

Epidemiology, Risk Factors and Diagnosis of Small Bowel Adenocarcinoma

Thomas Aparicio ^{1,*}, Atanas Pachev ², Pierre Laurent-Puig ³ and Magali Svrcek ⁴

¹ Gastroenterology and Digestive Oncology, Saint Louis Hospital, Assistance Publique Hôpitaux de Paris (APHP), Université de Paris, 75010 Paris, France

² Radiology Department, Saint Louis Hospital, Assistance Publique Hôpitaux de Paris (APHP), Université de Paris, 75010 Paris, France; atanas.pachev@aphp.fr

³ Department of Biology, Georges Pompidou Hospital, Assistance Publique Hôpitaux de Paris (APHP), Université de Paris, 75010 Paris, France; pierre.laurent-puig@parisdescartes.fr

⁴ Department of Pathology, Saint Antoine Hospital, Assistance Publique Hôpitaux de Paris (APHP), Sorbonne Université, 75012 Paris, France; magali.svrcek@aphp.fr

* Correspondence: thomas.aparicio@aphp.fr; Tel.: +33-01-4249-9597; Fax: +33-01-4249-9168

Simple Summary: Small bowel adenocarcinoma is a rare tumor. Diagnosis is often obtained at an advanced stage and prognosis remains poor. The aim of this review is to report the recent epidemiological and risk factor data related to small bowel adenocarcinoma. New diagnostic tools are also described in this review.

Abstract: Adenocarcinomas of the small intestine are rare tumors but their incidence is increasing. There is a slight male predominance. The median age at diagnosis is the 6th decade. The most frequent primary location is the duodenum. There is no clearly identified environmental risk factor, but adenocarcinomas of the small intestine are associated in almost 20% of cases with predisposing diseases (Crohn's disease, Lynch syndrome, familial adenomatous polyposis, Peutz–Jeghers syndrome and celiac disease).

Keywords: small bowel adenocarcinoma; Crohn's disease; Lynch syndrome; enteroscopy; videocapsule endoscopy

Citation: Aparicio, T.; Pachev, A.; Laurent-Puig, P.; Svrcek, M. Epidemiology, Risk Factors and Diagnosis of Small Bowel Adenocarcinoma. *Cancers* **2022**, *14*, 2268. <https://doi.org/10.3390/cancers14092268>

Academic Editors: Fortunato Ciardiello and Masako Nakanishi

Received: 7 February 2022

Accepted: 22 April 2022

Published: 2 May 2022

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Copyright: © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

Adenocarcinomas of the small bowel are rare tumors but their incidence is increasing. The most frequent primary location is the duodenum. These cancers are more frequently associated with predisposing diseases than colon cancers and their carcinogenesis remains poorly understood. The diagnosis is most often made after a complication (hemorrhage or occlusion).

2. Incidence and Risk Factors

2.1. Epidemiology

Although the small bowel represents 75% of the length of the digestive tract and 90% of its mucosal surface, cancers of the small bowel remain rare and represent around 3% of digestive cancers according to recent US cancer statistics [1]. The incidence of small bowel cancers has slightly risen in recent decades. It increased from 1.18 per 100,000 in 1973 to 2.27 per 100,000 in 2004 in the United States [2]. Likewise, in France, the incidence increased during the period 1976–2001 [3] but also during the period 1996–2015 [4]. Four main histologic types are present in the small bowel: adenocarcinomas, neuroendocrine tumors, stromal tumors and lymphomas. Small bowel adenocarcinomas (SBAs) account for about 40% of small bowel cancers, at the same level as neuroendocrine tumors [3–5].

Incidence of SBA has increased in the United States and Europe [2,3,5], particularly SBA of the duodenum [5]. In a population-based study in France, the age-standardized incidence rate of SBA was 0.69 per 100,000 in the 1996–2000 period and increased to 0.8 per 100,000 in the 2011–2015 period in men and it increased from 0.37 per 100,000 in the 1996–2000 period to 0.51 per 100,000 in the 2011–2015 period in women [4]. In the Netherlands, the age-standardized incidence of SBA increased from 0.5 per 100,000 in 1999 to 0.7 per 100,000 in 2013 [5]. According to EUROCARE data, the annual number of new cases of SBA estimated in Europe is 3600 [6]. The duodenum is the most frequently affected segment, accounting for 55–82% of cases, followed by the jejunum (11–25%) and ileum (7–17%) [7]. The increasing incidence is mainly due to duodenum adenocarcinoma. In a population-based study the Netherlands, a twofold increase in duodenal cases was observed from the 1999–2003 period to the 2009–2013 period [5]. SBA is most often diagnosed during the sixth decade and a slight male predominance is observed [5,8,9]. Thus, despite SBA not being a significant public health concern, its increasing incidence requires more attention and efforts to improve the treatment of this orphan disease.

2.2. Carcinogenesis

The large discrepancy in the incidence between SBA and colorectal adenocarcinoma suggests lower exposure to carcinogens. The molecular abnormalities demonstrated in SBA are common with those found in colonic adenocarcinomas but with different frequencies for some of them, which reflect a distinct carcinogenesis. The prevalence of molecular abnormality is presented in Table 1. Loss of expression of the adenomatous polyposis coli (APC) protein causes deregulation of β -catenin, which accumulates in the cytoplasm and then in the nucleus and acts as a transcription factor that stimulates the expression of genes involved in cell proliferation. Mutations in the *APC* gene are considered to be one of the major early events in colorectal carcinogenesis. The prevalence of *APC* mutations in SBA is low, from 13 to 27%, depending on the series [9–12], unlike colorectal cancers where this mutation is found in nearly 80% of cases. It seems more common in tumors of the duodenum [12]. A mutation in the *TP53* gene has been detected in 38% to 58% of tumors [9–12], less commonly in duodenal tumors and in the case of DNA repair abnormality (dMMR phenotype) [12]. Mutation of *TP53* is associated with dismal prognosis [13]. A *KRAS* mutation is found in 43% to 56% of cases [9–12]. Other *RAS* mutations are present in less than 5% of tumors [12]. Overexpression of the HER2 protein is observed more rarely, unlike in adenocarcinoma of the stomach [8,14]. However, alteration or amplification of the *ERBB2* gene has been reported in 7% to 14% of tumors [9–12]. A study reported an association of *ERBB2* mutation and duodenal location [12] but this was not confirmed by other studies [9,10]. One study reported an association with *ERBB2* mutation and dMMR tumors [12]. Moreover, *ERBB2* mutation was associated with a dismal prognosis in one study [15] but not in a larger study [10]. The *BRAF* mutation frequency ranges from 4% to 11% [9–12] but the majority of *BRAF* mutations were not the V600E, the most prevalent one in colorectal cancers. Mutation of *BRCA2* was reported in 5% of the tumors in one study [9]. Overall, a potentially targetable alteration was reported in 90% of SBAs in one study [11]. Nevertheless, a confirmation of the efficacy of targeted therapy remains to be demonstrated in SBA treatment. The presence or absence of a predisposing disease can modify the mutational landscape of SBA. Thus, *ERBB2* tumor mutations were more frequent in Lynch syndrome than in Crohn's disease, and *TP53* mutations and *IDH1* mutations were more frequent in Crohn's disease [10]. *SMAD4* mutations were also associated with Crohn's disease in one study [16]. A dMMR phenotype is found with a variable frequency, according to a study, in 5 to 35% of cases [7]. Methylation of the *MLH1* gene promoter appears to be less frequently involved in SBA than in colorectal cancers, suggesting that the dMMR phenotype is more frequently linked to Lynch syndrome [17]. The dMMR phenotype is more common in duodenal or jejunum tumors than in ileum tumors [8]. A dMMR phenotype was associated with a better prognosis [10,18]. Finally, an analysis of the exome of 106 SBAs found differences in mutational profiles between different

segments [9]. Altogether, the discrepancy in molecular abnormality according to different small bowel segments in different studies is an issue. Larger studies with a pooled database are needed to establish the molecular phenotype of SBA according to localization and etiologic factors. The prognostic and theragnostic value of molecular abnormalities is a major issue to be assessed in the near future.

