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## **Non-metastatic colon cancer: French Intergroup Clinical Practice Guidelines for diagnosis, treatments, and follow-up (TNCD, SNFGE, FFCD, GERCOR, UNICANCER, SFCD, SFED, SFRO, ACHBT, SFP, AFEF, and SFR)**

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## Guidelines

## Non-metastatic colon cancer: French Intergroup Clinical Practice Guidelines for diagnosis, treatments, and follow-up (TNCD, SNFGE, FFCD, GERCOR, UNICANCER, SFCD, SFED, SFRO, ACHBT, SFP, AFEF, and SFR)



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## ABSTRACT

**Introduction:** This article is a summary of the French intergroup guidelines regarding the management of non-metastatic colon cancer (CC), revised in November 2022.

**Methods:** These guidelines represent collaborative work of all French medical and surgical societies involved in the management of CC. Recommendations were graded in three categories (A, B, and C) according to the level of evidence found in the literature published up to November 2022.

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Surgery  
 Adjuvant chemotherapy  
 Follow-up

**Results:** Initial evaluation of CC is based on clinical examination, colonoscopy, chest-abdomen-pelvis computed tomography (CT) scan, and carcinoembryonic antigen (CEA) assay. CC is usually managed by surgery and adjuvant treatment depending on the pathological findings. The use of adjuvant therapy remains a challenging question in stage II disease. For high-risk stage II CC, adjuvant chemotherapy must be discussed and fluoropyrimidine monotherapy or oxaliplatin-based chemotherapy proposed according to the type and number of poor prognostic features. Oxaliplatin-based chemotherapy (FOLFOX or CAPOX) is the current standard for adjuvant therapy of patients with stage III CC. However, these regimens are associated with significant oxaliplatin-induced neurotoxicity. The results of the recent IDEA study provide evidence that 3 months of treatment with CAPOX is as effective as 6 months of oxaliplatin-based therapy in patients with low-risk stage III CC (T1–3 and N1). A 6-month oxaliplatin-based therapy remains the standard of care for high-risk stage III CC (T4 and/or N2). For patients unfit for oxaliplatin, fluoropyrimidine monotherapy is recommended.

**Conclusion:** French guidelines for non-metastatic CC management help to offer the best personalized therapeutic strategy in daily clinical practice. Each individual case must be discussed within a multidisciplinary tumor board and then the treatment option decided with the patient.

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## 1. Introduction

The present guidelines are exclusively limited to non-metastatic colon adenocarcinomas. It is a summary of the French intergroup guidelines published in November 2022 on the website of the Société Nationale Française de Gastroentérologie (SNFGE) ([www.tncc.org](http://www.tncc.org)) [1]. A multidisciplinary writing committee originating from 11 medical and surgical societies (SNFGE, Fédération Francophone de Cancérologie Digestive [FFCD], Groupe Coopérateur multidisciplinaire en Oncologie [GERCOR], Fédération Nationale des Centres de Lutte Contre le Cancer [UNICANCER] Société Française de Chirurgie Digestive [SFC], Société Française d'Endoscopie Digestive [SFED], Société Française de Radiothérapie Oncologique [SFR], Association de Chirurgie Hépatobiliaire-Pancréatique et Transplantation [ACHBT], Société Française de Pathologie [SFP], Association Française pour l'Étude du Foie [AFEF], and Société Française de Radiologie [SFR]) gathered experts from different specialties involved in the management of non-metastatic colon cancer (CC) (digestive surgeons, pathologists, medical oncologists, gastroenterologists, and radiologists). This committee reviewed the recent literature (PubMed search for studies published up to November 2022) and drafted an initial document after interactive discussions. The initial document was then reviewed and modified after further evaluation by a review committee. The final version was validated by the steering committee of the Thésaurus National de Cancérologie Digestive (TNCD). These guidelines are an up-to-date comprehensive overview of pre-therapeutic exams, medico-surgical therapeutic strategies, and adjuvant chemotherapeutic choices according to patient and tumor characteristics and follow-up. These recommendations based on the level of evidence received a grade of A–C, according to the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) system, with only an expert opinion (agreement or not, grade D) when there was no scientific evidence (Table 1).

