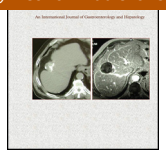
Digestive and Liver Disease 46 (2014) 97–104

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld



Review Article

Small bowel adenocarcinoma: Epidemiology, risk factors, diagnosis and treatment

Thomas Aparicio[a,*], Aziz Zaanan[b,c], Magali Svrcek[d], Pierre Laurent-Puig[c], Nicolas Carrere[e], Sylvain Manfredi[f], Christophe Locher[g], Pauline Afchain[h]

[a] Gastroenterology and Digestive Oncology Unit, Avicenne Hospital, HUPSSD, APHP, Université Paris 13, Sorbonne Paris Cité, Bobigny, France
[b] Gastroenterology and Digestive Oncology Unit, Georges Pompidou Hospital, APHP, Paris, France
[c] UMR-S775, INSERM, Paris, France
[d] Anatomopathology Unit, Saint Antoine Hospital, APHP, Paris France
[e] Digestive Surgery Unit, Purpan Hospital, Toulouse, France
[f] Hepato-Gastroenterology Unit, Pontchaillou Hospital, Rennes, France
[g] Hepato-Gastroenterology Unit, Meaux Hospital, Meaux, France
[h] Oncology Unit, Saint Antoine Hospital, APHP, Paris, France

ARTICLE INFO

Article history:
Received 7 January 2013
Accepted 29 April 2013
Available online 21 June 2013

Key words:
Carcinogenesis
Chemotherapy
Lynch syndrome
Prognostic factor
Rare tumour
Small intestine adenocarcinoma

ABSTRACT

Small bowel adenocarcinomas are rare tumours, but their incidence is increasing. Their most common primary location is the duodenum. The few studies that have collected data regarding small bowel adenocarcinoma are not homogeneous and are widely spread over time. Even though these tumours are most often sporadic, some predisposing diseases have been identified, among which Crohn's disease and genetic syndromes. Early diagnosis of small bowel adenocarcinoma remains difficult despite significant radiological and endoscopic progress. After surgical resection the main prognostic factor is node invasion; in this case, adjuvant chemotherapy can be expected to be beneficial, although this has not been established by randomised trials. For metastatic disease, platinum-based chemotherapy seems to be the most effective treatment. Targeted therapies have not yet been evaluated in this type of cancer.

1. Epidemiology

1.1. Incidence

Despite the fact that the small intestine makes up 75% of the length of the digestive tract and 90% of its mucosal surface area, small bowel cancer is rare, accounting for less than 5% of gastrointestinal cancers [1]. According to the United States National Cancer Database, the incidence of all small bowel cancers in the USA rose from 11.8 cases/million persons in 1973 to 22.7 cases/million persons in 2004 [2]. Similarly, in France, their incidence also rose over the 1976–2001 period [3]. Four histological types of cancer predominate in the small bowel: adenocarcinomas, neuroendocrine tumours, gastrointestinal stromal tumours and lymphomas.

Small bowel adenocarcinoma (SBA) accounts for around 40% of all cancers of the small bowel [2–4]; similarly, neuroendocrine tumours have roughly the same incidence. In the USA, the incidence of SBA has been estimated to be of 5300 new cases, with around 1100 deaths per year [5]. The median age at diagnosis is in the sixth decade of life. According to the EUROCARE data, the estimated number of annual new cases of SBA in Europe is 3600 [6]. The estimated incidence rate is 5.7 cases per million persons. In France the estimated incidence of SBA for the period 1989–2001 was 0.31/100,000 for men and 0.23/100,000 for women. According to the data from the Burgundy cancer registry, the number of new cases in France can be estimated to be 200 per year [3].

The duodenum is the most frequently involved segment, with 55–82% of cases, followed by the jejunum (11–25%) and ileum (7–17%) [2,3,7–10]. The increasing incidence of SBA is mainly due to the increase in duodenal tumours [11].

* Corresponding author at: Service de Gastroentérologie et Cancérologie Digestive, Hôpital Avicenne, HUPSSD, APHP, 125 rue de Stalingrad, 93000 Bobigny, France. Tel.: +33 1 48 95 54 31; fax: +33 1 48 95 54 39.
E-mail address: thomas.aparicio@avc.aphp.fr (T. Aparicio).

1590-8658
http://dx.doi.org/10.1016/j.dld.2013.04.013

2. Etiopathogenetic factors

2.1. Environmental factors

In contrast to colorectal cancer, studies on the pathogenesis of SBA are constrained by the rarity of the disease. Alcohol consumption [12] and smoking [13] have been associated with an increased risk of SBA. Other studies have reported an increased risk of SBA among the highest consumers of sugar, refined carbohydrates, red meat or smoked food, while a reduced risk was observed with higher intakes of coffee, fish, fruit, and vegetables [14,15].

The marked difference between the incidences of SBA and colorectal adenocarcinoma suggests different exposures to carcinogens. In the small bowel, the contact time between intestinal cells and xenobiotics or dietary carcinogens is shorter than in the colon, owing to the shorter transit time. In addition, the proximal small intestine contains low concentrations of aerophilic Gram-positive bacteria. The density of the microbiota increases in the distal ileum, but is still much lower than in the colon, where the microbiota produces xenobiotic transformation during which bile salts are deconjugated and dehydroxylated to form desoxycholic acid, which is a potential tumour promoter [16]. Moreover, the epithelial cells of the small bowel are equipped with a wide range of microsomal enzymes, including the benzopyrene hydroxylase, that may protect them against food-derived carcinogens [17]. Nevertheless, there is no clear explanation for the differing cancer incidences in the duodenum and jejuno-ileum.

2.2. Carcinogenesis in SBA

The biology of SBA has been investigated only in a small number of patients. The main genes involved in colorectal carcinogenesis have been studied also in SBA (Table 1).

The adenomatous polyposis coli (*APC*) gene has acquired a truncated mutation in up to 80% of sporadic colorectal cancers, resulting in a loss of regulation of β-CATENIN that accumulates in the nucleus as a result. This mutation is considered to be one of the main triggering events in colorectal carcinogenesis. The prevalence of the *APC* gene mutation in SBA was reported to be rather low: 0/21 [18], 1/15 (8%) [19] and 3/17 (18%) [20]. These data suggest that the carcinogenesis of SBA differs from colorectal carcinogenesis. Nevertheless, several studies have reported the nuclear accumulation of β-CATENIN, most probably due to a gain-of-function mutation in the *β-CATENIN* gene rather than a loss of regulation due to the *APC* mutation. Abnormal nuclear expression of β-CATENIN was found in variable proportions of the cases analysed: 10/21 (48%) [18], 12/61 (20%) [21] and 10/20 (50%) [22]. In another study [28], large deletions and insertions in the *β-CATENIN* gene, resulting in stabilisation of the aberrant β-CATENIN, were found exclusively in microsatellite stable carcinomas.

