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Review Article

Small bowel adenocarcinoma: French intergroup clinical practice guidelines for diagnosis, treatments and follow-up (SNFGE, FFCD, GERCOR, UNICANCER, SFCD, SFED, SFRO)

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ABSTRACT

Background: This document is a summary of the French intergroup guidelines regarding the management of small bowel adenocarcinoma published in October 2016.
Method: This collaborative work, co-directed by most French Medical Societies, summarizes clinical practice recommendations (guidelines) on the management of small bowel adenocarcinoma. Given the lack of specific data in the literature, all references are given by analogy with colon cancer. The classification used is the AJCC (American Joint Committee on Cancer) pTNM classification (7th edition 2009).
Results: Small bowel adenocarcinoma has a poor prognosis; less than 30% of patients survive for 5 years after the (first) diagnosis (5-year survival of less than 30%). Due to the rarity of the disease and the retrospective data, most recommendations are based on expert agreement. The initial evaluation is based on chest-abdomen-pelvis CT scan, CEA assay, GI endoscopy and colonoscopy in order detect lesions associated with a predisposing disease. Surgical treatment is currently the only curative option for stage I and II. Adjuvant chemotherapy can be discussed for Stage III and Stage II with T4 (expert agreement). With regard to metastatic tumors, treatment with fluoropyrimidine combined with platinum salts should be considered (expert agreement).
Conclusion: Few specific data exist in the literature on this type of tumor; most of the recommendations come from expert agreements or by analogy with colon cancer. Thus, each case must be discussed within a multidisciplinary team.
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1. Introduction

These guidelines are the result of a joint project conducted under the auspices of most of the French medical societies involved in the management of these tumors. The present 2017 version is based on the previous one published in 2012. A writing committee was designated to review recent literature until June 2016 and to write a first document after discussions and teleconferences. This initial document was reviewed and modified after further discussions and writing by a review committee and the final version was validated by the steering committee of the participating National Societies. The present paper is a summary of the French intergroup guidelines published in October 2016 on the web-site of the society SNFGE (2016 www.tncd.org). The grades of recommendations are listed in Table 1. All of the statements of the present paper correspond perfectly to the original full guidelines with no additional data or comments.

2. Epidemiology

Small bowel adenocarcinomas are rare malignant tumors that account for less than 2% of gastrointestinal tumors [1]. Among malignant tumors of the small bowel (SB), adenocarcinoma is the most frequent etiology in France followed by endocrine tumors, lymphomas or stromal tumors [2]. Recent trends show that SB neuroendocrine tumors outnumber SB adenocarcinoma in the US [3]. Epidemiological data estimate the annual incidence of small bowel adenocarcinoma at 2.2–5.7/million in developed countries [4]. In the French Côte d'Or study, the incidence of small bowel adenocarcinoma was 0.18/100,000 men and 0.1/100,000 women during the period 1996–2001, and which incidence increased with age [2]. However, and as is the case for colon cancer, the incidence of small bowel adenocarcinoma is increasing in the population [5]. Moreover, duodenal tumors are more frequent than tumors in other segments (jejunum and ileum) [6].

Indeed, duodenal tumors account for 50% of small bowel adenocarcinomas while tumors of the jejunum and ileum represent 30% and 20%, respectively [5]. The stage at diagnosis is usually advanced; in the series of Talamonti et al., 38% of the patients had synchronous metastases and 38% had lymph-node invasion [7]. In the MD Anderson study, the same distribution by stage was found (35% of metastatic patients and 39% with lymph-node invasion) [8].

Adenocarcinoma of the small bowel has a poor prognosis, with 5-year survival at less than 30% and median survival at 19 months [9]. Due to the lack of specific data in the literature, references are given by analogy with colon cancer.

3. Pre-treatment work-up

RECOMMENDATIONS: Physical (clinical) examination, chest-abdomen-pelvis CT scan for tumor localization and extension, CEA assay (expert agreement), GI endoscopy and colonoscopy for lesions associated with a predisposing disease (expert agreement).

OPTIONS: In patients with a predisposing disease affecting multiple sites of the small bowel, exploration of the small bowel by enteroscopy, enteroscan or videocapsule (in the absence of stenosing lesions) should be discussed (expert agreement).

Table 1
Grade of recommendations.

A: Strongly recommended based on highly robust scientific evidence.
B: Usually recommended based on scientific presumption.
C: Option according to expert opinion based on weak scientific evidence.
When there is no scientific evidence, it is only expert opinion or expert agreement

For duodenal sites, ultrasonography should be performed to determine the possibility of tumor resection in the absence of metastasis (expert agreement).