## 2. Pathological classification

Localized CC is staged after resection of the tumor and pathological examination of the resected specimen. The Union for International Cancer Control (UICC) “Tumor,” “Nodes,” “Metastases” (TNM) 8th edition (published in 2017) should be used for staging (Table 2) [2]. For adequate pN staging, at least 12 regional lymph nodes (LNs) must be examined [3]. This is particularly important for the determination of stage II status, evaluation of prognosis for patients with stage II and stage III disease, and the decision regarding the adjuvant chemotherapy regimen. For patients with stages II and III CC, an increased number of retrieved tumor-free LNs is

associated with a reduced risk of recurrence and improved cancer-specific survival.

The number of examined regional LNs must be noted in the pathological report. The following parameters should be also reported: presence or absence of macroscopic tumor perforation; histological type and grade; status of proximal, distal, and radial lymphovascular invasion; perineural invasion; tumor deposits; and tumor budding. These parameters should be noted in a standardized report.

## 3. Molecular tests

Microsatellite instability (*MSI*) is a hypermutable phenotype caused by a deficient DNA mismatch repair (*dMMR*) system [4]. The *dMMR* system includes the *MLH1*, *MSH2*, *MSH6*, and *PMS2* proteins. *dMMR/MSI* is detected in about 15% of all colorectal cancers (CRCs). Approximately 2%–4% of *dMMR/MSI* CRCs are associated with Lynch syndrome (LS) and 11%–13% are sporadic mostly caused by acquired somatic hypermethylation of the promoter of the *MLH1* gene. *BRAF V600E* mutation is frequently present in sporadic CC with hypermethylation of the promoter of the *MLH1* gene, but not in LS-associated CC. This discrepancy in *BRAF V600E* mutation between sporadic *MSI* CC and LS-associated CC might be used as part of the strategy to detect LS in families [5]. The prevalence of *dMMR/MSI* tumors is higher in elderly patients and in patients with stage II CC [4,6].

*dMMR/MSI* testing in the CC setting can assist clinicians in genetic counselling, has prognostic value and *dMMR/MSI* is a predictor of immunotherapy efficacy [4,7,8].

Recommendations:

- All non-metastatic CC should be tested for the *dMMR* status by immunohistochemistry (IHC) and/or molecular biology (grade A). It is useful to detect LS for prognostic determination (grade B).
- *dMMR* is evaluated either by IHC of the four *dMMR* proteins on a pathological tumor sample and/or by molecular techniques on tumor DNA (Pentaplex panel) [9,10].
- In the case of *dMMR* or *MSI* status, the second test should be performed to confirm the concordant *dMMR/MSI* status.
- In the case of a certain diagnosis of *MSI* by IHC and/or tumor DNA analysis, germline testing during a genetic consultation must be proposed.

Options:

- In the case of unresectable locally advanced CC, tumor *RAS* (*KRAS* and *NRAS*) and *BRAF* analyses on the biopsy are also required to guide treatment.

**Table 1**  
Grades of recommendations.

Grade	Quality of evidence	Definition
A	High	Strongly recommended based on highly robust scientific evidence (e.g., several randomized controlled trials/meta-analyses)
B	Moderate	Usually recommended based on scientific presumption (e.g., one randomized controlled trial) Additional research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate
C	Low	Option based on weak scientific evidence (e.g., one or several non-randomized trials) Additional research is very likely to have an important impact on our confidence in the estimate of the effect and is likely to change the estimate
D	Very low	Expert opinion (agreement or not) Any estimate of an effect is very uncertain

**Table 2**  
Clinical tumor, node, and metastasis (TNM) classification and stage groups (based on the 8th edition, 2017).