Other abnormal protein expressions have been reported in SBA. Reduced membrane expression of E-CADHERIN was found in 8/21 (38%) cases of SBA [18]. Overexpression of the p53 protein was detected in the nuclei of 5/21 (24%) [18], 4/15 (27%) [19], 26/62 (42%) [21], and 14/27 (52%) [23] tumours in different series of SBA cases. A loss of SMAD4 expression was found in 5/27 (18%) cases [23]. Moreover, abnormal expression of the vascular endothelial growth factor-A (VEGF-A) and the epidermal growth factor receptor (EGFR) was found in 50/54 (92%) and 36/54 (66%) cases, respectively, suggesting that this type of cancer could benefit from a treatment targeting the EGFR and VEGF pathways [24]. A *KRAS* mutation has been described in 12/21 (57%) [25] and 21/49 (43%) of cases [21]. A specific study of 78 duodenal tumours found a *KRAS* mutation in 34% of the cases [26]. HER2 expression has been assessed by immunohistochemistry in 2 studies: in the study of Overman et al., only one out of 54 (1.7%) tumours expressed HER2 [24]. Similarly, in the AGEO study, HER2 expression was observed in 2/51 (3.9%) cases, in both cases in the ileum [21].

Inactivation of the DNA mismatch repair (*MMR*) gene was found in around 15% of colorectal cancers [27]. A deficient *MMR* (dMMR) can be caused either by a germline mutation of one of the 4 *MMR* genes (usually *MSH2* or *MLH1*, and more rarely *MSH6* or *PMS2*) in the case of Lynch syndrome, or by hypermethylation of the *MLH1* promoter in sporadic tumours, especially those occurring in elderly patients [28]. In SBA, the frequency of the dMMR phenotype is variable, ranging from 5% to 35% of cases. Sporadic *MMR* deficiency was found in only 1/21 (≈5%) cases of SBA [18]. In another series of 89 SBA patients, the frequency of the dMMR phenotype was 16/89 (≈18%). In this latter study, immunohistochemistry revealed a loss of expression of MLH1 in 7/16 dMMR tumours. Amongst the patients under 60 years of age, the dMMR phenotype was found in 10/43 (23%) and loss of expression of the MLH1 and MSH2 proteins was observed with the same frequency [29]. Also, in this study the frequency of dMMR appeared to be greater in SBA than in colorectal cancer, as well as being higher in young patients, suggesting that dMMR is more often due to Lynch syndrome in SBA than in colorectal carcinoma. In another series of 54 SBA patients, a loss of expression of one of the MMR proteins occurred in 35% of patients. Loss of MSH2, MSH6, PMS2 and MLH1 was observed in 6%, 11%, 24% and 26% of patients, respectively. Loss of the MMR protein generally followed 2 patterns: the loss of the combination of either MSH2 and MSH6 (when the *MSH2* gene was affected) or PMS2 and MLH1 (when the *MLH1* gene was affected) [24]. In the AGEO study, a dMMR phenotype was observed in 14/61 patients (23%), mainly due to a loss of MLH1 expression [21]. In this latter study, a trend towards a more frequent dMMR phenotype was observed more often in duodenal (9/32) or jejunal (5/18) tumours than in ileal tumours (0/13) ($p = 0.07$). The characterisation of SBA according to genetic and epigenetic alterations was performed in a series of 37 tumours [30]. A chromosomal instability (CIN) was detected in 22/37 tumours (59%). A high level of DNA methylation was found in 16% of the CIN tumours, in 44% of microsatellite instable (MSI) tumours and in 44% of microsatellite and chromosomal-stable (MACS) tumours. A *KRAS* mutation was observed in 55% of CIN tumours, 0% of MSI tumours and 10% of MACS tumours. A *BRAF* mutation was detected in 6% of CIN tumours, 22% of MSI tumours and 22% of MACS tumours. These findings suggest that SBA and colorectal cancer could belong to different molecular subgroups [30].

Taken together, these findings suggest the existence of some common carcinogenesis pathways shared between SBA and colorectal carcinogenesis. Nevertheless, the *APC* mutation is less often observed in SBA than in colorectal cancer, even though the Wnt pathway is involved through *β-CATENIN* alteration. Moreover, the frequency of the dMMR phenotype appears to differ in the different SBA series, but it is generally slightly more frequent than in colorectal cancer. Nevertheless, a bias towards an over-representation of Lynch syndrome patients could be suspected in tertiary care series. Only a large study based on an unselected cohort will allow for the assessment of the frequencies of the various biological alterations involved in SBA carcinogenesis.

2.3. Genetic predisposition

2.3.1. Familial adenomatous polyposis (FAP)

FAP is a consequence of a germinal mutation of the *APC* gene. FAP patients are exposed to a very high incidence of colorectal cancer at a young age, and SBA is the second most common primary cancer location. In a pooled registry study of 1255 patients with FAP, 57 (4.5%) had an upper digestive tract adenocarcinoma. The primary location was the duodenum in 29 cases (50%), the ampulla of Vater in 10 (18%), the stomach in 7 (12%), the jejunum in 5 (8.5%),

Table 1
Molecular changes in small bowel adenocarcinoma.

Reference	Number of patients	Abnormal P53	Abnormal β-CATENIN	HER2 over-expression	APC mutation	*KRAS* mutation	dMMR phenotype
Wheeler et al. [18]	21	24%	48%	–	0%	–	5%
Arai et al. [19]	15	27%	–	–	8%	53%	–
Blaker et al. [20]	17	–	–	–	18%	–	12%
Aparicio et al. [21]	63	42%	20%	3.9%	–	43%	14%
Svrcek et al. [23]	27	52%	7.4%	–	–	–	7%
Overman et al. [24]	54	–	–	1.7%	–	–	35%
Blaker et al. [25]	21	–	24%	–	10%	57%	–
Planck et al. [29]	89	–	–	–	–	–	18%

and the ileum in 1 case (1.7%) [31]. In another study, the relative risks for duodenal adenocarcinoma or ampulloma in a FAP patient compared to those in the general population were 330 (95% CI, 132–681; $p < 0.001$), and 123 (95% CI, 33–316; $p < 0.001$), respectively [32]. Even though the risk of duodenal adenocarcinoma in a FAP patient remained less than 5%, this cancer is nevertheless the main cause of cancer-related death in patients who have undergone a coloproctectomy [33,34].

