Chapter 19
Small Intestine Cancer

Pedro Nazareth Aguiar Jr., Carmelia Maria Noia Barreto, Nora Manoukian Forones, Hakaru Tadokoro, and Ramon Andrade De Mello

Abstract Primary small intestine cancers are not frequent, accounting for <1% of all adult neoplasms. Various histologic types are associated with small intestine cancer. The most common used to be adenocarcinoma; however, carcinoid tumors are showing an improved incidence and are the most common histologic type in some series. Adenocarcinomas are more frequent in the duodenum, while carcinoid tumors are more common in the ileum. Other histologic types are lymphomas and sarcomas. The symptoms are vague and non-specific. Less of an index of suspicious can cause a late the diagnosis. The stage at diagnosis is the most important prognostic factor. Radiologic and endoscopic exams can be performed to achieve a specimen sample and to stage the disease. Early tumors can be treated properly with surgical resection. Adjuvant treatment for adenocarcinoma has not been studied in large trials, but it is indicated in extrapolating colon data. The treatment for advanced adenocarcinoma of the small intestine has only been studied in a few large cohorts. Treatment for other histologic types is discussed in a separated chapter.

P. N. Aguiar Jr.
Faculdade de Medicina do ABC, Santo André, Brazil

C. M. N. Barreto
Instituto Avanços em Medicina, São Paulo, SP, Brazil

N. M. Forones
Escola Paulista de Medicina, Federal University of São Paulo (UNIFESP), São Paulo, Brazil

H. Tadokoro
Division of Medical Oncology, Escola Paulista de Medicina, Federal University of São Paulo, São Paulo, Brazil

R. A. De Mello (✉)
Division of Medical Oncology, Federal University of São Paulo (UNIFESP) & Hospital Israelita Albert Einstein, São Paulo, Brazil

Department of Biomedical Sciences and Medicine, University of Algarve, Faro, Portugal
e-mail: ramello@ualg.pt; ramondemello@doctors.org.uk

R. A. De Mello et al. (eds.), *International Manual of Oncology Practice*,
https://doi.org/10.1007/978-3-030-16245-0_19

Keywords Small intestine · Cancer · Chemotherapy

Abbreviations

GI	Gastrointestinal
UE	Upper Endoscopy
VCE	Video Capsule Endoscopy
CT	Computed Tomography
PET	Positron Emission Tomography
AJCC	American Joint Committee on Cancer
ASCO	American Society of Clinical Oncology
FOLFOX	Fluouracil plus Oxaliplatin
FOLFIRI	Fluouracil plus Irinotecan
PD-1	Programmed-Death Receptor 1
FDA	Food and Drug Administration
ESMO	European Society of Medical Oncology

19.1 Epidemiology and Clinical Presentation

Primary small intestine neoplasms are relatively rare, representing only 3% of all gastrointestinal (GI) cancers and 0.5% of all cancers in the United States [1]. Although there is a small incidence, a variety of histologic types can arise within the small intestine: carcinoid tumors, adenocarcinoma, sarcomas, and lymphomas. Recently, carcinoid tumors surpassed adenocarcinoma as the most frequent histologic type. Data from National Cancer Database between 1985 and 2005 showed that the proportion of carcinoid tumors increased from 28% to 44%, while the proportion of adenocarcinoma decreased from 42% to 33% [2]. Generally, carcinoid tumors are more frequent in the ileum, while adenocarcinoma affects the duodenum more often. Sarcomas and lymphomas can develop in the entire organ [2].

There are two histologic types of adenocarcinomas that must be differentiated: pancreatobiliary and intestinal. The first seems to have a worse prognosis [3]. Some hypotheses have been proposed to explain the lower incidence of small intestine adenocarcinoma compared to the large intestine [4]: (1) the increased liquid content and the more rapid transit may provide less exposure to carcinogens and less irritation and (2) the higher concentration of benzpyrene hydroxylase and the much lower bacterial load may result in less carcinogen metabolites.

Data from the United States revealed that the incidence of small intestine cancer is rising [5]. This epidemiologic change seems to be caused by an increase of >4-fold of carcinoid tumors [2]. The incidence is slightly higher in men (1.5:1) [6]. The mean age at diagnosis is 60–62 years and 67–68 years for sarcomas and lymphomas and for adenocarcinoma and carcinoid tumors, respectively [5].