3.1. Search for predisposing diseases

Predisposing diseases are Familial Adenomatous Polyposis (FAP), Hereditary Non Polyposis Colorectal Cancer (HNPCC) syndrome, Peutz-Jeghers syndrome, Crohn's disease and celiac disease [10].

In celiac disease, the risk of developing small bowel adenocarcinoma is low (8 cases per 11,000 patients for the Swedish registry) [11]. Duodenal biopsies during the initial endoscopy and an anti-transglutaminase (IgA) or anti-transglutaminase (IgG) and anti-endomysium (IgG) antibody assay in cases of IgA deficiency are recommended.

The relative risk of developing small bowel adenocarcinoma in Crohn's disease is about 20 [12,13]. In Crohn's disease, the preferred location is the ileum and the age at onset is younger (4th decade) [14]. If there is a family history of Crohn's disease or if there are clinical symptoms, a morphological examination of the small bowel and a proctologic examination are recommended.

In cases of HNPCC (Lynch syndrome), the relative risk of developing adenocarcinoma of the small bowel is high: 291 in cases with the hMLH1 mutation and 103 in cases with the hMSH2 mutation in the Dutch register [15]. However, the cumulative risk remains low at around 1% [16]. The examination will look for a family history of cancers (colon, rectum, stomach, endometrium, ovary, bladder, ureter or renal excretory cavities). The indications for screening for microsatellite instability and for an oncogenetic consultation are the same as those for colon cancer.

In a series of multiple registries, 4.5% of patients with FAP developed adenocarcinoma of the upper digestive tract. Among these, 50% were adenocarcinomas of the duodenum, 18% of ampulloma and 12% of gastric adenocarcinoma [17]. Compared with the general population, the relative risk of having a duodenal adenocarcinoma was 330 and an ampulloma 123 [18].

The diagnosis of FAP will be confirmed at the colonoscopy and lead to a genetic consultation.

Peutz–Jeghers syndrome is a rare syndrome that causes intestinal diffuse polyposis. A study that gathered six publications estimated the relative risk of developing small bowel adenocarcinoma at 520 compared with the general population [19].

Adenomas of the small bowel which are large, villous or located in the peri-ampullary area also present a risk of degeneration [20].

For these predisposing diseases, exploration of the small intestine by enteroscopy, enteroscan or videocapsule could be performed [21,22].

4. TNM classification of small bowel carcinoma (AJCC: 7th edition 2009)

pTis	Carcinoma in situ
pT1	Tumor invading the mucosa or submucosa
pT1a	Tumor invading the mucosa
pT1b	Tumor invading the submucosa
pT2	Tumor invading the muscularis without exceeding it
pT3	Tumor invading sub-serous or perivascular tissue not covered with peritoneum (mesentery or retroperitoneum*), ≤2 cm
pT4	Tumor perforating the visceral peritoneum (T4a) or infiltrating organs (T4b) or structures (other intestinal loops, mesentery, retroperitoneum > 2 cm, abdominal wall through the serosa, and in the case of the duodenum only, invasion of the pancreas)
	*Mesentery in the case of the jejunum or the ileum, of retroperitoneum in areas of the duodenum where the serosa is Absent.

■ **Regional lymph nodes**

pN0	No lymph node metastasis
pN1	1–3 metastatic regional lymph nodes
pN2	≥4 metastatic regional lymph nodes

According to the UICC recommendations, it is necessary to examine at least 6 regional lymph nodes for the correct evaluation of lymph node status. However, in the absence of lymph node invasion, even if the number of lymph nodes usually examined is not reached, the tumor will be classified pN0.

■ **Remote metastases**

pM0	No remote metastasis
pM1	Presence of distant metastasis (s)

■ **Stage classification by UICC 2009—small bowel cancer**

Stage UICC	TNM		
Stage 0	Tis	N0	M0
Stage I	T1, T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T4	N0	M0
Stage IIIA	T1, T2	N1	MO
Stage IIIB	T3, T4	N1	MO
Stage IIIC	All T	N2	MO
Stage IV	All T	All T	M1

5. Treatments

The curative treatment is surgical.

5.1. Operability and resectability criteria

It depends on many different factors related to the tumor (site, stage, size) and the patient (comorbidity, age, refusal of surgery).