2.3.2. Lynch syndrome

Lynch syndrome is caused by a germline mutation of a DNA mismatch repair gene, which exposes the patient to various types of neoplasia, such as colorectal and endometrial cancers; he less frequently ovarian, urothelial, gastric, biliary tract cancers and SBA. Various levels of increased risk for SBA have been reported for patients with Lynch syndrome. According to data from a Dutch study, the relative risk of SBA for a patient with Lynch syndrome has been estimated to range from 25 in the early phases of the syndrome [35] to 291 (95% CI, 71–681) in case of an *MLH1* mutation and 103 (95% CI, 14–729) in case of an *MSH2* mutation [36]. Nevertheless, the lifetime cumulative risk remains low: 0.6% and 1% according to Finnish and French registries, respectively [37,38]. So far, it has not been recommended to screen Lynch syndrome patients for SBA. However, analysis of the MMR phenotype is systematically recommended in SBA, because it could reveal the presence of Lynch syndrome [39,40].

2.3.3. Peutz–Jeghers syndrome

The Peutz–Jeghers syndrome is an autosomal dominant disorder due to the *STK11* suppressor gene mutation that predisposes to hamartomatous gastrointestinal tract polyposis. A relative risk of 520 (95% CI, 220–1306) for SBA was observed in Peutz–Jeghers syndrome patients [41]. The adenocarcinoma probably originates from the intra-epithelial neoplasia observed in the hamartomatous lesion.

2.4. Other predisposing conditions

2.4.1. Crohn's disease

Crohn's disease induces chronic inflammation in every segment of the digestive tract, and the distal ileum is the most frequently involved. The chronic inflammation releases cytokines that interact with cell surface receptors and target genes that can promote carcinogenesis [16]. The increased relative risk of SBA in Crohn's disease has been estimated in several population-based studies to range from 17 to 41 compared to the general population [42,43]. The SBA arises in an inflamed small bowel segment. In contrast to sporadic SBA, in Crohn's disease, this cancer appears in younger patients (fourth decade of life), and mainly in the ileal segment. The cumulative risk is estimated to be 0.2% after 10 years of Crohn's disease and 2.2% after 25 years [44]. Another estimation, based on the extensive SEER database and restricted to patients over 65 years old, identified 923 cases of small bowel cancer and 142,273 controls, and confirmed the increased risk of SBA in Crohn's disease (OR = 12.07; 95% CI, 6.07–20.80; $p < 0.001$). In this study, the prevalence of Crohn's disease in patients with small bowel cancer was low (1.6%); nevertheless many cases of SBA could have been missed in the SEER database as the median age of onset of SBA in Crohn's disease patients is less than 65 years [45]. Another study suggests that patients who have undergone a small bowel resection or prolonged treatment with salicylate have a lower risk of developing SBA [46].

2.4.2. Coeliac disease

Coeliac disease is characterised by a lymphocytic infiltrate that induces immunological disruption and damage to the epithelial cells that can include premalignant changes, and could increase the risk of both SBA and small bowel lymphoma. A cohort of 235 patients with coeliac disease showed an 8% prevalence of SBA [47]. In a British survey study that included 395 cases of small bowel cancer (107 lymphomas, 175 SBAs and 79 neuroendocrine tumours), coeliac disease was found in 13% of cases of SBA and 39% of cases of lymphoma; primary location of SBA was usually jejunal [48]. In a Swedish registry study, the relative risk of SBA in patients with coeliac disease versus the general population was estimated to be 10 [49].

The preliminary results of the French NADEGE cohort that prospectively included 127 patients with SBA from March 2009 to September 2010, revealed a genetic syndrome or a predisposing disease in 20% of the patients: Crohn's disease (8.6%), FAP (3%), Lynch syndrome (3%), coeliac disease (1.5%) and Peutz–Jeghers syndrome (0.8%) (7). These preliminary results indicate that a predisposing disease or genetic syndrome is considerably more frequent in SBA than in colorectal cancer.

3. Diagnosis

3.1. Clinical presentation

The clinical presentation and diagnosis of SBA is usually delayed. The symptoms are initially rather non-specific. In a single-centre study of 217 patients with SBA, 66% of the patients had abdominal pain when diagnosed. SBA was usually diagnosed in the context of an emergency involving an occlusion (40%) or bleeding (24%). Bowel obstruction was mainly observed in cases of jejunal and ileal tumour, and less frequently in duodenal tumours (47% vs 34%; $p = 0.06$) [8]. In this study, diagnoses in the more recent period (after 1988) were obtained by upper gastrointestinal endoscopy (28%), surgery (26%), small bowel barium transit (22%), CT scan (18%), ultrasound (3%) or physical examination (3%). The diagnosis was mainly obtained at advanced stages, when 35% of the patients had synchronous metastases and 39% had tumours with lymph-node invasion [8]. A similar stage distribution was found in another study of 129 tumours in which 38% of the patients had synchronous metastases and 38% had lymph-node invasion [50]. In

Crohn's disease, the diagnosis is mainly obtained postoperatively after resection of an obstructed small bowel segment [44].

3.2. Diagnosis

For SBA, small bowel barium transit has a sensitivity of about 50% [51], and CT scans have an overall accuracy rate of 47% [52,53]. It should be pointed out that in a context of obscure bleeding after upper and lower endoscopy, a small bowel investigation should systematically be done. New investigation tools, such as CT enteroclysis, MR enteroclysis, capsule endoscopy, and enteroscopy now allow for an extensive exploration of small bowel and should thus make early diagnosis possible. CT enteroclysis has a sensitivity of 85–95% for the diagnosis of small bowel tumour, and a specificity of 90–96% [51,54]. A study including 150 patients who were clinically suspected of having a small-bowel neoplasm, and whose previous upper and lower gastrointestinal endoscopy findings were normal, underwent MR enteroclysis. The overall sensitivity, specificity, and accuracy in identifying patients with small bowel lesions were 86% (19 of 22), 98% (126 of 128), and 97% (145 of 150), respectively. Two MR enteroclysis examinations yielded false-positive findings, and 3 yielded false-negative findings [55].