As observed in colon cancer, most small intestine adenocarcinomas arise from adenomas; however, unlike the large intestine, there are few data on this issue [7]. Some hereditary cancer syndromes are related to the development of large and small intestine adenocarcinoma: hereditary non-polyposis colorectal cancer [8], familial adenomatous polyposis [9], and Peutz-Jeghers syndrome [10]. Patients with inflammatory bowel disease are at an increased risk for developing adenocarcinoma, according to the extent and duration of small bowel involvement [11]. There is an association between multiple endocrine neoplasia type I with rare cases of carcinoid tumor of the small intestine [12]. Risk factors for other histologic types are not yet completely known.

The main symptoms are abdominal pain, weight loss, nausea, and vomiting, GI bleeding, and intestinal obstruction. In the case of a duodenal primary mass, jaundice is a possible sign of the disease [13]. Since the symptoms are often vague and non-specific, the level of suspicion of small intestine neoplasms are often low, and this can result in the majority of patients being diagnosed with advanced disease (58%, stage III or IV) [14].

Carcinoid tumors of the small intestine are more frequently well differentiated. This means that these neoplasms usually have a characteristic morphologic aspect, and they can produce biologically active amines. The majority of these tumors are asymptomatic on presentation due to hepatic metabolism of the active amines and its indolent growth. Metastatic disease is present in 90% of symptomatic patients. The mass effect of the tumor is generally the cause of symptoms such as abdominal pain and obstruction. Carcinoid syndrome occurs when active amines have gained access to the blood circulation, and it is typically in the setting of liver metastasis [15]. Details on this syndrome are discussed in a separate chapter.

Primary GI lymphoma is the most common extranodal form of lymphoma. The stomach and small intestine are the most common sites [16]. More information on this subject can be found in another chapter. Epidemiology and clinical manifestation of GI stromal tumors are also discussed in another chapter.

19.2 Diagnosis and Staging

The vague and non-specific symptoms in combination with the lack of physical findings can delay the diagnosis for up to several months [17]. The stage of diagnosis is a prognostic factor for overall survival. Therefore, a higher suspicion is necessary when evaluating symptomatic patients. There are radiographic and endoscopic tests to help physicians determine the diagnosis and staging of small intestine cancer; however, there is not a consensus on the right sequence of tests.

Upper endoscopy (UE) may provide a direct evaluation of the mucosa, and it can provide a specimen sample and resection of benign lesions [18]. However, only the duodenum can be assessed by UE. Although colonoscopy can also provide a specimen sample and direct evaluation of the mucosa, it can only assess the terminal

ileum [19]. Wireless video capsule endoscopy (VCE) is an interesting option for evaluating the entire small intestine. In a meta-analysis of 24 studies, VCE failed to identify tumors in 20 of 106 cancers cases (false negative rate, 19%) [20]. In a retrospective study at Mount Sinai Medical Center from 2001–2003, 562 individuals with non-specific GI symptoms underwent VCE, which detected small intestine tumors in 8.9% of the patients with only one false-positive result [21]. However, VCE cannot be performed in patients with a high suspicion of GI obstruction, because there is a high risk of capsule retention, which necessitates emergency laparoscopy [22]. In addition, VCE cannot provide a specimen sample, and it is fundamental to determine the diagnosis of small intestine cancer. Alternatively, double balloon enteroscopy is a very good option when available. It can directly evaluate the small intestine and provide tissue sampling. However, it is a difficult technique, and it is not available at the majority of institutions. Enteroscopy is another possibility, it is a very long standing exam and available in a very few hospitals.

CT is very important in staging, especially of adenocarcinomas. It can provide an evaluation of local and distant commitment caused by the disease. CT can detect abnormalities in up to 80% of patients with small intestine neoplasms [23]. CT enterography is an option when there is suspicion of GI obstruction and enteroscopy cannot be performed. However, similar to VCE, CT enterography cannot provide a specimen sample. In a study on 219 patients with a high index of suspicion and normal endoscopy, CT enterography detected 155 abnormalities with 5 false-positives. Among 164 patients with a normal result, a small bowel tumor was later found in 9 [24]. PET is largely used in cases of lymphomas and stromal tumors; however, PET is not currently indicated for adenocarcinomas. It can be used to evaluate the response to initial treatment (i.e., a decrease in the uptake value) [25]. The Tumor, Node, and Metastasis Staging System of small intestine cancers is presented as follows [26].

19.2.1 Adenocarcinoma Staging

The 8th version of the American Joint Committee on Cancer (AJCC) released in 2017 changed the staging as follows:

For T3 and T4, there is not necessary to describe the extension of penetration into the retroperitoneum [27]. The reason is that it is not a validated prognostic factor. Moreover, it is not reliably reported in the pathology assessment [27].