T0	No detectable tumor
Tis	Carcinoma <i>in situ</i> : intra-epithelial or invasion of lamina propria
T1	Tumor invading the submucosa
T2	Tumor invading the muscularis propria
T3	Tumor invading through the muscularis propria into the pericolorectal tissues
T4	Tumor invading other organs or structures and/or perforates the visceral peritoneum
	T4a Tumor invading through the peritoneum
	T4b Tumor invading the surrounding organ(s)
N0	No regional lymph node (LN) metastasis
N1	Metastases in 1–3 regional LNs
	N1a Metastases in 1 regional LN
	N1b Metastases in 2–3 regional LNs
	N1c Tumor deposit(s) in the subserosa, mesentery, or non-peritonealized pericolic or perirectal tissues without regional LN metastasis
N2	Metastasis in ≥ 4 regional LNs
	N2a Metastasis in 4–6 regional LNs
	N2b Metastasis in ≥ 7 regional LNs
M0	No metastasis
M1	Distant metastasis (M)
	M1a Metastasis confined to one organ (liver, lung, ovary, or non-regional LN) without peritoneal metastases
	M1b Metastasis in more than one organ
	M1c Metastasis to the peritoneum with or without other organ involvement
The pT and pN categories are identical to T and N. The prefix “y” is used when the category is established after neoadjuvant treatment.	
Stage 0	pTis N0 M0
Stage I	pT1–2 N0 M0
Stage IIA	pT3 N0 M0
Stage IIB	pT4a N0 M0
Stage IIC	pT4b N0 M0
Stage IIIA	pT1–T2 N1/N1c M0; pT1 N2a M0
Stage IIIB	pT3–T4a N1/N1c M0; pT2–T3 N2a M0; pT1–T2 N2b M0
Stage IIIC	pT4a N2a M0; pT3–T4a N2b M0; pT4b N1–N2 M0
Stage IVA	any T, any N, M1a
Stage IVB	any T, any N, M1b
Stage IVC	any T, any N, M1c

- Consensus molecular classification of CC (CMS) and multigene assays such as Oncotype DX<sup>®</sup> colon and ColoPrint<sup>®</sup> are not recommended in clinical practice.

#### 4. Pre-treatment assessment

Pre-therapy assessment typically begins by evaluating the patient’s status (clinical history, personal and familial history of cancer, performance status, anemia, nutritional status, and comorbidities) and tumor extension.

##### 4.1. Diagnosis

Recommendations:

- Endoscopy is the main procedure for diagnosis and should be carried out preferably with a total high-quality colonoscopy before surgery. Colonoscopy allows one to determine the localization of the lesion and to take biopsies, to detect synchronous

precancerous or cancerous lesions, and to remove resectable lesions endoscopically.

- Whenever possible, any diagnostic endoscopic biopsy should aim to maximize the number of tumor samples collected (10–15 biopsies) (*expert opinion*).
- If not carried out before surgery, a complete high-quality colonoscopy should be carried out within 6 months after surgery or at the end of adjuvant chemotherapy (*grade B*).

##### 4.2. Staging

The time delay between staging and treatment must be as short as possible. Patients > 75 years old need a geriatric assessment with ONCODAGE. If their ONCODAGE score is ≤ 14, then they must receive a complete geriatric assessment [11].

Recommendations:

- Clinical examination.
- Thoraco-abdominopelvic computed tomography (CT) scan with injection (or liver magnetic resonance imaging [MRI] with

gadolinium and chest CT scan without injection if injection is not possible) [12]. Liver MRI and/or fluorine-18 fluorodeoxyglucose positron emission tomography (18-FDG PET/CT) can be useful if there is doubt regarding metastatic lesions.

- Rectal MRI only if there is doubt between an upper rectal lesion or a CC.

Options:

- CT colonography in a case where complete colonoscopy is not possible.
- Carcinoembryonic antigen (CEA) serum level (*expert opinion*) [13].
- Upper gastrointestinal endoscopy if there is suspicion of right-sided CC spread to the duodenum or if there is associated colorectal polyposis.

#### 4.3. Screening for hereditary colon cancer syndrome

LS and familial adenomatous polyposis (FAP) represent the two main hereditary CRC forms.