Capsule endoscopy allows carrying out a complete small bowel exploration as an outpatient procedure, however it should not be performed in a context of sub-occlusion. When it is performed to explore obscure bleeding, the sensitivity for diagnosing a small bowel tumour is between 88.9% and 95% and its specificity 75–95% [56,57]. Double balloon enteroscopy can be used for a wide range of small bowel investigations. Nevertheless, this procedure is less convenient than capsule endoscopy, and should be used only if a biopsy or preoperative tattoo are required [58]. In some cases, however, enteroscopy can diagnose a small bowel tumour missed by videocapsule endoscopy [59].

3.3. Other recommended investigations after SBA diagnosis

The French guidelines (www.tncd.org, last updated in 2013) recommend performing a thoraco-abdomino-pelvic CT scan to assess distant metastases, and an upper and lower gastrointestinal endoscopy to look for other tumours suggesting a predisposing genetic disease. A baseline plasmatic carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19.9 assay should be done, especially in cases of advanced disease, since the levels of these markers are of prognostic value [60].

In a context of a predisposing genetic disease or Crohn's disease, a full small bowel exploration should be performed (with enteroscanner or capsule endoscopy if there is no small bowel stenosis) to detect synchronous tumours.

An assay of anti-transglutaminase A antibodies and a duodenal biopsy are recommended to detect coeliac disease.

Two different tests can be used to detect Lynch syndrome: the first identifies microsatellite instability by testing 5 microsatellite loci, and the second confirms the lack of expression of 1 or 2 mismatch repair proteins by means of immunohistochemical techniques.

4. Prognosis

SBA carries a poor prognosis at all stages, with a 5-year overall survival (OS) rate ranging from 14% to 33% [2,3,6,8,10]. The 5-year OS is correlated to the tumour stage (Tables 2 and 3): 50–60% for stage I (incidence from 4% to 12%), 39–55% for stage II (incidence from 14% to 30%), 10–40% for stage III (incidence from 19% to 27%) and 3–5% for stage IV (incidence from 32% to 46%) [7–10,50,61]. SBA prognosis appears to be intermediate between those of colon and gastric cancers, and surgery for complete resection (R0) remains the only potentially curative treatment [50]. The frequency of locally-advanced unresectable cancer is not reported in most of the studies, however, in the preliminary report of the NADEGE cohort, a locally-advanced cancer occurred in 5% of the cases [7].

Lymph-node invasion is the main prognostic factor for local SBA [8,50]; moreover, the number of lymph nodes assessed and the number of positive lymph nodes are of prognostic value. In stage III patients, a positive number of invaded lymph nodes ≥3 had a worse 5-year disease-free survival (DFS) rate than patients with 1–2 invaded lymph nodes (37% vs 57%) [62]. For jejuno-ileal tumours, when 10 or more lymph nodes were examined, the OS rate increased non-significantly in stage I (73.2% vs 55.6%, NS) and significantly in stage II (61.8% vs 32.9%, $p < 0.001$). Multivariate analysis identified advanced age, advanced stage, ileal location, the recovery of <10 lymph nodes, and the number of positive nodes as

Table 2
TNM classification of small intestine adenocarcinomas.

Primary tumour (T)	
Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ
T1	Tumour invades the lamina propria, muscularis mucosa or submucosa.
T1a	Tumour invades the lamina propria or muscularis mucosa
T1b	Tumour invades the submucosa
T2	Tumour invades the muscularis propria
T3	Tumour invades 2 cm or less into the subserosa or into the non-peritonealized perimuscular tissue (mesentery or retroperitoneum[a])
T4	Tumour perforates the visceral peritoneum or directly invades other organs or structures, including: – other loops of the small intestine, mesentery or retroperitoneum by more than 2 cm – through the serosa into the abdominal wall – the pancreas (only for tumours in the duodenum)
Regional lymph nodes (N)	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1–3 regional lymph nodes
N2	Metastasis in 4 or more regional lymph nodes
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

From Sobin et al. [82].
[a] *Note*: The non-peritonealized perimuscular tissue for the jejunum and ileum is part of the mesentery. For the duodenum, it is part of the retroperitoneum in areas where there is no serosa.

Table 3
Tumour stages of small intestine adenocarcinoma.

Stage	T	N	M
0	Tis	N0	M0
1	T1, T2	N0	M0
2A	T3	N0	M0
2B	T4	N0	M0
3A	Any T	N1	M0
3B	Any T	N2	M0
4	Any T	Any M	M1

From Sobin et al. [82].
T, tumour; N, nodes; M, metastases; Tis, in situ.

significant predictors of poor OS [63]. Thus, a curative resection at an early stage (stages I and II) should systematically include a regional lymphadenectomy.

Several studies suggest that a duodenal primary tumour has a worse prognosis than a jejunal or ileal primary tumour [8,9,62]. Other factors for poor prognosis have also been reported: advanced age, pT4 tumour stage, poorly differentiated tumour, positive resection margins, lymphovascular invasion and a lymph node ratio of ≥10% [9,64,65]. One study has reported 12/74 (16%) second cancers after a curative resection, 5 of which could have corresponded to Lynch syndrome. This high frequency of second cancers justifies a prolonged follow-up after SBA treatment [66].

In metastatic or locally-advanced SBA treated with chemotherapy, a retrospective study found that impaired WHO performance status and an above-normal value of CEA or CA 19.9 were prognostic factors for poor survival [60].

5. Treatment

5.1. Localised cancer

Complete resection (R0) of the primary tumour with locoregional lymph node resection is mandatory. In the context of posterior invasion, pre-operative treatment should be considered, and resection reconsidered after 2–3 months of chemotherapy.

In the context of unresectable metastases, primary tumour resection is not recommended except in an emergency such as bowel obstruction, perforation or uncontrolled bleeding. If a multidisciplinary evaluation concludes that the metastases are resectable, resection of the metastases can consist of either 1 or 2 surgical procedures, possibly with chemotherapy during the interval between the procedures. However, more data are required to evaluate the value of metastasis resection in SBA.

For duodenal tumours, a Whipple resection should be performed [8] for a tumour in the second segment of the duodenum or for an infiltrating tumour in the proximal or distal duodenum. Additionally, resection of the peri-duodenal, peri-pancreatic, and hepatic lymph nodes should also be performed, as well as resection of the right side of the coeliac and superior mesenteric arteries. A duodenal resection alone could be performed for a proximal duodenal tumour or a distal duodenal tumour with no infiltration of adjacent organs [67], despite the fact that this procedure is associated with poor prognosis [68]. An R0 resection is to be preferred, as R1 or R2 resections are strongly associated with poor prognosis [69].

