Chapter 15
Small Intestine Cancer

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15.1 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.

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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 >four-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.

15.2 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 to 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.

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].

15.2.1 Staging

15.2.1.1 Adenocarcinoma

The following is the tumor staging classification for adenocarcinoma: Tx, the primary tumor cannot be assessed; T0, no evidence of a primary tumor; Tis, 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) with an extension of $\leq$2 cm; T4, the tumor is perforating the visceral peritoneum or is directly invading other organs or structures (including other loops of the small intestine,

mesentery, or retroperitoneum by >2 cm; 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 to three regional lymph nodes; N2, metastasis in ≥4 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.

15.2.2 Carcinoid Tumors

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; 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, N0, and M0; stage IIB: T3, N0, and M0; stage IIIA: T4, N0, and M0; stage IIIB: any T, N1, or M0; and stage IV: any T, N, or M1.

15.2.3 Sarcomas

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

15.2.4 Lymphomas

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

15.3 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.

15.3.1 Stages I and II

Initial tumors can be treated with surgical resection, which can achieve a 5-year survival >75 % [27, 28]. 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 [29].

15.3.2 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 [30]. 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 [31], except for adenocarcinoma of the duodenum [32]. 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 [33]. 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) [34]. However, a large retrospective series on 491 patients by the Mayo Clinic did not show any benefit with adjuvant chemotherapy [35].

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 [36]. 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 [37]. 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].

15.3.3 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 [38]. 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 [39]. 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 [40]. 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) [41].

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 [42].

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 [43].

15.4 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 [44].

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