Resectability depends on the local (T) and metastatic (M) extension:

- In the absence of distant metastasis (M0), first resection, unless posterior invasion preventing R0 resection of the cancer and involved organs and structures. In this case, preoperative treatment can be discussed to make this lesion removable (expert opinion).
- In cases of non-resectable metastatic disease, no formal indication for initial treatment of the primary cancer, unless occlusive syndrome or perforation. Initial chemotherapy can be discussed (expert opinion).
- In cases of resectable metastatic disease, resection of the primary tumor and metastasis in one or two stages according to the symptoms and localizations. Chemotherapy between the two surgical steps should be discussed according to the extension (expert opinion).

5.2. Surgical treatment

The principle of surgical treatment is the resection of the cancer with a distal and proximal margin of at least 5 cm, a healthy circumferential margin and en-bloc exeresis of the adjoining mesentery with location of the vascular pedicle (distal ganglia), while performing adequate loco-regional lymph-node dissection.

- The “no-touch” technique and the first ligature of the vessels are optional (expert agreement).
- Celioscopic resection is possible (expert agreement). The celioscopic approach should be avoided in cases of T4 tumors or a suspicion of synchronous peritoneal carcinosis (expert opinion).
- In cases of uncertainty about the radicality of the resection, it is necessary to enlarge the exeresis (expert opinion).
- In cases of uncertainty about the existence of hepatic metastases, an intra-operative ultrasound is recommended.

The type of resection depends on the stage and the tumor location [23,24].

- For duodenal tumors, cephalic duodenopancreatectomy is indicated for tumors of the second portion of the duodenum, and for proximal and distal infiltrating tumors (Grade C). Regional lymph node dissection must be performed, including the periduodenal and antero-posterior peripancreatic relays, hepatic relay of the right margin of the celiac trunk and the superior mesenteric artery. Extended lymph node dissection is not recommended (expert opinion). Segmental duodenal resection is possible in cases of proximal (first portion of the duodenum) or distal tumors (third portion of the duodenum, to the left of the superior mesenteric artery), non-infiltrating tumors, or tumors of the duodeno-Jejunal angle (expert opinion).
- For tumors located in the jejunum or ileum, segmental resection with lymph node dissection and jejuno-jejunal or ileo-ileal anastomosis (expert agreement).
- For tumors involving the last ileal loop or the ileocecal valve, ileocecal resection or right hemicolectomy with resection of the ileal loop and ligature of the ileocolic artery at its origin, allowing the lymph node dissection (expert opinion).

The prognostic factors identified are the quality of the resection (R0) and the TNM stage [8,23–25]. Palliative surgical treatment (resection or derivation) may be indicated in cases of symptomatic tumor (hemorrhagic or occlusive).

5.3. Adjuvant therapy

5.3.1. General information

Surgery is the only potentially curative treatment; however, 40% of patients have relapse after primary tumor resection [7]. The main prognostic factors are lymph node invasion and localization, with duodenal tumors having a worse prognosis [8,26]. Five-year survival in cases of lymph node invasion is poor (28–32%) [7,8].

No studies have evaluated adjuvant therapy after the resection of small bowel adenocarcinoma. A prospective international Phase III study comparing adjuvant chemotherapy vs observation is currently underway (PRODIGE 33-BALLAD study; NCT02502370).

Because of the high risk of recurrence, the approach proposed for non-metastatic colon cancer has been adopted for the adjuvant treatment of adenocarcinomas of the small bowel [27,28].

5.3.2. Stage I: T1–2, N0, M0

Recommendation: Surgery only.

5.3.3. Stage II: T3, T4, N0, M0

RECOMMENDATION: Surgery only.

OPTION: Adjuvant chemotherapy for T4 (expert agreement).

CLINICAL TRIAL: PRODIGE 33-BALLAD stages I/II/III: Randomization between adjuvant chemotherapy (capecitabine/LV5FU2 or CAPOX/FOLFOX) versus observation.

5.3.4. Stage III: All T, N1–2, M0

NO RECOMMENDATIONS

OPTIONS: Surgery followed by 6 months of adjuvant chemotherapy with simplified FOLFOX4 or LV5FU2 or oral 5FU: capecitabine (expert agreement).

Table 2
Chemotherapy regimen.

FOLFOX 6 m (modified) also called simplified FOLFOX 4.
Oxaliplatin 85 mg/m^2 given as an intravenous (IV) infusion over 2 h in 250 ml of glucose 5% with concurrent (using a Y tube) folinic acid (400 mg/m^2 dl form or 200 mg/m^2 l form) given as an intravenous infusion over 2 h in glucose 5% followed by 5-FU 400 mg/m^2 as a bolus IV injection over 2 min followed by 5-FU 2400 mg/m^2 given as an IV infusion over 46 h.
FOLFIRI
Irinotecan 180 mg/m^2 given as an intravenous (IV) infusion over 2 h in 250 ml of glucose 5% with concurrent (using a Y tube) folinic acid (400 mg/m^2 dl form or 200 mg/m^2 l form) given as an intravenous infusion over 2 h in glucose 5% followed by 5-FU 400 mg/m^2 as a bolus IV injection over 2 min followed by 5-FU 2400 mg/m^2 given as an IV infusion over 46 h.