For jejunal and ileal tumours, an R0 resection with lymph node resection and jejuno-jejunal or ileo-ileal anastomosis should be performed. If the last ileal loop or Bauhin's valve are involved, an ileocoecal or right hemicolectomy should be performed with ligation of the ileocolic artery so as to allow for lymph node resection.

To date, no standard adjuvant regimen has been defined due to the lack of randomised controlled trials. The only data available are those from retrospectives studies. The inability to control for the various prognostic factors influencing the original decision to administer adjuvant therapy has been a major limitation of retrospective studies, as the patients who receive adjuvant therapy tend to be those at greater risk of disease recurrence on basis of the currently-used prognostic factors.

In a review of the US National Cancer Database, 11% of patients received radiotherapy with or without chemotherapy mainly for duodenal primary tumours [9]. Nevertheless, in a retrospective study of 48 duodenal adenocarcinomas resected with a curative intent, chemoradiotherapy did not improve survival [68]. The data available do not establish a clear recommendation for radiotherapy in R1 or R2 resection or locally-advanced duodenal cancer.

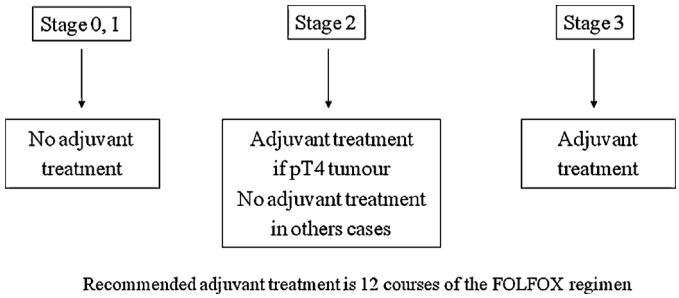


Fig. 1. Treatment for localised small bowel adenocarcinoma after an R0 resection according to the 2013 French guidelines (www.tncd.org).

Several retrospective studies have found no benefit in adjuvant chemotherapy after potentially curative surgical resections of SBA [8,64,70,71]. These negative results may be due to the small number of patients treated, a bias in selecting patients for treatment or an inadequate chemotherapy regimen.

In a single-centre, retrospective study including 54 patients treated with an R0 resection between 1990 and 2008, 30 (56%) patients received adjuvant therapy. In multivariate analysis, the use of adjuvant therapy was found to be associated with an improvement in the DFS (HR 0.27; 95% CI 0.07–0.98, $p = 0.05$), but not in the OS (HR 0.47; 95% CI 0.13–1.62, $p = 0.23$). In patients with a high risk of recurrence (defined as a lymph node ratio [invaded/without metastasis] ≥10%), adjuvant therapy appeared to improve OS ($p = 0.04$), but not DFS ($p = 0.15$) [65]. Despite the lack of evidence supporting the delivery of adjuvant chemotherapy for SBA, an analysis in the USA of the National Cancer Database has shown an increase in the use of chemotherapy from 8% in 1985 to 24% in 2005 [2].

The reported efficacy of fluoropyrimidine and oxaliplatin in advanced SBA [60,72], and the efficacy of the same regimen in the adjuvant chemotherapy of CRC have led to the French recommendation of an adjuvant fluoropyrimidine and oxaliplatin-based chemotherapy after a curative R0 resection of a stage-III SBA (www.tncd.org, last updated in 2013). For stage-II tumours, adjuvant chemotherapy is optional for pT4. Nevertheless, given the cumulative evidence of poor prognosis for poorly-differentiated tumours with a resected lymph node number <10, adjuvant chemotherapy should be discussed in such cases (Fig. 1).

A prospective international phase-III study (the BALAD study), promoted by the International Rare Cancer Initiative, comparing observation to adjuvant chemotherapy after R0 resection of SBA should begin soon.

5.2. Metastatic SBA

Very few studies have been published on the type of chemotherapy used for advanced SBA (Table 4). Most of the studies available are small, retrospective or involve old chemotherapy regimens. Overall, they report a median OS of 8–18 months and objective response rates (ORR) ranging from 5% to 37% [73–78]. Several retrospective studies suggest that chemotherapy prolongs OS in patients with advanced SBA [8,74,75], but there is no agreed frontline regimen owing to the lack of randomised trials. A retrospective comparison of OS, according to whether palliative chemotherapy was prescribed, showed a significant increase of survival in treated patient (12 months vs 2 months, $p = 0.02$) [8]. In another series from the registry of British Columbia, patients who received chemotherapy ($n = 16$) had an OS of 15.6 months, while patients who did not ($n = 21$) had an OS of 7.7 months [74]. Only few studies compared a specific regimen of chemotherapy to other protocols. A retrospective study of 44 patients suggests that

Table 4
Studies evaluating chemotherapy in advanced small bowel adenocarcinoma.

Reference	Regimen	Number of patients	Response rate (%)	Progression free survival (months)	Overall survival (months)
Crawley et al. [73]	5FU	8	37	7.8	13.0
Locher et al. [78]	5FU + cisplatin	20	21	8.0	14.0
Gibson et al. [76]	5FU + doxorubicin + MMC	38	18	5.0	8.0
Zaanan et al. [60]	FOLFOX	48	34	6.9	17.8
	LV5FU2	10	0	7.7	13.5
	LV5FU2 + cisplatin	19	30	6.0	9.6
	FOLFIRI	16	9	4.8	10.6
Overman et al. [79]	5FU + cisplatin	29	41	8.7	14.8
	5FU without cisplatin	41	17	3.9	12.0
Overman et al. [72]	Capecitabine + oxaliplatin	30	52	11.3	20.0
Zaanan et al. [81]	FOLFIRI (second line)	28	20	3.2	10.5