Table 1. Main molecular alterations observed in small bowel adenocarcinoma.

Publication	N	KRAS Mutation	TP53 Mutation	PIK3CA Mutation	APC Mutation	SMAD 4 Mutation	ERBB2 Overexpression or Mutation	dMMR Phenotype
Aparicio et al. (2021)	125	44%	38%	20%	18%	14%	7%	28%
Hänninen et al. (2018) *	91	47%	48%	9%	24%	15%	14%	14%
Schrock et al. (2016)	358	56%	58%	16%	27%	17%	8%	7%
Laforest et al. (2014)	83	43%	41%	9%	13%	9%	12%	21%

* Gene mutation frequency is reported only in pMMR tumors.

2.3. Risk Factors for Small Bowel Adenocarcinoma

The rarity of the pathology makes epidemiological studies difficult. Several hypotheses try to explain the low incidence of SBA. Owing to the shorter transit time in the small bowel compared to the colon, dietary carcinogens and xenobiotics have a shorter contact time with intestinal cells. Moreover, there is a lower concentration of aerophilic Gram-positive bacteria in the small bowel compared to the colon, even if the microbiota increase in the distal ileum [19]. Basal reactive oxygen species levels and antioxidant enzyme activities are lower in the small bowel than in the colon. Moreover, DNA adducts are more common due to oxidative stress in the colon than in the small intestine and therefore there is lower risk of small bowel transformation [20]. Finally, the epithelial cells of the small intestine have enzymatic equipment, in particular benzopyrene hydroxylases, which can protect against certain carcinogens [21]. The highest frequency of duodenal adenocarcinoma compared to distal SBA may be explained by a chronic irritation of acid gastric chyme as well as irritation by bile and pancreatic enzymes.

The presence of a predisposing disease or a genetic syndrome appears more frequently in SBA than in colorectal adenocarcinoma, and reached 20% in a large cohort [22]. Nevertheless, in the majority of cases no predisposing disease is involved.

2.3.1. Lifestyle Factors

Evidence of lifestyle factors is difficult to obtain due to low incidence of the disease. A few studies give some conflicting results [23–27]. A systematic review of lifestyle risk factors and SBA suggests that alcohol intake (highest versus lowest category: 1.51 [95% CI: 0.83–2.75]) and smoking (highest versus lowest category: 1.24 [95% CI: 0.71–2.17]) are associated with a higher risk of SBA [28]. The systematic review also suggests that high fiber intakes and normal body weight may be protective, while high intakes of red/processed meat and sugary drinks may increase the risk of SBA [28]. Occupation risk factors were explored by one study that suggested that building caretakers, housekeepers, general farm laborers, dockers, dry cleaners, textile workers and welders were at risk for SBA [29]. Nevertheless, this explorative study needs further evaluation. Indeed, obtaining evidence of lifestyle factors or specific carcinogens for this rare disease is challenging.

2.3.2. Genetic Syndromes

Lynch syndrome is a hereditary syndrome resulting from germline mutations in DNA mismatch repair genes (*MLH1*, *MSH2*, *MSH6* and *PMS2*). SBA is part of Lynch syndrome. However, the cumulative risk of developing this tumor remains low in patients with Lynch syndrome. It is estimated at 1% according to the ERISCAN study [30]. In a large recent study on Lynch syndrome, a gene-specific cumulative cancer risk for duodenal adenocarcinoma was reported, which was 6.5% for *MLH1* and 2.0% for *MSH2* carriers,

but no SBA mutation was observed in patients with *MSH6* or *PMS2* mutations [31]. It is recommended to thoroughly explore the entire duodenum and distal ileum during the usual control endoscopies but not systematic exploration by capsule endoscopy [32]. However, an SBA can reveal Lynch syndrome [33] which implies that an MMR phenotyping must be systematically carried out for all SBAs according to guidelines [34,35]. In the NADEGE cohort, Lynch syndrome was reported in 7% of patients. The tumors were located in the duodenum in 61% of cases, the jejunum in 30% of cases and the ileum in 9% of cases [22] (Table 2). The localization of SBA in the jejunum should be kept in mind during the follow-up of a patient with Lynch syndrome and the whole small bowel should be explored in case of symptoms such as bleeding, anemia or unexplained abdominal pain.

Table 2. Differences according to predisposing disease observed in the NADEGE cohort [22].

Tumor Characteristics	No Predisposing Disease <i>n</i> = 278	Crohn's Disease <i>n</i> = 30	Lynch Syndrome <i>n</i> = 24	<i>p</i> Value
Median age (range)	64 (24–90)	48 (33–82)	56 (23–74)	<0.0001
Primary: Duodenum	66.7%	6.9%	60.9%	<0.0001
Jejunum	19.9%	10.3%	30.4%	
Ileum	13.4%	82.8%	8.7%	
Differentiation:				
Well and moderate	81.6%	60.7%	68.2%	0.0166
Poorly differentiated	18.4%	39.3%	31.8%	

Familial adenomatous polyposis (FAP) is related to mutation of the *APC* gene that results in numerous colon polyps and colorectal adenocarcinoma. Adenocarcinoma of the duodenum and adenocarcinoma of the ampulla of Vater are the second tumor localizations after colon cancer and they are the main cause of death [36]. A large registry study of patients with FAP reports that 4.5% of the patients develop an upper digestive tract adenocarcinoma. Among them, the most frequent primary location was duodenum in 50% of cases, follow by Vater ampulla in 18%, stomach in 12%, jejunum in 8.5% and ileum in 1.7% [37]. A tight screening for adenoma in the duodenum is recommended for individuals affected by FAP throughout their lifetime [38]. In another study, the relative risks for duodenal adenocarcinoma or ampulloma adenocarcinoma in FAP patients compared to the general population were 330 and 123, respectively [39]. FAP was reported in 2% of patients in the NADEGE cohort, 5/6 of patients had a duodenum tumor and 1/6 a jejunum tumor [22]. Despite the fact that SBA beyond the duodenum is rare in FAP, the exploration of all the small bowel is indicated in case of relevant symptoms and normal upper endoscopy.