Now, N1 is defined as one or two positive nodes and N2 as more than two positive nodes. The reason for this change is to harmonize small intestine cancer staging with the rest of the upper gastrointestinal tumors.

The last change is that although all histology are assigned TNM, it has a prognostic meaning only for adenocarcinoma.

The following is the most recent tumor staging classification for adenocarcinoma: Tx, the primary tumor cannot be assessed; T0, no evidence of a primary tumor; Tis, high-grade dysplasia or carcinoma in situ; T1a, the tumor is invading the

lamina propria; T1b, the tumor is invading the submucosa; T2, the tumor is invading the muscularis propria; T3, the tumor is invading through the muscularis propria into the subserosa or into the non-peritonealized perimuscular tissue (mesentery or retroperitoneum) without serosal penetration; T4, the tumor is perforating the visceral peritoneum or is directly invading other organs or structures (including other loops of the small intestine and mesentery; the abdominal wall by way of the serosa; the duodenum only, with invasion of the pancreas or bile duct); Nx, the regional lymph nodes cannot be assessed; N0, no regional lymph node metastasis; N1, metastasis in one or two regional lymph nodes; N2, metastasis in ≥3 regional lymph nodes; M0, no distant metastasis; and M1, distant metastasis.

The following are the stages of adenocarcinoma: stage 0: Tis, N0, and M0; stage I: T1–2, N0, and M0; stage IIA: T3, N0, and M0; stage IIB: T4, N0, and M0; stage IIIA: any T, N1, or M0; stage IIIB, any T, N2, or M0; and stage IV: any T, N, or M1.

19.2.2 Carcinoid Tumors Staging

Regarding carcinoid tumors, AJCC 8th edition proposes a new classification of nodal involvement, called N2; stages I–IV were simplified without substages A or B [27]. Moreover, duodenum has now a specific classification apart from small intestine [27].

The following is the tumor staging classification for carcinoid tumors: Tx, a primary tumor cannot be assessed; T0, no evidence of a primary tumor; T1, the tumor is invading the lamina propria or submucosa and is ≤1 cm in size; T2, the tumor is invading the muscularis propria or is >1 cm in size; T3, the tumor is invading through the muscularis propria into the subserosal tissue without penetrating the overlying serosa (jejunal or ileal tumors) or invading the pancreas or retroperitoneum (ampullary or duodenal tumors) or into the non-peritonealized tissues; T4, the tumor is invading the visceral peritoneum (serosa) or other organs. For any T, add (m) for multiple tumors. Nx indicates that the regional lymph nodes cannot be assessed; N0 represents no regional lymph nodes metastasis; N1 indicates regional lymph nodes metastasis less than 12 nodes; N2 is used for large mesenteric masses (>2 cm) and/or extensive nodal deposits (12 or greater), especially those that encase the superior mesenteric vessels; M0, represents no distant metastasis; and M1, represents distant metastasis.

The following are the stages of carcinoid tumors: stage I: T1, N0, and M0; stage IIA: T2-3, N0, and M0; stage III: T4, N0, and M0 or any T, N1-2, and M0; and stage IV: any T, N, or M1.

19.2.3 Sarcomas Staging

The staging system of small intestine sarcoma is discussed in a separate chapter.

19.2.4 Lymphomas Staging

Lymphomas of the small intestine have the same staging system as other lymphomas, and this subject is discussed in a separate chapter.

19.3 Treatment

The treatment of carcinoid tumors, sarcomas, and lymphomas arising from the small intestine are discussed in separate chapters for each histologic subtype. The treatment of adenocarcinoma is discussed in the following.

19.3.1 Stages I and II

Initial tumors can be treated with surgical resection, which can achieve a 5-year survival >75% [28, 29]. Duodenopancreatectomy is the best procedure for tumors arising from the first and second portions of the duodenum. However, for tumors arising in the third and fourth portions of the duodenum, local resection can be performed with much less morbidity and comparable rates of disease control [30].

19.3.2 Stage III (Metastasis to the Regional Lymph Nodes)

There is a lack of information regarding the benefit of adjuvant therapy (chemotherapy, radiotherapy, or both) in the treatment of small intestine adenocarcinoma. A meta-analysis concluded that there were no suitable trials to analyze [31]. In a study on 146 patients undergoing curative resection, 56 relapsed at a median time of 25 months, and systemic was more frequent than local recurrence [32], except for adenocarcinoma of the duodenum [33]. Patients with metastasis to the lymph nodes have a 5-year survival rate shorter than patients with stage I or II disease (35%, 65%, and 48%, respectively) [14]. The number of lymph nodes resected (>10) is also an important prognostic factor for overall survival [34]. Few retrospective trials address this topic, and their results are conflicting.