gemcitabine and irinotecan-based chemotherapy gives better results than 5FU monotherapy [75]. A retrospective, single-centre study of 80 patients with metastatic SBA suggested that platinum-based chemotherapy gave a higher ORR than other chemotherapy regimens (46% vs 16%; $p = 0.01$) and longer median progression-free survival (PFS) (8.7 vs 3.9 months; $p \leq 0.01$), although the median OS was not significantly different (14.8 vs 12.0 months; $p = 0.10$) [79]. However, this study did not address the respective risk-benefit ratios of the different platinum salts (cisplatin, oxaliplatin, etc.), even though the clinical efficacy and antitumour mechanisms of these drugs are very different [80]. A prospective phase-II trial of capecitabine plus oxaliplatin has given interesting results in patients with advanced small-bowel and ampullary adenocarcinomas, with an ORR of 50%, a median time to progression of 11.3 months, and a median OS of 20.4 months [72]. Another retrospective multicentre study evaluated LV5FU2 ($n = 10$), FOLFOX ($n = 48$), FOLFIRI ($n = 19$) and LV5FU2-cisplatin ($n = 16$) in 93 consecutive patients. The median PFS times in patients treated with LV5FU2, FOLFOX, FOLFIRI and LV5FU2-cisplatin were 7.7, 6.9, 6.0 and 4.8 months, respectively, while the median OS times were 13.5, 17.8, 10.6 and 9.3 months, respectively. In a multivariate analysis, the WHO performance status ($p < 0.0001$) and the elevated CEA ($p = 0.02$) and CA 19.9 ($p = 0.03$) serum levels were the only variables significantly associated with poor OS. In the subgroup of patients treated with platinum-based chemotherapy, multivariate analysis showed that LV5FU2-cisplatin was associated with poorer PFS ($p < 0.0001$) and OS ($p = 0.02$) than FOLFOX [60]. From the same series, the effectiveness of FOLFIRI in second-line chemotherapy was investigated in 28 patients who had been treated with platinum salts in first line therapy: the objective response rate was 20% and the disease control rate was 52%, while the median PFS and OS were 3.2 and 10.5 months, respectively. This suggests that the FOLFIRI regimen exhibits modest activity as a second-line treatment in patients with advanced SBA after failure of a platinum salt-based first-line chemotherapy [81].

So far, no data is available for targeted therapy. The oxaliplatin-based chemotherapy seems to be the best choice, and it is recommended as a first line treatment by the French guidelines (www.tncd.org, last updated in 2013) (Fig. 2).

Overall, advanced SBA had a worse prognosis than colorectal cancer, but a better prognosis than gastric or pancreatic cancer, with a median OS exceeding 12 months.

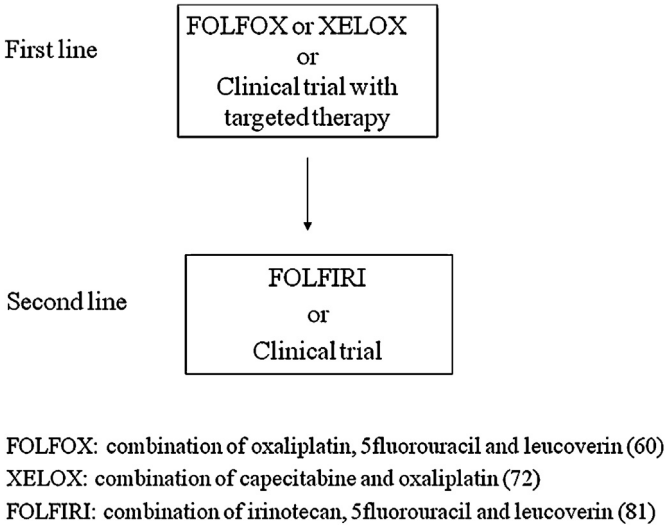


Fig. 2. Treatment for metastatic small bowel adenocarcinoma according to the 2013 French guidelines (www.tncd.org).

References

[1] Neugut AI, Jacobson JS, Suh S, et al. The epidemiology of cancer of the small bowel. Cancer Epidemiology, Biomarkers & Prevention 1998;7:243–51.
[2] Bilimoria KY, Bentrem DJ, Wayne JD, et al. Small bowel cancer in the United States: changes in epidemiology, treatment, and survival over the last 20 years. Annals of Surgery 2009;249:63–71.
[3] Lepage C, Bouvier AM, Manfredi S, et al. Incidence and management of primary malignant small bowel cancers: a well-defined French population study. The American Journal of Gastroenterology 2006;101:2826–32.
[4] Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2008. CA: A Cancer Journal for Clinicians 2008;58:71–96.
[5] Kummar S, Ciesielski TE, Fogarasi MC. Management of small bowel adenocarcinoma. Oncology (Williston Park) 2002;16:1364–9.
[6] Faivre J, Trama A, De Angelis R, et al. Incidence, prevalence and survival of patients with rare epithelial digestive cancers diagnosed in Europe in 1995–2002. European Journal of Cancer 2012;48:1417–24.
[7] Aparicio T, Manfredi S, Coriat R, et al. CA.D Nationale ADEnocarcinome intestin GrêlE (NADEGE): faisabilité et état d'avancement; 2011 www.jfhod.com
[8] Dabaja BS, Suki D, Pro B, Bonnen M, Ajani J. Adenocarcinoma of the small bowel: presentation, prognostic factors, and outcome of 217 patients. Cancer 2004;101:518–26.
[9] Howe JR, Karnell LH, Menck HR, et al. The American College of Surgeons Commission on Cancer and the American Cancer Society. Adenocarcinoma of the small bowel: review of the National Cancer Data Base, 1985–1995. Cancer 1999;86:2693–706.
[10] Moon YW, Rha SY, Shin SJ, et al. Adenocarcinoma of the small bowel at a single Korean institute: management and prognosticators. Journal of Cancer Research and Clinical Oncology 2010;136:387–94.
[11] Chow JS, Chen CC, Ahsan H, et al. A population-based study of the incidence of malignant small bowel tumours: SEER, 1973–1990. International Journal of Epidemiology 1996;25:722–8.
[12] Wu AH, Yu MC, Smoking Mack TM. alcohol use, dietary factors and risk of small intestinal adenocarcinoma. International Journal of Cancer 1997;70:512–7.
[13] Kaerlev L, Teglbjaerg PS, Sabroe S, 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 2000;11:791–7.
[14] Chow WH, Linet MS, McLaughlin JK, et al. Risk factors for small intestine cancer. Cancer Causes Control 1993;4:163–9.
[15] Negri E, Bosetti C, La Vecchia C, et al. Risk factors for adenocarcinoma of the small intestine. International Journal of Cancer 1999;82:171–4.
[16] Schottenfeld D, Beebe-Dimmer JL, Vigneau FD. The epidemiology and pathogenesis of neoplasia in the small intestine. Annals of Epidemiology 2009;19:58–69.

