-ileum and the appendix including goblet cell carcinomas. Neuroendocrinology. 2012;95:135–56.
10. Sainz-Esteban A, Olmos R, Gonzalez-Sagrado M, et al. Contribution of 111In-pentetreotide SPECT/CT imaging to conventional somatostatin receptor scintigraphy in the detection of neuroendocrine tumours. Nucl Med Commun. 2015;36:251–9.
11. Lewis BS, Eisen GM, Friedman S. A pooled analysis to evaluate results of capsule endoscopy trials. Endoscopy. 2005;37(10):960.
12.• Haanstra J, Al-Toma A, Dekker E, et al. Prevalence of small-bowel neoplasia in Lynch syndrome assessed by video capsule endoscopy. Gut. 2015;64:1578–83. **Large, prospective study to assess if video capsule endoscopy was a useful screening tool for small bowel tumors in patients with Lynch syndrome. The results showed that the three patients who developed small bowel tumors had them all within reach of a gastroduodenoscope in the duodenum, one of which was missed on a capsule study, suggesting that capsule endoscopy should be used not universally but in specific clinical scenarios**.
13. Berner JS, Mauer K, Lewis BS. Push and sonde enteroscopy for the diagnosis of obscure gastrointestinal bleeding. Am J Gastroenterol. 1994;89:2139–42.
14. Triester SL, Leighton JA, Leontiadis GI, et al. A meta-analysis of the yield of capsule endoscopy compared to other diagnostic modalities in patients with obscure gastrointestinal bleeding. Am J Gastroenterol. 2005;100:2407–18.
15. Islam S, Leighton JA, Pasha SF. Evaluation and management of small-bowel tumors in the era of deep enteroscopy. Gastrointest Endosc. 2014;79:732–40.
16. Chen W-G, Shan G-D, Zhang H, et al. Double-balloon enteroscopy in small bowel tumors: a Chinese single-center study. World J Gastroenterol : WJG. 2013;19(23):3665–71.
17. Pasha SF, Leighton JA, Das A, et al. Double-balloon enteroscopy and capsule endoscopy have comparable diagnostic yield in small-bowel disease: a meta-analysis. Clin Gastroenterol Hepatol. 2008;6:671–6.
18. Talamonti MS, Goetz LH, Rao S, et al. Primary cancers of the small bowel: analysis of prognostic factors and results of surgical management. Arch Surg. 2002;137(5):564.
19. Bajetta E, Ferrari L, Martinetti A, et al. Chromogranin A, neuron specific enolase, carcinoembryonic antigen, and hydroxyindole acetic acid evaluation in patients with neuroendocrine tumors. Cancer. 1999;86:858–65.
20. Raghav K, Overman MJ. Small bowel adenocarcinomas—existing evidence and evolving paradigms. Nat Rev Clin Oncol. 2013;10(9):534–44.
21. Halfdanarson TR, McWilliams RR, Donohue JH, et al. A single-institution experience with 491 cases of small bowel adenocarcinoma. Am J Surg. 2010;199(6):797.
22.• Aparicio T, Svrcek M, Zaanan A, et al. Small bowel adenocarcinoma phenotyping, a clinicobiological prognostic study. Br J Cancer. 2013;109:3057–66. **One of the largest studies assessing the clinical and biological characteristics of small bowel adenocarcinoma in 63 patients that showed a similarity between the pathogenesis of small bowel adenocarcinoma and colorectal carcinoma, and less similarity with gastric adenocarcinoma**.
23. T Howe JR, Karnell LH, Menck HR, et al. The American College of Surgeons Commission on Cancer and the American Cancer Society. Adenocarcinoma of the small bowel: review of the National Cancer Data Base, 1985–1995. Cancer. 1999;86(12):2693.
24. Dabaja BS, Suki D, Pro B, et al. Adenocarcinoma of the small bowel: presentation, prognostic factors, and outcome of 2 patients. Cancer. 2004;101(3):518.
25. Sohn TA, Lillemoe KD, Cameron JL, et al. Adenocarcinoma of the duodenum: factors influencing long-term survival. J Gastrointest Surg. 1998;2(1):79.
26. Abrahams NA, Halverson A, Fazio VW, et al. Adenocarcinoma of the small bowel: a study of 37 cases with emphasis on histologic prognostic factors. Dis Colon Rectum. 2002;45(11):1496.
27.• Ecker BL, McMillan MT, Datta J, et al. Efficacy of adjuvant chemotherapy for small bowel adenocarcinoma: a propensity score-matched analysis. Cancer. 2015. doi:10.1002/cncr.29840. **This study shows that adjuvant chemotherapy provided higher median survival for stage III adenocarcinoma patients as compared to a group that received surgery alone**.
28. Syngal S, Brand RE, Church JM, et al. ACG Clinical Guideline: genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol. 2015;110:223–63.
29. Koornstra JJ. Small bowel endoscopy in familial adenomatous polyposis and Lynch syndrome. Best Pract Res Clin Gastroenterol. 2012;26:359–68.
30. Giardiello FM, Brensinger JD, Tersmette AC, et al. Very high risk of cancer in familial Peutz–Jeghers syndrome. Gastroenterology. 2000;119:1447–53.