In a retrospective analysis of 54 patients treated at the MD Anderson Cancer Center, adjuvant chemotherapy improved disease-free survival (hazard ratio = 0.27; 95% confidence interval: 0.07–0.98; P = 0.05) with no benefit for overall survival (P = 0.23) [35]. However, a large retrospective series on 491 patients by the Mayo Clinic did not show any benefit with adjuvant chemotherapy [36].

In a study on genome hybridization, a comparison between adenocarcinoma of the small intestine with colorectal and gastric adenocarcinoma showed that adenocarcinoma was more genetically similar to colorectal than stomach cancer

[37]. Because of the paucity of trials and this genetic pattern, it is acceptable to extrapolate the data from colorectal cancer and offer adjuvant chemotherapy to patients who underwent complete resection for positive lymph nodes. A common regimen is the combination of oxaliplatin and 5-fluorouracil (5-FU), because this was the regimen that showed improved survival over 5-FU and leucovorin alone in patients with colon cancer in the MOSAIC trial [38]. Based on the safety and activity of the combination of oxaliplatin and capecitabine in the metastatic setting, this regimen is also an option.

In addition, for duodenal adenocarcinomas with positive margins because of the high risk of local recurrence, adjuvant therapy with 5-FU based chemoradiotherapy in addition to a course of systemic therapy is a reasonable option [9].

19.3.3 Stage IV (Metastatic Disease)

Small intestine cancer is a rare disease, and it is very difficult to develop phase III trials in order to evaluate the best treatment approach. Several years ago, proximal neoplasms were treated like gastric cancers, and distal tumors were treated like colorectal neoplasms. In a retrospective series on 80 patients, the treatment regimen of cisplatin and 5-FU showed higher response rates and longer disease-free with no benefit for overall survival [39]. The most encouraging study was conducted by the MD Anderson Cancer Center, which included 31 patients. Among 25 metastatic individuals, the combination of capecitabine (750 mg/m^2 twice daily on days 1–14) and oxaliplatin (130 mg/m^2 on day 1, every 21 days) showed a 52% response rate (with 3 complete responses) and a median overall survival of 15.5 months [40]. The appropriate dose of capecitabine is still debatable, because several trials on colon cancer have used a dose of 850 mg/m^2 twice daily; however, the only evidence specific to the treatment of small intestine adenocarcinoma was described previously, and the study used 750 mg/m^2 twice daily. Another encouraging study was presented at the 2014 ASCO annual meeting, which used mFOLFOX 6 in a multicenter phase II trial with 24 patients; a 45% response rate was reported, and the median progression-free and overall survival were 5.9 months and 17.3 months, respectively [41]. In a retrospective French multicenter study, 93 patients were treated with different regimens of FOLFOX (48 patients), infusional 5-FU [10], FOLFIRI [19], and infusional 5-FU plus cisplatin [16]. Although this trial was not designed to compare treatment regimens, FOLFOX achieved a higher response rate (13 of 38 partial responses, 34%), a longer median disease-free survival (7.7 months), and a longer overall survival (17.8 months) [42].

As second-line treatment, a retrospective French study included 28 patients who were treated with FOLFIRI after failure with FOLFOX or infusional 5-FU. This trial demonstrated an objective response of 20%, a median disease-free survival of 3.2 months, and a median overall survival of 10.5 months [43].

The role of biologic or targeted therapy has not yet been established. Only a few case reports or small series exist on cases using bevacizumab or cetuximab.

Cytoreductive surgery and intraperitoneal hyperthermic chemotherapy were used in a series of 17 patients, and a 1-year and 3-year survival rate of 52% and 23%, respectively, was reported. However, up to 47% of the individuals had complications from the treatment, and two required a surgical approach. Therefore, these treatments must be discussed on a case-by-case basis, and they can only be performed at centers with a high expertise [44].

19.3.4 Future Perspectives – Immunotherapy

Although there is not any specific study on immunotherapy for small intestine cancer, recent trials found that immune checkpoint inhibitors are effective against tumors with mismatch repair defect including small intestine cancer [45].