[17] Delaunoit T, Neczyporenko F, Limburg PJ, et al. Pathogenesis and risk factors of small bowel adenocarcinoma: a colorectal cancer sibling. The American Journal of Gastroenterology 2005;100:703–10.
[18] Wheeler JM, Warren BF, Mortensen NJ, et al. An insight into the genetic pathway of adenocarcinoma of the small intestine. Gut 2002;50:218–23.
[19] Arai M, Shimizu S, Imai Y, et al. Mutations of the Ki-ras, p53 and APC genes in adenocarcinomas of the human small intestine. International Journal of Cancer 1997;70:390–5.
[20] Blaker H, von Herbay A, Penzel R, et al. Genetics of adenocarcinomas of the small intestine: frequent deletions at chromosome 18q and mutations of the SMAD4 gene. Oncogene 2002;21:158–64.
[21] Aparicio T, Svrcek M, laforest A, et al. Small bowel adenocarcinoma phenotype according to the primary localisation. Annals of Oncology 2012;23, ix234.
[22] Breuhahn K, Singh S, Schirmacher P, et al. Large-scale N-terminal deletions but not point mutations stabilize beta-catenin in small bowel carcinomas, suggesting divergent molecular pathways of small and large intestinal carcinogenesis. The Journal of Pathology 2008;215:300–7.
[23] Svrcek M, Jourdan F, Sebbagh N, et al. Immunohistochemical analysis of adenocarcinoma of the small intestine: a tissue microarray study. Journal of Clinical Pathology 2003;56:898–903.
[24] Overman MJ, Pozadzides J, Kopetz S, et al. Immunophenotype and molecular characterisation of adenocarcinoma of the small intestine. British Journal of Cancer 2010;102:144–50.
[25] Blaker H, Helmchen B, Bonisch A, et al. Mutational activation of the RAS-RAF-MAPK and the Wnt pathway in small intestinal adenocarcinomas. Scandinavian Journal of Gastroenterology 2004;39:748–53.
[26] Fu T, Guzzetta AA, Jeschke J, et al. KRAS G>A mutation favors poor tumor differentiation but may not be associated with prognosis in patients with curatively resected duodenal adenocarcinoma. International Journal of Cancer 2012.
[27] Zaanan A, Meunier K, Sangar F, et al. Microsatellite instability in colorectal cancer: from molecular oncogenic mechanisms to clinical implications. Cellular Oncology (Dordrecht) 2011;34:155–76.
[28] Aparicio T, Schischmanoff O, Poupardin C, et al. Deficient mismatch repair phenotype is a prognostic factor for colorectal cancer in elderly patients. Digestive and Liver Disease 2012.
[29] Planck M, Ericson K, Piotrowska Z, et al. Microsatellite instability and expression of MLH1 and MSH2 in carcinomas of the small intestine. Cancer 2003;97:1551–7.
[30] Warth A, Kloor M, Schirmacher P, et al. Genetics and epigenetics of small bowel adenocarcinoma: the interactions of CIN, MSI, and CIMP. Modern Pathology 2011;24:564–70.
[31] Jagelman DG, DeCosse JJ, Bussey HJ. Upper gastrointestinal cancer in familial adenomatous polyposis. Lancet 1988;1:1149–51.
[32] Offerhaus GJ, Giardiello FM, Krush AJ, et al. The risk of upper gastrointestinal cancer in familial adenomatous polyposis. Gastroenterology 1992;102:1980–2.
[33] Bulow S, Alm T, Fausa O, et al. Duodenal adenomatosis in familial adenomatous polyposis. DAF Project Group. International Journal of Colorectal Disease 1995;10:43–6.
[34] Vasen HF, Bulow S, Myrhoj T, et al. Decision analysis in the management of duodenal adenomatosis in familial adenomatous polyposis. Gut 1997;40:716–9.
[35] Watson P, Lynch HT. Extracolonic cancer in hereditary nonpolyposis colorectal cancer. Cancer 1993;71:677–85.
[36] Vasen HF, Wijnen JT, Menko FH, et al. Cancer risk in families with hereditary nonpolyposis colorectal cancer diagnosed by mutation analysis. Gastroenterology 1996;110:1020–7.
[37] Aarnio M, Mecklin JP, Aaltonen LA, et al. Life-time risk of different cancers in hereditary non-polyposis colorectal cancer (HNPCC) syndrome. International Journal of Cancer 1995;64:430–3.
[38] Bonadona V, Bonaiti B, Olschwang S, et al. Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. Journal of the American Medical Association 2011;305:2304–10.
[39] Babba T, Schischmanoff O, Lagorce C, et al. Small bowel carcinoma revealing HNPCC syndrome. Gastroentérologie Clinique et Biologique 2010;34:325–8.
[40] Schulmann K, Brasch FE, Kunstmann E, et al. HNPCC-associated small bowel cancer: clinical and molecular characteristics. Gastroenterology 2005;128:590–9.
[41] Giardiello FM, Brensinger JD, Tersmette AC, et al. Very high risk of cancer in familial Peutz–Jeghers syndrome. Gastroenterology 2000;119:1447–53.
[42] Bernstein CN, Blanchard JF, Kliewer E, et al. Cancer risk in patients with inflammatory bowel disease: a population-based study. Cancer 2001;91:854–62.
[43] Jess T, Loftus Jr EV, Velayos FS, et al. Risk of intestinal cancer in inflammatory bowel disease: a population-based study from olmsted county, Minnesota. Gastroenterology 2006;130:1039–46.
[44] Palascak-Juif V, Bouvier AM, Cosnes J, et al. Small bowel adenocarcinoma in patients with Crohn's disease compared with small bowel adenocarcinoma de novo. Inflammatory Bowel Diseases 2005;11:828–32.
[45] Shaukat A, Virnig DJ, Howard D, et al. Crohn's disease and small bowel adenocarcinoma: a population-based case–control study. Cancer Epidemiology, Biomarkers & Prevention 2011;20:1120–3.
[46] Piton G, Cosnes J, Monnet E, et al. Risk factors associated with small bowel adenocarcinoma in Crohn's disease: a case-control study. The American Journal of Gastroenterology 2008;103:1730–6.
[47] Swinson CM, Slavin G, Coles EC, et al. Coeliac disease and malignancy. Lancet 1983;1:111–5.
[48] Howdle PD, Jalal PK, Holmes GK, et al. Primary small-bowel malignancy in the UK and its association with coeliac disease. Quarterly Journal of Medicine 2003;96:345–53.
[49] Askling J, Linet M, Gridley G, et al. Cancer incidence in a population-based cohort of individuals hospitalized with celiac disease or dermatitis herpetiformis. Gastroenterology 2002;123:1428–35.