Peutz–Jeghers syndrome is a rare autosomal dominant syndrome caused by a mutation in the tumor suppressor gene *STK11* which greatly increases the risk of developing SBA. The relative risk of developing SBA has been estimated as 520 compared with the general population [40]. The lifetime incidence for adenocarcinoma is 1.7–13% and rises rapidly in older patients [41]. However, this syndrome remains a rare etiology of SBA, and in the NADEGE cohort only two cases, i.e., 0.6% of patients, were reported [22]. Some cases of SBA have also been reported in juvenile polyposis syndrome related to *SMAD4* or *BMPR1A* mutation [41].

2.3.3. Other Predisposing Diseases

Crohn's disease is characterized by chronic inflammation of digestive tract mucosae. The colon and distal small bowel are the most frequently involved digestive tract segments. SBA arises most frequently in the distal ileum and in young patients in contrast to sporadic SBA [22]. A retrospective small series of SBA related to Crohn's disease estimated the cumulative risk to be 0.2% after 10 years and 2.2% after 25 years of Crohn's disease

[42]. A large cohort study of 11,759 patients with Crohn's disease estimated the standardized incidence ratio for SBA in patients with small bowel Crohn's disease. It was 34.9 (95% CI, 11.3–81.5) in all patients and 46.0 (95% CI, 12.5–117.8) in patients suffering from Crohn's disease for more than 8 years. This level of risk corresponds to one third of the risk of developing adenocarcinoma of the colon in Crohn's disease affecting the colon [43]. Patients who have had resection of small intestine segments or who have prolonged treatment with salicylate have a lower risk of developing SBA [44]. Dysplasia is found near the adenocarcinoma in 49% of cases [45]. Crohn's disease was reported in 9% of patients included in the NADEGE cohort. The median age of the patients is only 48 years and the tumor location is the duodenum in 7% of cases, the jejunum in 10% of cases and the ileum in 83% of cases [22]. The SBAs arising in Crohn's disease have an aggressive phenotype with frequent metastases and a frequent poor differentiation [22] (Table 2). SBA should be suspected in patients with prolonged Crohn's disease affecting the small bowel and that presents a worsening of symptoms or a resistance to usual treatment.

Celiac disease is associated with a relative risk of SBA compared to the general population which is estimated at 10 in a Swedish registry study [46]. A larger recent Swedish nationwide cohort of individuals with celiac disease reported a hazard ratio for SBA of only 3.05 [47]. In a large Italian cohort of celiac disease, 0.65% of the patients developed SBA [48]. In the NADEGE cohort, celiac disease was reported in 1.7% of the patients [22]. Celiac disease should be systematically screened after diagnosis of SBA as the cancer could reveal celiac disease with mild symptoms.

3. Clinical Presentation and Diagnostic Workup

3.1. Clinical Presentation

Due to the rarity of the disease, there is no screening program for SBA diagnosis. The symptoms are non-specific. In a study of 217 patients with SBA, most of the patients (66%) had abdominal pain at the time of diagnosis. Emergency diagnosis with occlusion or bleeding was reported in 40% and 24%, respectively. Symptoms differ according to localization. There is less bowel obstruction in case of duodenal tumors compared to jejuno-ileal tumors (34% vs. 47%; $p = 0.06$). At the time of this study (1978 to 1998), the diagnosis was made mainly by upper endoscopy (28%), during surgery (26%), by a small bowel barium transit (22%), by a CT scan (18%), ultrasound examination (3%) or physical examination (3%) [49]. In a more recent Japanese multicenter study, 43% of the duodenum adenocarcinomas were diagnosed without symptoms but this may be related to the gastric cancer screening ongoing in Japan [50]. In the NADEGE cohort, the contribution to diagnosis varied according to small bowel segment. Upper endoscopy gave a diagnosis for 49% of the duodenal adenocarcinoma, colonoscopy for 41% of the ileum adenocarcinoma and capsule endoscopy or CT scan with enteroclysis for 26% and 34% of the jejunum adenocarcinoma [22]. In Crohn's disease, the diagnosis is frequently reached postoperatively after resection of an obstructed small bowel segment [42].

In the event of occult bleeding, exploration by capsule endoscopy has a sensitivity of 88.9% to 95% and a specificity of 95% to 75% for detecting a tumor of the small intestine [51,52]. Exploration by capsule endoscopy should not be performed in the event of a sub-occlusive syndrome and verification of the permeability of the small intestine with a patency capsule should be performed in the slightest doubt. For patients with intestinal polypoid syndromes, capsule endoscopy may be used to screen jejuno-ileal polyps [53]. A study that compared capsule endoscopy with magnetic resonance enterography reported that capsule endoscopy misses large polyps more often than magnetic resonance enterography [54]. Moreover, capsule endoscopy may miss tumors located in the duodenum or proximal jejunum because of rapid transit [55]. Improvement of imaging techniques may allow differential tumor type diagnosis, as was suggested by a small study assessing SBA and primary small bowel lymphoma with spectral CT imaging [56]. According to a prospective study on 150 patients with a suspected small bowel disease, magnetic resonance

(MRI) enterography is more accurate than CT enterography for tumor detection [57]. Double balloon enteroscopy can then make it possible to obtain a preoperative histological diagnosis if necessary [58]. In patients with polyposis syndrome, device-assisted enteroscopy may be useful to remove polyps to prevent malignant transformation, bleeding or obstruction or to tattoo lesions before surgery [53]. Nevertheless, it must be pointed out that despite the new tools for diagnosis, there is no improvement in early diagnosis of SBA according to the result of a population-based study in the Netherlands [5].

Even in patients with predisposing disease, the early diagnosis is a challenge and no specific screening is recommended. In Crohn's disease, the diagnosis of small bowel adenocarcinoma is often difficult because the symptoms are similar to those of the underlying pathology [42]. A chronic small bowel sub-obstruction that is not improved by medical treatment should be considered for surgical resection. In Lynch syndrome, two studies have evaluated videocapsule endoscopy for small bowel neoplasia screening. A prevalence of 8.6% of neoplasia (including adenomas and cancers) was reported in one study [59] but in another study the screening by capsule endoscopy had a low diagnostic yield with evidence of a small bowel tumors in only 1.5% [60]. In those studies, duodenal location was the most frequent. Thus, in Lynch syndrome, it is not recommended to perform systematic capsule endoscopy screening but systematic exploration of the duodenum should be performed when an upper endoscopy is indicated. In FAP, it is recommended to systematically screen only ampullary and duodenal polyps [39].

3.2. Initial Workup and Staging

Guidelines recommend an initial basic workup and some more specific examinations according to localization or predisposing disease [34,35]. The basic assessment includes a contrast-enhanced thoraco-abdomino-pelvic CT scan to evaluate local and metastatic extension. Liver MRI may be useful in case of contra-indication for iodine contrast agent or if liver metastases are suspected on CT scan examination. If possible, liver MRI should be performed before biliary drainage or stenting to minimize artifacts. Positron emission tomography (PET) scanning is not routinely indicated but may be considered if there is doubt about metastasis on initial CT staging [61]. A gastric endoscopy and colonoscopy looking for other tumors are indicated in case of suspicion of genetic predisposition. In case of duodenal adenocarcinoma, an endoscopic ultrasound is recommended to assess vascular invasion and discern duodenal lesions from ampullary, biliary or pancreatic primary [62].