Tumors with mismatch repair defect have microsatellite instability, consequently, a large mutational burden. It is hypothesized that tumors with a higher mutational burden stimulate immune system more than tumors with lower mutational burden [46]. Pembrolizumab and nivolumab are monoclonal antibodies that stimulate lymphocytes against tumors by binding the lymphocyte Programmed Death Receptor 1 (PD-1). There are clinical trials assessing their efficacy for tumors with microsatellite instability, although only Pembrolizumab is approved by FDA in the US irrespective of the primary site. Pembrolizumab was studied in a study that included 86 patients with 12 different tumor types, including advanced small bowel cancers, whose tumors were mismatch repair deficient [47]. Approximately 9% of the tested small bowel adenocarcinomas were mismatch repair deficient. Among all included patients, the objective response rate was 53%, and complete response rate was 21%.

19.4 Follow-Up

Small intestinal cancers are rare tumors; thus, there are no guidelines for post-treatment surveillance from the ASCO, National Comprehensive Cancer Network, or the European Society of Medical Oncology (ESMO). Patients can be followed according to published post-treatment surveillance guidelines for colon cancer. According to THE ESMO's guideline, patients may be re-evaluated using a history and physical examination plus CEA testing every 3–6 months for 3 years and then every 6–12 months for 2 years. CT scanning of the abdomen and the chest may be performed every 6–12 months for 3 years. Endoscopic surveillance may be performed at 1 year and then every 3–5 years [48].

Key Points

Small intestinal neoplasms are relative rare.

Neuroendocrine tumors are more common than adenocarcinoma.

Adenocarcinoma treatment is almost all times extrapolated from colorectal cancer.

Immunotherapy showed promising results among patients with advanced mismatch repair deficient tumors.

Multiple-Choice Questions

1. Choose from the options below, the most frequent tumor histology of small intestine cancer:

   (a) Adenocarcinoma
   (b) Carcinoid tumors
   (c) Sarcoma
   (d) Lymphoma
   (e) Squamous cell carcinoma

   Answer: (b) Carcinoid tumors surpassed adenocarcinoma as the most frequent small intestine neoplasm.

2. What segment of small carcinoma is more common for adenocarcinoma?

   (a) Ileum
   (b) Duodenum
   (c) Vater ampola
   (d) Jejunum
   (e) None of the above

   Answer: (b) Small intestine adenocarcinoma is more common in the duodenum.

3. Which statements of the following are correct regarding small intestine carcinogenesis:

   I. The increased liquid content and the more rapid transit may provide less exposure to carcinogens and less irritation
   II. Small intestine is related to genetic syndromes
   III. p53 inactivation is related with small intestine carcinogenesis
   IV. The higher concentration of benzpyrene hydroxylase and the much lower bacterial load may result in less carcinogen metabolites.

   (a) All of the above are correct
   (b) I, II and III
   (c) I, III and IV
   (d) I and IV
   (e) IV

   Answer: (d) The two hypothesis for small intestine cancer are cited in I and IV.

4. A 62 years-old man started abdominal pain, weight loss and nausea 2 months ago. He visited a physician who suggested an upper endoscopy and colonoscopy.

Both exams were normal, the patient has no signal of GI obstruction, although she has a palpable periumbilical mass. What is the next step?

(a) Stop investigation
(b) Try a video capsule endoscopy
(c) Try a PET-Scan
(d) Perform an exploratory laparoscopy

Answer: (b) A video capsule endoscopy should demonstrate evidence of small intestine cancer in this patient.

5. A 57 years-old woman with a diagnostic of duodenum adenocarcinoma that invades the muscularis propria and spread to three locoregional lymphnodes. What is her tumor staging?

(a) T1b N1 M0
(b) T1b N2 M0
(c) T2 N1 M0
(d) T2 N2 M0
(e) T2 N1 M1

Answer: (d) According to AJCC 8th Edition her staging is T2 N2 M0.

6. Which of the following is not a symptom of carcinoid syndrome?

(a) Tachycardia
(b) Diarrhea
(c) Flushing
(d) Extremities Tremor
(e) Bleeding

Answer: (e) Bleeding is not a symptom of carcinoid syndrome. All other can be caused by systemic release of 5HT-3.

7. The 8th Edition of AJCC purposed a new Staging System for small intestine carcinoid tumors. Now, there is a new classification N2. What does it means?

(a) Large mesenteric masses (>2 cm)
(b) Extensive nodal deposits (12 or greater)
(c) Lymph nodes that encase the superior mesenteric vessels
(d) All of the above
(e) None of the above

Answer: (d) All sentences are definitions of N2.