CLINICAL TRIAL: PRODIGE 33-BALLAD stages I/II/III: Randomization between adjuvant chemotherapy (capecitabine/LV5FU2 or CAPOX/FOLFOX) versus observation.

5.4. Treatment of non-resectable or metastatic tumors

Data on chemotherapy in the context of palliative care are limited. A retrospective study suggested that palliative chemotherapy improved survival (12 months vs 2 months, p = 0.02) [8]. Due to the rarity of this disease, few retrospective studies have evaluated different chemotherapy protocols.

Nevertheless, a series of 8 patients treated with 5FU in continuous infusion reported overall survival of 13 months [29] whereas another series of 20 patients treated with a combination of 5FU and platinum salts (mainly cisplatin) reported overall survival of 14 months [30]. Moreover, a prospective study of 38 patients evaluated a combination of 5FU-adriamycin-mitomycin, which gave a disappointing overall survival of 8 months [31]. Furthermore, a retrospective study of 83 patients with adenocarcinoma of the small bowel or ampulla suggested that survival was better with 5FU + platinum salts than with 5FU without platinum salt (median survival 17.0 vs 12.7 months) [32]. Recently, a retrospective French multicenter series that included 95 patients treated with FOLFOX, LV5FU2, LV5FU2-cisplatin or FOLFIRI reported a median survival of 15.1 months. Patients treated with FOLFOX in the first line had the best survival (17.8 months) [33]. Finally, a prospective study reported encouraging results for oxaliplatin + capecitabine in 30 patients, with 52% of objective responses [34].

In the NADEGE cohort, first-line chemotherapy was FOLFOX in 80% of cases, FOLFIRI in 12% and LV5FU2 in 5% (Aparicio et al., NADEGE prospective cohort demographic data of 335 patients with small bowel adenocarcinomas. Congress 2013; A2466). Overall, the 5FU and platinum salt combinations were the most used and seemed to provide the best results.

A retrospective study of 28 patients who received FOLFIRI in the second line after failure of platinum-based chemotherapy showed a 20% response rate, 50% disease control, median progression-free survival of 3.5 months and a median overall survival of 10.5 months [35]. Chemotherapy regimen was detailed in Table 2.

In cases of peritoneal carcinosis, peritonectomy with hyperthermic intraperitoneal chemotherapy should be reserved for expert centers. This cumbersome and not yet standardized procedure concerns only patients in good general condition with macroscopically resectable carcinosis [36].

RECOMMENDATIONS: There is no standard with consensual agreement.

OPTIONS: Fluoropyrimidine combination, such as 5FU or capecitabine, +oxaliplatin or cisplatin [26,28–30] (expert opinion).

LV5FU2 if contraindication to cisplatin and oxaliplatin.

6. Post-treatment follow-up

The main sites of distant recurrence are the liver and lung [25]. Follow-up is mainly of interest for patients who are able to tolerate a new surgery or chemotherapy. There are no data about systematic exploration of the small bowel after surgery for adenocarcinoma [37].

RECOMMENDATIONS based on expert opinion:

- During the first 5 years after treatment: Clinical examination every 3 months for 2 years and then every 6 months for 3 years. Abdominal ultrasound and Chest X ray or chest-abdomen-pelvis CT scan every 3 to 6 months for 2 years and then every 6 months for 3 years.
- During palliative chemotherapy: Clinical examination every 2–3 months. Paraclinical examinations to evaluate the efficiency of and tolerance to chemotherapy.

Conflict of interest

Christophe Locher: Roche, Novartis, Ipsen. Pauline Afchain: Novartis, Roche, Ipsen. Emmanuelle Samalin: Sanofi, Ipsen, Merck, Amgen, Novartis, Lilly, Roche. Christophe Cellier: Fujifilm, Jansen, Aptalis, Mayoly, Ferring, Dr. Schar, Vifor. Blaise Batumona, Nicolas Carrère, Thomas Aparicio, Yves Becouarn, Laurent Bedenne, Pierre Michel, Yann Parc, Marc Pocard, Benoit Chibaudel: authors have no conflict of interest. Olivier Bouché: Merck, roche, Amgen, Lilly, Novartis.

Appendix A.

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