Dosage of CEA and CA 19-9 is useful at the initial workup, particularly in the event of a metastatic tumor, due to their prognostic value [34]. In Crohn's disease, exploration of the entire intestine with MRI enterography or capsule endoscopy should be done to diagnose other synchronous tumor lesions. Testing for anti-transglutaminase A antibodies and duodenal biopsies are routinely recommended to detect celiac disease. Systematic screening for microsatellite instability or loss of expression of one of the MMR proteins should be systematically carried out to screen for Lynch syndrome and, for it, prognostic and predictive value for immunotherapy [10].

After diagnosis, follow-up with clinical examination, imaging and tumor marker dosage for a total duration of 5 years are recommended after a curative resection [34,35].

Staging is based on TNM staging (Table 3). It is recommended to assess a minimum of eight lymph nodes to have an adequate staging [34,35]. In western countries, the repartition of stages at diagnosis is: stage I (T1–T2, N0, M0) in 5% to 8%, stage II (T3–T4, N0, M0) in 20% to 29%, stage III (T1–4, N1–2, M0) in 24% to 29% and stage IV (M1) in 33% to 36% [5,22,63]. This is in contrast to a Japanese series that reported early stage diagnosis with 33% of the patients diagnosed at stage I, 17% at stage II, 24% at stage III and 26% at stage IV [50]. It must be pointed out that, in this study, early stage diagnosis was mainly reported for duodenal primary that could be explained by a screening program of gastric cancer in Japan. In the NADEGE cohort, there is no difference in stage at diagnosis according to predisposing disease or primary localization except 9% of unresectable localized tumors in duodenum primary with unknown precise staging [22].

Table 3. TNM staging from 8th edition 2017 [64].

Primary tumor (T)	
T0	There is no evidence of a primary tumor
Tis	Carcinoma in situ
T1	Tumor invades the mucosa, muscularis mucosa or submucosa
T1a	Tumor invades the lamina propria or muscularis mucosa
T1b	Tumor invades the submucosa
T2	Tumor invades the muscularis propria
T3	Tumor invades the subserosa or into the non-peritonealized perimuscular tissue (mesentery or retroperitoneum)
T4	Tumor perforates the visceral peritoneum (T4a) or directly invades other organs or structures (T4b), including: <ul style="list-style-type: none"> - other loops of the small intestine, mesentery or retroperitoneum - through the serosa into the abdominal wall - the pancreas (only for tumors in the duodenum)
Regional lymph nodes (N)	
N0	No regional lymph node metastasis
N1	Metastasis in 1–2 regional lymph nodes
N2	Metastasis in 3 or more regional lymph nodes
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
Cancer staging	
Stage 0: Tis, N0, M0	
Stage I: T1 or T2, N0, M0	
Stage IIA: T3, N0, M0	
Stage IIB: T4, N0, M0	
Stage IIIA: any T, N1, M0	
Stage IIIB: any T, N2, M0	
Stage IV: any T, any N, M1	

3.3. Histological Diagnosis

Small intestine adenocarcinomas can occur anywhere in the gastrointestinal tract between the pylorus and the ileocecal valve [65]. In recent years, ampullary tumors have been considered a separate entity from head of pancreas and lower biliary tract tumors [66]. The region of ampulla is a crossroads between intestinal-type and pancreatobiliary-type epithelia. Thus, clinically and pathologically, it can be very challenging to distinguish between a tumor of the ampulla, an extra-ampullary duodenal tumor, or a metastatic tumor from the immediately neighboring regions of bile duct and pancreas. In this case, a careful macroscopic examination and dissection of pancreatoduodenectomy specimens is crucial and a tumor is considered to be of ampullary origin when its epicenter is the ampulla [67]. In the same way, the criterion for defining the duodenal origin of a tumor arising in the vicinity of the ampulla is the lack of both gross and microscopic involvement of the ampulla [68].

Histologically, small intestine adenocarcinomas resemble their colorectal counterparts. However poorly differentiated tumors with glandular, squamous and undifferentiated components are more frequently observed [65]. Extra-ampullary duodenal adenocarcinomas demonstrate histologic heterogeneity and can be divided into two major phenotypes: (i) intestinal-type adenocarcinomas, morphologically similar to their colorectal counterpart, and (ii) gastric-type adenocarcinomas, commonly associated with gastric foveolar metaplasia (63% of the cases) or Brunner gland hyperplasia (53% of the cases), which are two characteristics only observed in that setting. The frequent association with

adenomas for intestinal-type adenocarcinomas could suggest that duodenal adenocarcinomas develop in pre-existing adenomas, with an adenoma-carcinoma sequence similar to that described in colorectal carcinogenesis [69]. The intestinal type is associated with longer survival. Intestinal-type adenocarcinomas generally express CDX-2, MUC2 and CD10, whereas the gastric-type adenocarcinomas express MUC5AC and MUC6 [68]. Immunohistochemistry is not required to distinguish the gastric and intestinal phenotypes, but may be helpful in challenging cases.

It can also be difficult to distinguish between a metastatic adenocarcinoma, notably of colorectal origin, and a primary small intestine adenocarcinoma. In this case, the presence of a pre-cancerous lesion adjacent to the invasive lesion cannot be used to make a decision, because the small intestinal mucosa tends to mimic a pre-existing adenoma.

Tumors arising in the region of the ampulla may have either intestinal or pancreatobiliary type of differentiation. However, about 40% of cases harbor mixed or hybrid phenotypes. Panels of immunohistochemistry including MUC1, MUC2, CDX2, CK20 and MUC5AC can help in the classification of adenocarcinomas as intestinal or pancreatobiliary type in a substantial proportion of cases [70].

In the NADEGE cohort, around 80% of SBAs are well or moderately differentiated, but it must be pointed out that a poor differentiation is observed in 40% of Crohn's disease cases, around 30% of tumors related to Lynch syndrome and 37% of ileum tumors [22].

4. Conclusions

In conclusion, SBA is a rare disease but with an increasing incidence. Duodenal adenocarcinoma may be diagnosed with upper endoscopy that should explore, as far as possible, the whole duodenum in case of macroscopic or occult bleeding. Except in FAP, no systematic screening is recommended in case of other predisposing diseases but clinicians should be aware of the risk of SBA. Early diagnosis remains infrequent and most SBAs are diagnosed at an advance stage. Several molecular abnormalities may be targeted by specific drugs. Currently, only immunotherapy in case of dMMR tumors has demonstrated significant efficacy. A global effort is needed to better understand risk factors and early carcinogenesis of this orphan disease.