[50] Talamonti MS, Goetz LH, Rao S, et al. Primary cancers of the small bowel: analysis of prognostic factors and results of surgical management. Archives of Surgery 2002;137:564–70.
[51] Boudiaf M, Jaff A, Soyer P, et al. Small-bowel diseases: prospective evaluation of multi-detector row helical CT enteroclysis in 107 consecutive patients. Radiology 2004;233:338–44.
[52] Buckley JA, Siegelman SS, Jones B, et al. The accuracy of CT staging of small bowel adenocarcinoma: CT/pathologic correlation. Journal of Computer Assisted Tomography 1997;21:986–91.
[53] Horton KM, Fishman EK. The current status of multidetector row CT and three-dimensional imaging of the small bowel. Radiologic Clinics of North America 2003;41:199–212.
[54] Pilleul F, Penigaud M, Milot LS, et al. Possible small-bowel neoplasms: contrast-enhanced and water-enhanced multidetector CT enteroclysis. Radiology 2006;241:796–801.
[55] Masselli G, Polettini E, Casciani E, et al. Small-bowel neoplasms: prospective evaluation of MR enteroclysis. Radiology 2009;251:743–50.
[56] Hartmann D, Schmidt H, Bolz G, et al. A prospective two-center study comparing wireless capsule endoscopy with intraoperative enteroscopy in patients with obscure GI bleeding. Gastrointestinal Endoscopy 2005;61:826–32.
[57] Pennazio M, Santucci R, Rondonotti E, et al. Outcome of patients with obscure gastrointestinal bleeding after capsule endoscopy: report of 100 consecutive cases. Gastroenterology 2004;126:643–53.
[58] Hadithi M, Heine GD, Jacobs MA, et al. A prospective study comparing video capsule endoscopy with double-balloon enteroscopy in patients with obscure gastrointestinal bleeding. The American Journal of Gastroenterology 2006;101:52–7.
[59] Ross A, Mehdizadeh S, Tokar J, et al. Double balloon enteroscopy detects small bowel mass lesions missed by capsule endoscopy. Digestive Diseases and Sciences 2008;53:2140–3.
[60] Zaanan A, Costes L, Gauthier M, et al. Chemotherapy of advanced small-bowel adenocarcinoma: a multicenter AGEO study. Annals of Oncology 2010;21:1786–93.
[61] Overman MJ, Hu CY, Kopetz S, et al. A population-based comparison of adenocarcinoma of the large and small intestine: insights into a rare disease. Annals of Surgical Oncology 2012;19:1439–45.
[62] Overman MJ, Hu CY, Wolff RA, et al. Prognostic value of lymph node evaluation in small bowel adenocarcinoma: analysis of the surveillance, epidemiology, and end results database. Cancer 2010;116:5374–82.
[63] Nicholl MB, Ahuja V, Conway WC, et al. Small bowel adenocarcinoma: understaged and undertreated. Annals of Surgical Oncology 2010;17:2728–32.
[64] Halfdanarson TR, McWilliams RR, Donohue JH, et al. A single-institution experience with 491 cases of small bowel adenocarcinoma. The American Journal of Surgery 2010;199:797–803.
[65] Overman MJ, Kopetz S, Lin E, et al. Is there a role for adjuvant therapy in resected adenocarcinoma of the small intestine. Acta Oncologica 2010;49:474–9.
[66] Veyrieres M, Baillet P, Hay JM, et al. Factors influencing long-term survival in 100 cases of small intestine primary adenocarcinoma. The American Journal of Surgery 1997;173:237–9.
[67] Kaklamanos IG, Bathe OF, Franceschi D, et al. Extent of resection in the management of duodenal adenocarcinoma. The American Journal of Surgery 2000;179:37–41.
[68] Sohn TA, Lillemoe KD, Cameron JL, et al. Adenocarcinoma of the duodenum: factors influencing long-term survival. Journal of Gastrointestinal Surgery 1998;2:79–87.
[69] Bakaeen FG, Murr MM, Sarr MG, et al. What prognostic factors are important in duodenal adenocarcinoma. Archives of Surgery 2000;135:635–41.
[70] Agrawal S, McCarron EC, Gibbs JF, et al. Surgical management and outcome in primary adenocarcinoma of the small bowel. Annals of Surgical Oncology 2007;14:2263–9.
[71] Wu TJ, Yeh CN, Chao TC, et al. Prognostic factors of primary small bowel adenocarcinoma: univariate and multivariate analysis. World Journal of Surgery 2006;30:391–8.
[72] Overman MJ, Varadhachary GR, Kopetz S, et al. Phase II study of capecitabine and oxaliplatin for advanced adenocarcinoma of the small bowel and ampulla of Vater. Journal of Clinical Oncology 2009;27:2598–603.
[73] Crawley C, Ross P, Norman A, Hill A, et al. The Royal Marsden experience of a small bowel adenocarcinoma treated with protracted venous infusion 5-fluorouracil. British Journal of Cancer 1998;78:508–10.
[74] Czaykowski P, Hui D. Chemotherapy in small bowel adenocarcinoma: 10-year experience of the British Columbia Cancer Agency. Clinical Oncology: A Journal of the Royal College of Radiologists 2007;19:143–9.
[75] Fishman PN, Pond GR, Moore MJ, et al. Natural history and chemotherapy effectiveness for advanced adenocarcinoma of the small bowel: a retrospective review of 113 cases. American Journal of Clinical Oncology 2006;29:225–31.
[76] Gibson MK, Holcroft CA, Kvols LK, et al. Phase II study of 5-fluorouracil, doxorubicin, and mitomycin C for metastatic small bowel adenocarcinoma. Oncologist 2005;10:132–7.
[77] Jigyasu D, Bedikian AY, Stroehlein JR. Chemotherapy for primary adenocarcinoma of the small bowel. Cancer 1984;53:23–5.

[78] Locher C, Malka D, Boige V, et al. Combination chemotherapy in advanced small bowel adenocarcinoma. Oncology 2005;69:290–4.
[79] Overman MJ, Kopetz S, Wen S, et al. Chemotherapy with 5-fluorouracil and a platinum compound improves outcomes in metastatic small bowel adenocarcinoma. Cancer 2008;113:2038–45.
[80] Kelland L. The resurgence of platinum-based cancer chemotherapy. Nature Reviews Cancer 2007;7:573–84.
[81] Zaanan A, Gauthier M, Malka D, et al. 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 2011;117:1422–8.
[82] Sobin LH, Gospodarowicz MK, Wittekind C, editors. TNM classification of malignant tumours. 7th ed. Wiley Blackwell; 2009. p. 153–9.