8. A 65 years-old patient with signal and symptoms suggestive of small intestine cancer presents to you with signal of partial GI obstruction. Which of the following exam is not indicated?

(a) Upper Endoscopy
(b) CT Endoscopy

(c) PET-Scan
(d) Video Capsule Endoscopy
(e) None

Answer: (d) Video Capsule Endoscopy is contra indicated in cases with GI obstruction.

9. Somatostatin analogues are the cornerstone of carcinoid tumors treatment. What is the most common adverse event with this medication?

(a) Nausea
(b) Diarrhea
(c) Gallbladder stone
(d) Anorexia
(e) Alopecia

Answer: (c) The most frequent adverse event seen with somatostatin analogues is gallbladder stone due to the low gallbladder mobility caused by somatostatin analogues.

10. Small intestine adenocarcinoma is a rare disease with a paucity of therapeutic options for advanced disease. Recently, immunotherapy suggested some activity among mismatch repair deficient tumors. Which mismatch repair proteins we test?

(a) MSH 2
(b) MLH 1
(c) MSH 6
(d) PMS 2
(e) All of the above

Answer: (e) All of the above are proteins related to mismatch repair.

11. You ordered a immunohistochemistry assay to test mismatch repair proteins in the tumor of a patient with small intestine cancer. The results are MSH 2 negative, MLH 1 positive, PMS 2 positive and MSH 6 positive. What is the conclusion of the test?

(a) Mismatch Repair deficient
(b) Microsatellite instability Low
(c) Mismatch Repair proficient
(d) Inconclusive
(e) None of the above

Answer: (a) A negative immunohistochemistry for any protein is a positive finding for mismatch repair deficiency or microsatellite instability.

Clinical Case

A 62 years-old male started abdominal pain, anorexia, and weight loss 6 months ago. He made an Upper Endoscopy that found a tumor in the duodenum. After

tumor resection, he came in the clinic with the following pathology findings: well-differentiated intestinal adenocarcinoma of duodenum, pT2 pN1 cMx, tumor margin positive for tumor infiltration. The physical examination is normal and no image exams found any signal of metastatic disease.

Does this patient have indication for adjuvant therapy?

Although small intestine adenocarcinoma is a very rare disease, retrospective series found that adjuvant treatment prolonged survival compared to surgery alone.

What is the best strategy for adjuvant therapy in this case?

Once again, there is not any prospective trial to evaluate the best strategy for small intestine cancer adjuvant therapy. Even tough, this patient was treated with 5-Fluouracil based chemoradiation because of the neoplasm infiltration into tumor margins.

Is there any other recommendation in this case?

A majority of patients with resectable duodenum adenocarcinoma is treated with gastroduodenopancreatectomy. After this surgery, it is very important that this patient see a nutritionist in order to recovery his weight.

What is the follow-up in this case?

After chemoradiation, this patient is seen every 3 months with physical examination and CT during the two first years after treatment.

References

1. Siegel RL, Miller KD, Jemal A (2015) Cancer statistics, 2015. CA Cancer J Clin 65(1):5–29
2. Bilimoria KY, Bentrem DJ, Wayne JD, Ko CY, Bennett CL, Talamonti MS (2009) Small bowel cancer in the United States: changes in epidemiology, treatment, and survival over the last 20 years. Ann Surg 249(1):63–71
3. Westgaard A, Tafjord S, Farstad IN, Cvancarova M, Eide TJ, Mathisen O et al (2008) Pancreatobiliary versus intestinal histologic type of differentiation is an independent prognostic factor in resected periampullary adenocarcinoma. BMC Cancer 8:170
4. Chow WH, Linet MS, McLaughlin JK, Hsing AW, Chien HT, Blot WJ (1993) Risk factors for small intestine cancer. Cancer Causes Control 4(2):163–169
5. Hatzaras I, Palesty JA, Abir F, Sullivan P, Kozol RA, Dudrick SJ et al (2007) Small-bowel tumors: epidemiologic and clinical characteristics of 1260 cases from the connecticut tumor registry. Arch Surg 142(3):229–235
6. Haselkorn T, Whittemore AS, Lilienfeld DE (2005) Incidence of small bowel cancer in the United States and worldwide: geographic, temporal, and racial differences. Cancer Causes Control 16(7):781–787
7. Wheeler JM, Warren BF, Mortensen NJ, Kim HC, Biddolph SC, Elia G et al (2002) An insight into the genetic pathway of adenocarcinoma of the small intestine. Gut 50(2):218–223
8. Zhang MQ, Chen ZM, Wang HL (2006) Immunohistochemical investigation of tumorigenic pathways in small intestinal adenocarcinoma: a comparison with colorectal adenocarcinoma. Mod Pathol 19(4):573–580
9. Abrahams NA, Halverson A, Fazio VW, Rybicki LA, Goldblum JR (2002) Adenocarcinoma of the small bowel: a study of 37 cases with emphasis on histologic prognostic factors. Dis Colon Rectum 45(11):1496–1502
10. Giardiello FM, Brensinger JD, Tersmette AC, Goodman SN, Petersen GM, Booker SV et al (2000) Very high risk of cancer in familial Peutz-Jeghers syndrome. Gastroenterology 119(6):1447–1453