##### 4.3.1. Lynch syndrome

LS is the most common hereditary CRC form, accounting for 2%–4% of all CRCs. This syndrome results from germline mutations in an MMR gene (mostly *MLH1*, *MLH2*, *MSH6*, and *PMS2*). Clinical Amsterdam II criteria and revised Bethesda guidelines, which are based on age and family history of cancer, suffer from a lack of sensitivity and specificity to identify LS. Consequently, all patients with CC should have MMR IHC (dMMR versus proficient MMR [pMMR]) and/or DNA molecular screening (*MSI* versus microsatellite stability [*MSS*]) [5,10,14,15].

MMR IHC and molecular tests guide germline genetic testing of MMR genes. If loss of *MLH1* expression (alone or concurrently with loss of *PMS2* expression) is observed, then methylation analysis of the *MLH1* promoter and/or analysis for somatic *BRAF V600E* mutation should be carried out before germline testing of MMR genes [5]. When there is hypermethylation of the *MLH1* promoter and/or somatic *BRAF V600E* mutation, it is probably a sporadic dMMR/*MSI* CC.

Recommendations:

Genetic counseling is needed (*grade A*):

- In a patient with a personal history of LS-associated cancer (colorectal, endometrial, ovarian, pancreatic, biliary tract, renal pelvis, or ureter) irrespective of the age of onset;
- In a patient with a familial history (at least two first degree relatives) of LS-associated cancer with at least one case that occurred in a person < 50 years old;
- In a patient diagnosed with CC before 40 years of age;
- In a dMMR/*MSI* tumor without *BRAF V600E* mutation and/or without hypermethylation of the *MLH1* promoter.

##### 4.3.2. Familial adenomatous polyposis

FAP should be suspected if more than 10 synchronous or metachronous colorectal adenomas are detected [14,16]. The classical form of FAP is characterized by > 100 colorectal adenomas, and the attenuated form is characterized by between 10 and 100 adenomas. When colorectal polyposis is diagnosed, upper gastrointestinal endoscopy must be performed to identify potential duodenal adenomatous polyposis and gastric fundic gland polyposis. A lateral view of the papilla to detect an ampulloma is also recommended.

“Classic” FAP syndrome is due to germline mutations in the *APC* gene or rarely the *MUTYH* gene. *APC*-associated FAP is inherited in an autosomal dominant pattern, whereas *MUTYH*-associated FAP is

inherited in an autosomal recessive pattern. *APC*-associated FAP accounts for < 1% of CRCs and constitutes the most frequent cause of polyposis with a known genetic cause.

Recommendations:

In the case of multiple colorectal adenomas, consider germline testing for (*expert agreement*):

- Patients from 60 years of age with a lifetime total of  $\geq 20$  adenomas;
- Patients from 60 years of age with a lifetime total of  $\geq 10$  adenomas and a personal or family history of CRC;
- Patients under 60 years of age with a lifetime total of  $\geq 10$  adenomas;
- Patients with a lifetime total of  $\geq 5$  advanced adenomas with at least one of the following criteria: before 40 years, duodenal adenomas, and cutaneous sebaceous cysts.

French experts defined a panel of 14 genes of confirmed clinical interest in the context of a suspicion of familial predisposition to cancers of the digestive tract: *APC*, *BMPRI1A*, *CDH1*, *EPCAM*, *MLH1*, *MSH2*, *MSH6*, *MUTYH*, *PMS2*, *POLD1*, *POLE*, *PTEN*, *SMAD4*, and *STK11* [17]. Some of the rarest hereditary CRC syndromes are not developed here, such as hamartomatous polyposis syndromes, which include Peutz–Jeghers syndrome and juvenile polyposis syndrome.

## 5. Treatments

For treatment of non-metastatic CC, the criteria of operability and resectability first need to be established.