31. Win AK, Lindor NM, Young JP, et al. Risks of primary extracolonic cancers following colorectal cancer in lynch syndrome. J Natl Cancer Inst. 2012;104:1363–72.
32. Koornstra JJ, Kleibeuker JH, Vasen HF. Small-bowel cancer in Lynch syndrome: is it time for surveillance? Lancet Oncol. 2008;9:901–05.
33. Beaugerie L, Itzkowitz SH. Cancers complicating inflammatory bowel disease. N Engl J Med. 2015;372:1441–52.
34. Palascak-Juif V, Bouvier AM, Cosnes J, et al. Small bowel adenocarcinoma in patients with Crohn's disease compared with small bowel adenocarcinoma de novo. Inflamm Bowel Dis. 2005;11(9):828.
35. Cahill C, Gordon PH, Petrucci A, et al. Small bowel adenocarcinoma and Crohn's disease: any further ahead than 50 years ago? WJG. 2014;20(33):11486–95.

36. Michelassi F, Testa G, Pomidor WJ, et al. Adenocarcinoma complicating Crohn's disease. Dis Colon Rectum. 1993;36(7):654.
37. Swinson CM, Slavin G, Coles EC, et al. Coeliac disease and malignancy. Lancet. 1983;1:111–5.
38. Askling J, Linet M, Gridley G, et al. Cancer incidence in a population-based cohort of individuals hospitalized with celiac disease or dermatitis herpetiformis. Gastroenterology. 2002;123: 1428–35.
39. Weber HC, Venzon DJ, Lin JT, et al. Determinants of metastatic rate and survival in patients with Zollinger-Ellison syndrome: a prospective long-term study. Gastroenterology. 1995;108(6):1637.
40. Saha S, Hoda S, Godfrey R, et al. Carcinoid tumors of the gastrointestinal tract: a 44-year experience. South Med J. 1989;82(12): 1501.
41. Kim MK, Warner RR, Roayaie S, et al. Revised staging classification improves outcome prediction for small intestinal neuroendocrine tumors. J Clin Oncol. 2013;31(30):3776–81.
42. Nikou GC, Lygidakis NJ, Toubanakis C, et al. Current diagnosis and treatment of gastrointestinal carcinoids in a series of 101 patients: the significance of serum chromogranin-A, somatostatin receptor scintigraphy and somatostatin analogues. Hepatogastroenterology. 2005;52(63):731.
43. Mayo SC, de Jong MC, Pulitano C, et al. Surgical management of hepatic neuroendocrine tumor metastasis: results from an international multi-institutional analysis. Ann Surg Oncol. 2010;17(12):3129.
44. Sarmiento JM, Heywood G, Rubin J, et al. Surgical treatment of neuroendocrine metastases to the liver: a plea for resection to increase survival. J Am Coll Surg. 2003;197(1):29–37.
45. Koch P, del Valle F, Berdel WE, et al. Primary gastrointestinal non-Hodgkin's lymphoma: I. Anatomic and histologic distribution, clinical features, and survival data of 371 patients registered in the German Multicenter Study GIT NHL 01/92. J Clin Oncol. 2001;19(18):3861.
46. Isaacson PG. Gastrointestinal lymphoma. Hum Pathol. 1994;25(10):1020.
47. Nijeboer P, Malamut G, Mulder CJ, et al. Enteropathy-associated T-cell lymphoma: improving treatment strategies. Dig Dis. 2015;33: 231–5.
48. Miettinen M, Kopczynski J, Makhlouf HR, et al. Gastrointestinal stromal tumors, intramural leiomyomas, and leiomyosarcomas in the duodenum: a clinicopathologic, immunohistochemical, and molecular genetic study of 167 cases. Am J Surg Pathol. 2003;27(5): 625.
49. Rubin BP, Fletcher JA, Fletcher CD. Molecular insights into the histogenesis and pathogenesis of gastrointestinal stromal tumors. Int J Surg Pathol. 2000;8(1):5.
50. Bresalier RS, Blechacz B. Chapter 125. Tumors of the small intestine. In: Felman M, Friedman LS, Brandt LJ, editors. Sleisenger and Fordtran's gastrointestinal and liver disease, 10th Ed, Saunders Elsevier, 2016. pp. 2196-2212.
51. Corless CL, Ballman KV, Antonescu CR, et al. Pathologic and molecular features correlate with long-term outcome after adjuvant therapy of resected primary GI stromal tumor: the ACOSOG Z9001 trial. J Clin Oncol. 2014;32(15):1563.
52. Demetri GD, von Mehren M, Blanke CD, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. N Engl J Med. 2002;347(7):472.
53. Kemp CD, Russell RT, Sharp KW. Resection of benign duodenal neoplasms. Am Surg. 2007;73(11):1086.
54. Spigelman AD, Williams CB, Talbot IC, et al. Upper gastrointestinal cancer in patients with familial adenomatous polyposis. Lancet. 1989;2(8666):783.
55. Adler DG, Qureshi W, Davila R, et al. The role of endoscopy in ampullary and duodenal adenomas. Gastrointest Endosc. 2006;64(6):849.
56. Murray MA, Zimmerman MJ, Ee HC. Sporadic duodenal adenoma is associated with colorectal neoplasia. Gut. 2004;53(2):261.