11. Jess T, Winther KV, Munkholm P, Langholz E, Binder V (2004) Intestinal and extra-intestinal cancer in Crohn's disease: follow-up of a population-based cohort in Copenhagen County, Denmark. Aliment Pharmacol Ther 19(3):287–293
12. Wu AH, Yu MC, Mack TM (1997) Smoking, alcohol use, dietary factors and risk of small intestinal adenocarcinoma. Int J Cancer 70(5):512–517
13. Ciresi DL, Scholten DJ (1995) The continuing clinical dilemma of primary tumors of the small intestine. Am Surg 61(8):698–702. discussion -3
14. Howe JR, Karnell LH, Menck HR, Scott-Conner C (1999) 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 86(12):2693–2706
15. Saha S, Hoda S, Godfrey R, Sutherland C, Raybon K (1989) Carcinoid tumors of the gastrointestinal tract: a 44-year experience. South Med J 82(12):1501–1505
16. Koch P, del Valle F, Berdel WE, Willich NA, Reers B, Hiddemann W et al (2001) 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 19(18):3861–3873
17. Maglinte DD, O'Connor K, Bessette J, Chernish SM, Kelvin FM (1991) The role of the physician in the late diagnosis of primary malignant tumors of the small intestine. Am J Gastroenterol 86(3):304–308
18. Zollinger RM (1986) Primary neoplasms of the small intestine. Am J Surg 151(6):654–658
19. Estrin HM, Farhi DC, Ament AA, Yang P (1987) Ileoscopic diagnosis of malignant lymphoma of the small bowel in acquired immunodeficiency syndrome. Gastrointest Endosc 33(5):390–391
20. Lewis BS, Eisen GM, Friedman S (2005) A pooled analysis to evaluate results of capsule endoscopy trials. Endoscopy 37(10):960–965
21. Cobrin GM, Pittman RH, Lewis BS (2006) Increased diagnostic yield of small bowel tumors with capsule endoscopy. Cancer 107(1):22–27
22. Wiarda BM, Mensink PB, Heine DG, Stolk M, Dees J, Hazenberg H et al (2012) Small bowel Crohn's disease: MR enteroclysis and capsule endoscopy compared to balloon-assisted enteroscopy. Abdom Imaging 37(3):397–403
23. Laurent F, Raynaud M, Biset JM, Boisserie-Lacroix M, Grelet P, Drouillard J (1991) Diagnosis and categorization of small bowel neoplasms: role of computed tomography. Gastrointest Radiol 16(2):115–119
24. Pilleul F, Penigaud M, Milot L, Saurin JC, Chayvialle JA, Valette PJ (2006) Possible small-bowel neoplasms: contrast-enhanced and water-enhanced multidetector CT enteroclysis. Radiology 241(3):796–801
25. Kalady MF, Clary BM, Clark LA, Gottfried M, Rohren EM, Coleman RE et al (2002) Clinical utility of positron emission tomography in the diagnosis and management of periampullary neoplasms. Ann Surg Oncol 9(8):799–806
26. Edge S, Byrd D, Compton C et al (eds) (2010) AJCC cancer staging manual, 7th edn. Springer, New York. 181 p
27. Edge S, Gfeene F, Byrd D, Brookland R, Washington M, Gershenwald J et al (eds) (2017) AJCC American Joint Committee on Cancer Staging Manual, 8th edn. Springer, Chicago. 983 p
28. Frost DB, Mercado PD, Tyrell JS (1994) Small bowel cancer: a 30-year review. Ann Surg Oncol 1(4):290–295
29. DiSario JA, Burt RW, Vargas H, McWhorter WP (1994) Small bowel cancer: epidemiological and clinical characteristics from a population-based registry. Am J Gastroenterol 89(5):699–701
30. Bakaeen FG, Murr MM, Sarr MG, Thompson GB, Farnell MB, Nagorney DM et al (2000) What prognostic factors are important in duodenal adenocarcinoma? Arch Surg 135(6):635–641. discussion 41–2.
31. Singhal N, Singhal D (2007) Adjuvant chemotherapy for small intestine adenocarcinoma. Cochrane Database Syst Rev 3:CD005202