Author Contributions: Conceptualization, T.A.; writing—original draft preparation, T.A.; writing—review and editing, A.P., P.L.-P., M.S. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Siegel, R.L.; Miller, K.D.; Jemal, A. Cancer Statistics, 2019. *CA Cancer J. Clin.* **2019**, *69*, 7–34. <https://doi.org/10.3322/caac.21551>.
2. Chow, J.S.; Chen, C.C.; Ahsan, H.; Neugut, A.I. A Population-Based Study of the Incidence of Malignant Small Bowel Tumours: SEER, 1973–1990. *Int. J. Epidemiol.* **1996**, *25*, 722–728. <https://doi.org/10.1093/ije/25.4.722>.
3. Lepage, C.; Bouvier, A.-M.; Manfredi, S.; Dancourt, V.; Faivre, J. Incidence and Management of Primary Malignant Small Bowel Cancers: A Well-Defined French Population Study. *Am. J. Gastroenterol.* **2006**, *101*, 2826–2832. <https://doi.org/10.1111/j.1572-0241.2006.00854.x>.
4. Bouvier, A.-M.; Robaszkiewicz, M.; Jooste, V.; Cariou, M.; Drouillard, A.; Bouvier, V.; Nousbaum, J.-B.; French Network of Cancer Registries (FRANCIM) Trends in Incidence of Small Bowel Cancer According to Histology: A Population-Based Study. *J. Gastroenterol.* **2020**, *55*, 181–188. <https://doi.org/10.1007/s00535-019-01636-z>.
5. Legué, L.M.; Bernards, N.; Gerritse, S.L.; van Oudheusden, T.R.; de Hingh, I.H.J.T.; Creemers, G.-J.M.; Ten Tije, A.J.; Lemmens, V.E.P.P. Trends in Incidence, Treatment and Survival of Small Bowel Adenocarcinomas between 1999 and 2013: A Population-Based Study in The Netherlands. *Acta Oncol. Stockh. Swed.* **2016**, *55*, 1183–1189. <https://doi.org/10.1080/0284186X.2016.1182211>.
6. Faivre, J.; Trama, A.; De Angelis, R.; Elferink, M.; Siesling, S.; Audisio, R.; Bosset, J.F.; Cervantes, A.; Lepage, C.; RARECARE Working Group Incidence, Prevalence and Survival of Patients with Rare Epithelial Digestive Cancers Diagnosed in Europe in 1995–2002. *Eur. J. Cancer* **2012**, *48*, 1417–1424. <https://doi.org/10.1016/j.ejca.2011.10.038>.

7. Aparicio, T.; Zaan, A.; Svrcek, M.; Laurent-Puig, P.; Carrere, N.; Manfredi, S.; Locher, C.; Afchain, P. Small Bowel Adenocarcinoma: Epidemiology, Risk Factors, Diagnosis and Treatment. *Dig. Liver Dis.* **2014**, *46*, 97–104. <https://doi.org/10.1016/j.dld.2013.04.013>.
8. Aparicio, T.; Svrcek, M.; Zaan, A.; Beohou, E.; Laforest, A.; Afchain, P.; Mitry, E.; Taieb, J.; Di Fiore, F.; Gornet, J.-M.; et al. Small Bowel Adenocarcinoma Phenotyping, a Clinicobiological Prognostic Study. *Br. J. Cancer* **2013**, *109*, 3057–3066. <https://doi.org/10.1038/bjc.2013.677>.
9. Hänninen, U.A.; Katainen, R.; Tanskanen, T.; Plaketti, R.-M.; Laine, R.; Hamberg, J.; Ristimäki, A.; Pukkala, E.; Taipale, M.; Mecklin, J.-P.; et al. Exome-Wide Somatic Mutation Characterization of Small Bowel Adenocarcinoma. *PLoS Genet.* **2018**, *14*, e1007200. <https://doi.org/10.1371/journal.pgen.1007200>.
10. Aparicio, T.; Svrcek, M.; Henriques, J.; Afchain, P.; Lièvre, A.; Tougeron, D.; Gagniere, J.; Terrebonne, E.; Piessen, G.; Legoux, J.-L.; et al. Panel Gene Profiling of Small Bowel Adenocarcinoma: Results from the NADEGE Prospective Cohort. *Int. J. Cancer* **2021**, *148*, 1731–1742. <https://doi.org/10.1002/ijc.33392>.
11. Schrock, A.B.; Devoe, C.E.; McWilliams, R.; Sun, J.; Aparicio, T.; Stephens, P.J.; Ross, J.S.; Wilson, R.; Miller, V.A.; Ali, S.M.; et al. Genomic Profiling of Small-Bowel Adenocarcinoma. *JAMA Oncol.* **2017**, *3*, 1546–1553. <https://doi.org/10.1001/jamaoncol.2017.1051>.
12. Laforest, A.; Aparicio, T.; Zaan, A.; Silva, F.P.; Didelot, A.; Desbeaux, A.; Le Corre, D.; Benhaim, L.; Pallier, K.; Aust, D.; et al. ERBB2 Gene as a Potential Therapeutic Target in Small Bowel Adenocarcinoma. *Eur. J. Cancer* **2014**, *50*, 1740–1746. <https://doi.org/10.1016/j.ejca.2014.04.007>.
13. Alvi, M.A.; McArt, D.G.; Kelly, P.; Fuchs, M.-A.; Alderdice, M.; McCabe, C.M.; Bingham, V.; McGready, C.; Tripathi, S.; Emmert-Streib, F.; et al. Comprehensive Molecular Pathology Analysis of Small Bowel Adenocarcinoma Reveals Novel Targets with Potential for Clinical Utility. *Oncotarget* **2015**, *6*, 20863–20874. <https://doi.org/10.18632/oncotarget.4576>.
14. Overman, M.J.; Pozadzides, J.; Kopetz, S.; Wen, S.; Abbruzzese, J.L.; Wolff, R.A.; Wang, H. Immunophenotype and Molecular Characterisation of Adenocarcinoma of the Small Intestine. *Br. J. Cancer* **2010**, *102*, 144–150. <https://doi.org/10.1038/sj.bjc.6605449>.