32. Dabaja BS, Suki D, Pro B, Bonnen M, Ajani J (2004) Adenocarcinoma of the small bowel: presentation, prognostic factors, and outcome of 217 patients. Cancer 101(3):518–526
33. Barnes G, Romero L, Hess KR, Curley SA (1994) Primary adenocarcinoma of the duodenum: management and survival in 67 patients. Ann Surg Oncol 1(1):73–78
34. Nicholl MB, Ahuja V, Conway WC, Vu VD, Sim MS, Singh G (2010) Small bowel adenocarcinoma: understaged and undertreated? Ann Surg Oncol 17(10):2728–2732
35. Overman MJ, Kopetz S, Lin E, Abbruzzese JL, Wolff RA (2010) Is there a role for adjuvant therapy in resected adenocarcinoma of the small intestine. Acta Oncol 49(4):474–479
36. Halfdanarson TR, McWilliams RR, Donohue JH, Quevedo JF (2010) A single-institution experience with 491 cases of small bowel adenocarcinoma. Am J Surg 199(6):797–803
37. Haan JC, Buffart TE, Eijk PP, van de Wiel MA, van Wieringen WN, Howdle PD et al (2012) Small bowel adenocarcinoma copy number profiles are more closely related to colorectal than to gastric cancers. Ann Oncol 23(2):367–374
38. André T, Boni C, Navarro M, Tabernero J, Hickish T, Topham C et al (2009) Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. J Clin Oncol 27(19):3109–3116
39. Overman MJ, Kopetz S, Wen S, Hoff PM, Fogelman D, Morris J et al (2008) Chemotherapy with 5-fluorouracil and a platinum compound improves outcomes in metastatic small bowel adenocarcinoma. Cancer 113(8):2038–2045
40. Overman MJ, Varadhachary GR, Kopetz S, Adinin R, Lin E, Morris JS et al (2009) Phase II study of capecitabine and oxaliplatin for advanced adenocarcinoma of the small bowel and ampulla of Vater. J Clin Oncol 27(16):2598–2603
41. Nakayama N, Horimatsu T, Takagi S, Moriwaki T, Hirashima Y (2014) A phase II study of 5-FU/l-LV/oxaliplatin (mFOLFOX6) in patients with metastatic or unresectable small bowel adenocarcinoma. J Clin Oncol 32(15_suppl):3646
42. Zaanan A, Costes L, Gauthier M, Malka D, Locher C, Mitry E et al (2010) Chemotherapy of advanced small-bowel adenocarcinoma: a multicenter AGEO study. Ann Oncol 21(9):1786–1793
43. Zaanan A, Gauthier M, Malka D, Locher C, Gornet JM, Thirot-Bidault A et al (2011) Second-line chemotherapy with fluorouracil, leucovorin, and irinotecan (FOLFIRI regimen) in patients with advanced small bowel adenocarcinoma after failure of first-line platinum-based chemotherapy: a multicenter AGEO study. Cancer 117(7):1422–1428
44. Sun Y, Shen P, Stewart JH, Russell GB, Levine EA (2013) Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal carcinomatosis from small bowel adenocarcinoma. Am Surg 79(6):644–648
45. Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD et al (2015) PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med. [Internet]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26028255
46. Aguiar PN, Tadokoro H, Forones NM, de Mello RA (2015) MMR deficiency may lead to a high immunogenicity and then an improvement in anti-PD-1 efficacy for metastatic colorectal cancer. Immunotherapy 7(11):1133–1134. [Internet]. Available from: http://www.futuremedicine.com/doi/10.2217/imt.15.84
47. Le DT, Durham JN, Smith KN, Wang H, Bartlett BR, Aulakh LK et al (2017) Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science 357(6349):409–413. [Internet]. NIH Public Access; [cited 2017 Oct 9]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/28596308
48. Labianca R, Nordlinger B, Beretta GD, Mosconi S, Mandalà M, Cervantes A et al (2013) Early colon cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 24(Suppl 6):vi64–vi72