15. Adam, L.; San Lucas, F.A.; Fowler, R.; Yu, Y.; Wu, W.; Liu, Y.; Wang, H.; Menter, D.; Tetzlaff, M.T.; Ensor, J.; et al. DNA Sequencing of Small Bowel Adenocarcinomas Identifies Targetable Recurrent Mutations in the ERBB2 Signaling Pathway. *Clin. Cancer Res.* **2019**, *25*, 641–651. <https://doi.org/10.1158/1078-0432.CCR-18-1480>.
16. Liao, X.; Li, G.; McBride, R.; Houldsworth, J.; Harpaz, N.; Polydorides, A.D. Clinicopathological and Molecular Characterisation of Crohn's Disease-Associated Small Bowel Adenocarcinomas. *J. Crohns Colitis* **2020**, *14*, 287–294. <https://doi.org/10.1093/ecco-jcc/jjz135>.
17. Svrcek, M.; Jourdan, F.; Sebbagh, N.; Couvelard, A.; Chatelain, D.; Mourra, N.; Olschwang, S.; Wendum, D.; Fléjou, J.-F. Immunohistochemical Analysis of Adenocarcinoma of the Small Intestine: A Tissue Microarray Study. *J. Clin. Pathol.* **2003**, *56*, 898–903. <https://doi.org/10.1136/jcp.56.12.898>.
18. Vanoli, A.; Grillo, F.; Guerini, C.; Neri, G.; Arpa, G.; Klersy, C.; Nesi, G.; Giuffrida, P.; Sampietro, G.; Ardizzone, S.; et al. Prognostic Role of Mismatch Repair Status, Histotype and High-Risk Pathologic Features in Stage II Small Bowel Adenocarcinomas. *Ann. Surg. Oncol.* **2021**, *28*, 1167–1177. <https://doi.org/10.1245/s10434-020-08926-4>.
19. Schottenfeld, D.; Beebe-Dimmer, J.L.; Vigneau, F.D. The Epidemiology and Pathogenesis of Neoplasia in the Small Intestine. *Ann. Epidemiol.* **2009**, *19*, 58–69. <https://doi.org/10.1016/j.annepidem.2008.10.004>.
20. Sanders, L.M.; Henderson, C.E.; Hong, M.Y.; Barhoumi, R.; Burghardt, R.C.; Carroll, R.J.; Turner, N.D.; Chapkin, R.S.; Lupton, J.R. Pro-Oxidant Environment of the Colon Compared to the Small Intestine May Contribute to Greater Cancer Susceptibility. *Cancer Lett.* **2004**, *208*, 155–161. <https://doi.org/10.1016/j.canlet.2003.12.007>.
21. Delaunoy, T.; Neczyporenko, F.; Limburg, P.J.; Erlichman, C. Pathogenesis and Risk Factors of Small Bowel Adenocarcinoma: A Colorectal Cancer Sibling? *Am. J. Gastroenterol.* **2005**, *100*, 703–710. <https://doi.org/10.1111/j.1572-0241.2005.40605.x>.
22. Aparicio, T.; Henriques, J.; Manfredi, S.; Tougeron, D.; Bouché, O.; Pezet, D.; Piessen, G.; Coriat, R.; Zaan, A.; Legoux, J.-L.; et al. Small Bowel Adenocarcinoma: Results from a Nationwide Prospective ARCAD-NADEGE Cohort Study of 347 Patients. *Int. J. Cancer* **2020**, *147*, 967–977. <https://doi.org/10.1002/ijc.32860>.
23. Wu, A.H.; Yu, M.C.; Mack, T.M. Smoking, Alcohol Use, Dietary Factors and Risk of Small Intestinal Adenocarcinoma. *Int. J. Cancer* **1997**, *70*, 512–517. [https://doi.org/10.1002/\(sici\)1097-0215\(19970304\)70:5<512::aid-ijc4>3.0.co;2-0](https://doi.org/10.1002/(sici)1097-0215(19970304)70:5<512::aid-ijc4>3.0.co;2-0).
24. Kaerlev, L.; Teglbjaerg, P.S.; Sabroe, S.; Kolstad, H.A.; Ahrens, W.; Eriksson, M.; Guénel, P.; Hardell, L.; Launoy, G.; Merler, E.; et al. Is There an Association between Alcohol Intake or Smoking and Small Bowel Adenocarcinoma? Results from a European Multi-Center Case-Control Study. *Cancer Causes Control CCC* **2000**, *11*, 791–797. <https://doi.org/10.1023/a:1008920502888>.
25. Negri, E.; Bosetti, C.; La Vecchia, C.; Fioretti, F.; Conti, E.; Franceschi, S. Risk Factors for Adenocarcinoma of the Small Intestine. *Int. J. Cancer* **1999**, *82*, 171–174. [https://doi.org/10.1002/\(sici\)1097-0215\(19990719\)82:2<171::aid-ijc3>3.0.co;2-t](https://doi.org/10.1002/(sici)1097-0215(19990719)82:2<171::aid-ijc3>3.0.co;2-t).
26. Cross, A.J.; Hollenbeck, A.R.; Park, Y. A Large Prospective Study of Risk Factors for Adenocarcinomas and Malignant Carcinoid Tumors of the Small Intestine. *Cancer Causes Control CCC* **2013**, *24*, 1737–1746. <https://doi.org/10.1007/s10552-013-0251-8>.
27. Cross, A.J.; Leitzmann, M.F.; Subar, A.F.; Thompson, F.E.; Hollenbeck, A.R.; Schatzkin, A. A Prospective Study of Meat and Fat Intake in Relation to Small Intestinal Cancer. *Cancer Res.* **2008**, *68*, 9274–9279. <https://doi.org/10.1158/0008-5472.CAN-08-2015>.
28. Bennett, C.M.; Coleman, H.G.; Veal, P.G.; Cantwell, M.M.; Lau, C.C.L.; Murray, L.J. Lifestyle Factors and Small Intestine Adenocarcinoma Risk: A Systematic Review and Meta-Analysis. *Cancer Epidemiol.* **2015**, *39*, 265–273. <https://doi.org/10.1016/j.canep.2015.02.001>.

29. Kaerlev, L.; Teglbjaerg, P.S.; Sabroe, S.; Kolstad, H.A.; Ahrens, W.; Eriksson, M.; González, A.L.; Guénel, P.; Hardell, L.; Launoy, G.; et al. Occupation and Small Bowel Adenocarcinoma: A European Case-Control Study. *Occup. Environ. Med.* **2000**, *57*, 760–766. <https://doi.org/10.1136/oem.57.11.760>.
30. Bonadona, V.; Bonaïti, B.; Olschwang, S.; Grandjouan, S.; Huiart, L.; Longy, M.; Guimbaud, R.; Buecher, B.; Bignon, Y.-J.; Caron, O.; et al. Cancer Risks Associated with Germline Mutations in MLH1, MSH2, and MSH6 Genes in Lynch Syndrome. *JAMA* **2011**, *305*, 2304–2310.
31. Møller, P.; Seppälä, T.T.; Bernstein, I.; Holinski-Feder, E.; Sala, P.; Gareth Evans, D.; Lindblom, A.; Macrae, F.; Blanco, I.; Sijmons, R.H.; et al. Cancer Risk and Survival in Path_MMR Carriers by Gene and Gender up to 75 Years of Age: A Report from the Prospective Lynch Syndrome Database. *Gut* **2018**, *67*, 1306–1316. <https://doi.org/10.1136/gutjnl-2017-314057>.
32. Vasen, H.F.A.; Blanco, I.; Aktan-Collan, K.; Gopie, J.P.; Alonso, A.; Aretz, S.; Bernstein, I.; Bertario, L.; Burn, J.; Capella, G.; et al. Revised Guidelines for the Clinical Management of Lynch Syndrome (HNPCC): Recommendations by a Group of European Experts. *Gut* **2013**, *62*, 812–823. <https://doi.org/10.1136/gutjnl-2012-304356>.
33. Babba, T.; Schischmanoff, O.; Lagorce, C.; Wind, P.; Des Guetz, G.; Aparicio, T.; Benamouzig, R. Small Bowel Carcinoma Revealing HNPCC Syndrome. *Gastroenterol. Clin. Biol.* **2010**, *34*, 325–328. <https://doi.org/10.1016/j.gcb.2010.04.007>.
34. Locher, C.; Batumona, B.; Afchain, P.; Carrère, N.; Samalin, E.; Cellier, C.; Aparicio, T.; Becouarn, Y.; Bedenne, L.; Michel, P.; et al. Small Bowel Adenocarcinoma: French Intergroup Clinical Practice Guidelines for Diagnosis, Treatments and Follow-up (SNFGE, FFCD, GERCOR, UNICANCER, SFCD, SFED, SFRO). *Dig. Liver Dis.* **2018**, *50*, 15–19. <https://doi.org/10.1016/j.dld.2017.09.123>.
35. Benson, A.B.; Venook, A.P.; Al-Hawary, M.M.; Arain, M.A.; Chen, Y.-J.; Ciombor, K.K.; Cohen, S.A.; Cooper, H.S.; Deming, D.A.; Garrido-Laguna, I.; et al. Small Bowel Adenocarcinoma, Version 1.2020, NCCN Clinical Practice Guidelines in Oncology. *J. Natl. Compr. Cancer Netw. JNCCN* **2019**, *17*, 1109–1133. <https://doi.org/10.6004/jnccn.2019.0043>.
36. Gallagher, M.C.; Phillips, R.K.S.; Bulow, S. Surveillance and Management of Upper Gastrointestinal Disease in Familial Adenomatous Polyposis. *Fam. Cancer* **2006**, *5*, 263–273. <https://doi.org/10.1007/s10689-005-5668-0>.
37. Jagelman, D.G.; DeCosse, J.J.; Bussey, H.J. Upper Gastrointestinal Cancer in Familial Adenomatous Polyposis. *Lancet* **1988**, *331*, 1149–1151. [https://doi.org/10.1016/s0140-6736\(88\)91962-9](https://doi.org/10.1016/s0140-6736(88)91962-9).
38. Bülow, S.; Björk, J.; Christensen, I.J.; Fausa, O.; Järvinen, H.; Moesgaard, F.; Vasen, H.F.A.; DAF Study Group Duodenal Adenomatosis in Familial Adenomatous Polyposis. *Gut* **2004**, *53*, 381–386. <https://doi.org/10.1136/gut.2003.027771>.
39. Offerhaus, G.J.; Giardiello, F.M.; Krush, A.J.; Booker, S.V.; Tersmette, A.C.; Kelley, N.C.; Hamilton, S.R. The Risk of Upper Gastrointestinal Cancer in Familial Adenomatous Polyposis. *Gastroenterology* **1992**, *102*, 1980–1982. [https://doi.org/10.1016/0016-5085\(92\)90322-p](https://doi.org/10.1016/0016-5085(92)90322-p).
40. Giardiello, F.M.; Brensinger, J.D.; Tersmette, A.C.; Goodman, S.N.; Petersen, G.M.; Booker, S.V.; Cruz-Correa, M.; Offerhaus, J.A. Very High Risk of Cancer in Familial Peutz-Jeghers Syndrome. *Gastroenterology* **2000**, *119*, 1447–1453. <https://doi.org/10.1053/gast.2000.20228>.
41. Shenoy, S. Genetic Risks and Familial Associations of Small Bowel Carcinoma. *World J. Gastrointest. Oncol.* **2016**, *8*, 509–519. <https://doi.org/10.4251/wjgo.v8.i6.509>.
42. Palascak-Juif, V.; Bouvier, A.M.; Cosnes, J.; Flourié, B.; Bouché, O.; Cadot, G.; Lémann, M.; Bonaz, B.; Denet, C.; Marteau, P.; et al. Small Bowel Adenocarcinoma in Patients with Crohn's Disease Compared with Small Bowel Adenocarcinoma de Novo. *Inflamm. Bowel Dis.* **2005**, *11*, 828–832. <https://doi.org/10.1097/01.mib.0000179211.03650.b6>.
43. Elriz, K.; Carrat, F.; Carbonnel, F.; Marthey, L.; Bouvier, A.M.; Beaugerie, L.; CESAME study group Incidence, Presentation, and Prognosis of Small Bowel Adenocarcinoma in Patients with Small Bowel Crohn's Disease: A Prospective Observational Study. *Inflamm. Bowel Dis.* **2013**, *19*, 1823–1826. <https://doi.org/10.1097/MIB.0b013e31828c84f2>.
44. Piton, G.; Cosnes, J.; Monnet, E.; Beaugerie, L.; Seksik, P.; Savoye, G.; Cadot, G.; Flourie, B.; Capelle, P.; Marteau, P.; et al. Risk Factors Associated with Small Bowel Adenocarcinoma in Crohn's Disease: A Case-Control Study. *Am. J. Gastroenterol.* **2008**, *103*, 1730–1736. <https://doi.org/10.1111/j.1572-0241.2008.01847.x>.
45. Svrcek, M.; Piton, G.; Cosnes, J.; Beaugerie, L.; Vermeire, S.; Geboes, K.; Lemoine, A.; Cervera, P.; El-Murr, N.; Dumont, S.; et al. Small Bowel Adenocarcinomas Complicating Crohn's Disease Are Associated with Dysplasia: A Pathological and Molecular Study. *Inflamm. Bowel Dis.* **2014**, *20*, 1584–1592. <https://doi.org/10.1097/MIB.0000000000000112>.
46. Askling, J.; Linet, M.; Gridley, G.; Halstensen, T.S.; Ekström, K.; Ekblom, A. Cancer Incidence in a Population-Based Cohort of Individuals Hospitalized with Celiac Disease or Dermatitis Herpetiformis. *Gastroenterology* **2002**, *123*, 1428–1435. <https://doi.org/10.1053/gast.2002.36585>.
47. Emilsson, L.; Semrad, C.; Lebowitz, B.; Green, P.H.R.; Ludvigsson, J.F. Risk of Small Bowel Adenocarcinoma, Adenomas, and Carcinoids in a Nationwide Cohort of Individuals With Celiac Disease. *Gastroenterology* **2020**, *159*, 1686–1694.e2. <https://doi.org/10.1053/j.gastro.2020.07.007>.
48. Caio, G.; Volta, U.; Ursini, F.; Manfredini, R.; De Giorgio, R. Small Bowel Adenocarcinoma as a Complication of Celiac Disease: Clinical and Diagnostic Features. *BMC Gastroenterol.* **2019**, *19*, 45. <https://doi.org/10.1186/s12876-019-0964-6>.
49. Dabaja, B.S.; Suki, D.; Pro, B.; Bonnen, M.; Ajani, J. Adenocarcinoma of the Small Bowel: Presentation, Prognostic Factors, and Outcome of 217 Patients. *Cancer* **2004**, *101*, 518–526. <https://doi.org/10.1002/cncr.20404>.
50. Sakae, H.; Kanzaki, H.; Nasu, J.; Akimoto, Y.; Matsueda, K.; Yoshioka, M.; Nakagawa, M.; Hori, S.; Inoue, M.; Inaba, T.; et al. The Characteristics and Outcomes of Small Bowel Adenocarcinoma: A Multicentre Retrospective Observational Study. *Br. J. Cancer* **2017**, *117*, 1607–1613. <https://doi.org/10.1038/bjc.2017.338>.

51. Hartmann, D.; Schmidt, H.; Bolz, G.; Schilling, D.; Kinzel, F.; Eickhoff, A.; Huschner, W.; Möller, K.; Jakobs, R.; Reitzig, P.; et al. A Prospective Two-Center Study Comparing Wireless Capsule Endoscopy with Intraoperative Enteroscopy in Patients with Obscure GI Bleeding. *Gastrointest. Endosc.* **2005**, *61*, 826–832. [https://doi.org/10.1016/s0016-5107\(05\)00372-x](https://doi.org/10.1016/s0016-5107(05)00372-x).
52. Pennazio, M.; Santucci, R.; Rondonotti, E.; Abbiati, C.; Beccari, G.; Rossini, F.P.; De Franchis, R. Outcome of Patients with Obscure Gastrointestinal Bleeding after Capsule Endoscopy: Report of 100 Consecutive Cases. *Gastroenterology* **2004**, *126*, 643–653. <https://doi.org/10.1053/j.gastro.2003.11.057>.
53. Kim, E.R. Roles of Capsule Endoscopy and Device-Assisted Enteroscopy in the Diagnosis and Treatment of Small-Bowel Tumors. *Clin. Endosc.* **2020**, *53*, 410–416. <https://doi.org/10.5946/ce.2020.161>.
54. Gupta, A.; Postgate, A.J.; Burling, D.; Ilangoan, R.; Marshall, M.; Phillips, R.K.S.; Clark, S.K.; Fraser, C.H. A Prospective Study of MR Enterography versus Capsule Endoscopy for the Surveillance of Adult Patients with Peutz-Jeghers Syndrome. *AJR Am. J. Roentgenol.* **2010**, *195*, 108–116. <https://doi.org/10.2214/AJR.09.3174>.
55. Cheung, D.Y.; Kim, J.S.; Shim, K.-N.; Choi, M.-G.; Korean Gut Image Study Group The Usefulness of Capsule Endoscopy for Small Bowel Tumors. *Clin. Endosc.* **2016**, *49*, 21–25. <https://doi.org/10.5946/ce.2016.49.1.21>.
56. Yang, C.-B.; Yu, N.; Jian, Y.-J.; Yu, Y.; Duan, H.-F.; Zhang, X.-R.; Ma, G.-M.; Guo, Y.; Duan, X. Spectral CT Imaging in the Differential Diagnosis of Small Bowel Adenocarcinoma From Primary Small Intestinal Lymphoma. *Acad. Radiol.* **2019**, *26*, 878–884. <https://doi.org/10.1016/j.acra.2018.08.020>.
57. Masselli, G.; Di Tola, M.; Casciani, E.; Poletti, E.; Laghi, F.; Monti, R.; Bernieri, M.G.; Gualdi, G. Diagnosis of Small-Bowel Diseases: Prospective Comparison of Multi-Detector Row CT Enterography with MR Enterography. *Radiology* **2016**, *279*, 420–431. <https://doi.org/10.1148/radiol.2015150263>.
58. Hadithi, M.; Heine, G.D.N.; Jacobs, M.A.J.M.; van Bodegraven, A.A.; Mulder, C.J.J. A Prospective Study Comparing Video Capsule Endoscopy with Double-Balloon Enteroscopy in Patients with Obscure Gastrointestinal Bleeding. *Am. J. Gastroenterol.* **2006**, *101*, 52–57. <https://doi.org/10.1111/j.1572-0241.2005.00346.x>.
59. Saurin, J.-C.; Pilleul, F.; Soussan, E.B.; Manière, T.; D'Halluin, P.N.; Gaudric, M.; Cellier, C.; Heresbach, D.; Gaudin, J.-L.; Capsule Commission of the French Society of Digestive Endoscopy (SFED) Small-Bowel Capsule Endoscopy Diagnoses Early and Advanced Neoplasms in Asymptomatic Patients with Lynch Syndrome. *Endoscopy* **2010**, *42*, 1057–1062. <https://doi.org/10.1055/s-0030-1255742>.
60. Haanstra, J.F.; Al-Toma, A.; Dekker, E.; Vanhoutvin, S.A.L.W.; Nagengast, F.M.; Mathus-Vliegen, E.M.; van Leerdam, M.E.; de Vos tot Nederveen Cappel, W.H.; Sanduleanu, S.; Veenendaal, R.A.; et al. Prevalence of Small-Bowel Neoplasia in Lynch Syndrome Assessed by Video Capsule Endoscopy. *Gut* **2015**, *64*, 1578–1583. <https://doi.org/10.1136/gutjnl-2014-307348>.
61. Cronin, C.G.; Lohan, D.G.; Browne, A.M.; Roche, C.; Murphy, J.M. Magnetic Resonance Enterography in the Evaluation of the Small Bowel. *Semin. Roentgenol.* **2009**, *44*, 237–243. <https://doi.org/10.1053/j.ro.2009.05.006>.
62. Nyland, K.; Ødegaard, S.; Hausken, T.; Folvik, G.; Lied, G.A.; Viola, I.; Hauser, H.; Gilja, O.-H. Sonography of the Small Intestine. *World J. Gastroenterol.* **2009**, *15*, 1319–1330. <https://doi.org/10.3748/wjg.15.1319>.
63. Halfdanarson, T.R.; McWilliams, R.R.; Donohue, J.H.; Quevedo, J.F. A Single-Institution Experience with 491 Cases of Small Bowel Adenocarcinoma. *Am. J. Surg.* **2010**, *199*, 797–803. <https://doi.org/10.1016/j.amjsurg.2009.05.037>.
64. Small Intestine. In *AJCC Cancer Staging Manual*, 8th ed.; Springer: Berlin/Heidelberg, Germany, 2017; pp. 221–234.
65. Adsay, N.; Nagtegaal, I.; Reid, M. Non-Ampullary Adenocarcinoma. In *WHO Classification of Tumours, Digestive System Tumours*, 5th ed.; World Health Organization: 2019; pp. 124–126.
66. Adsay, N.; Reid, M. Ampullary Adenocarcinoma. In *WHO Classification of Tumours, Digestive System Tumours*, 5th ed.; World Health Organization: 2019; pp. 127–130.
67. Adsay, V.; Ohike, N.; Tajiri, T.; Kim, G.E.; Krasinskas, A.; Balci, S.; Bagci, P.; Basturk, O.; Bandyopadhyay, S.; Jang, K.-T.; et al. Ampullary Region Carcinomas: Definition and Site Specific Classification with Delineation of Four Clinicopathologically and Prognostically Distinct Subsets in an Analysis of 249 Cases. *Am. J. Surg. Pathol.* **2012**, *36*, 1592–1608. <https://doi.org/10.1097/PAS.0b013e31826399d8>.
68. Ushiku, T.; Arnason, T.; Fukayama, M.; Lauwers, G.Y. Extra-Ampullary Duodenal Adenocarcinoma. *Am. J. Surg. Pathol.* **2014**, *38*, 1484–1493. <https://doi.org/10.1097/PAS.0000000000000278>.
69. Maguire, A.; Sheahan, K. Primary Small Bowel Adenomas and Adenocarcinomas-Recent Advances. *Virchows Arch. Int. J. Pathol.* **2018**, *473*, 265–273. <https://doi.org/10.1007/s00428-018-2400-7>.
70. Perkins, G.; Svrcek, M.; Bouchet-Doumenq, C.; Voron, T.; Colussi, O.; Debove, C.; Merabtene, F.; Dumont, S.; Sauvanet, A.; Hammel, P.; et al. Can We Classify Ampullary Tumours Better? Clinical, Pathological and Molecular Features. Results of an AGEO Study. *Br. J. Cancer* **2019**, *120*, 697–702. <https://doi.org/10.1038/s41416-019-0415-8>.