### 5.1. Surgery

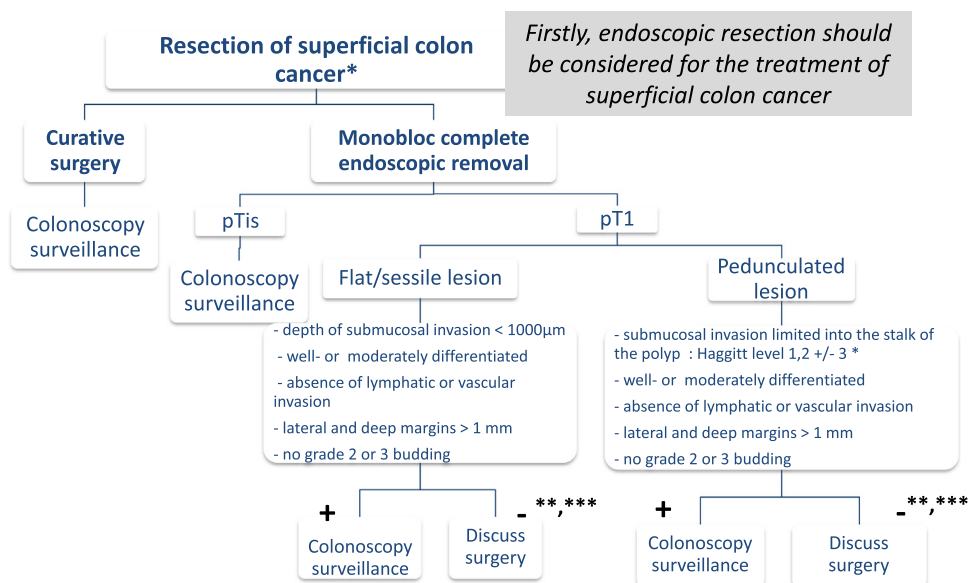
For resectable non-metastatic CC, front-line surgical resection is indicated. It must be complete to be considered curative (R0 resection).

For locally advanced unresectable CC, neoadjuvant treatment can be discussed to facilitate its resectability.

Recommendations:

- The resection should include a segment of the colon measuring at least 5 cm on either side of the tumor, with mesocolon excision in one piece including vascular vessels.
- Laparoscopic colectomy can be safely carried out (*grade A*).
- The types of surgery for non-metastatic CC according to the tumor localization are:
  - Right colon: right hemicolectomy with ileo-transversal anastomosis;
  - Transverse colon: right hemicolectomy extended to the transverse colon or subtotal colectomy extended to the left colon (*expert opinion*);
  - Left angle colon and descending colon: left colectomy with ligation of the left superior colic artery and colo-colic anastomosis or subtotal colectomy. The “classic” left hemicolectomy with ligation of the inferior mesenteric artery has now been almost abandoned;
  - Sigmoid colon: sigmoidectomy with colorectal anastomosis and with ligation of the inferior mesenteric artery and the left superior colic artery.
- For locally unresectable CC, neoadjuvant chemotherapy can be discussed to facilitate resectability (*grade C*) [18,19]. When a locally advanced tumor (T4) with bladder or uterine invasion is discovered during the surgery, a derivative colostomy may be necessary before proceeding with primary chemotherapy and secondary surgery.
- Obstructive CC can be treated in one- or two-stage surgical procedures with a curative intent. Two-stage procedures including colostomy followed by left colonic resection should





**Fig. 1.** Algorithm for the treatment of superficial colon cancer (pTis or pT1). \*: Haggitt classification: level 0 = carcinoma in situ or intramucosal carcinoma; level 1 = adenocarcinoma invading through the muscularis mucosa into the submucosa strictly limited to the head of the polyp; level 2 = carcinomas invading to the neck of the polyp; level 3 = invasion of the carcinoma into the stalk of the polyp; level 4 = signify invasion of the adenocarcinoma into the bowel wall below the polyp stalk, and is limited to the submucosa \*\*: all safety criteria not fulfilled; \*\*\*: if no surgery à a first surveillance colonoscopy 3 months after is recommended.

be preferred especially in case of suffering from the digestive bowel. Endoscopic stenting is not recommended for a secondary curative-intent surgery (*grade C*) [20].

- If there is a doubt regarding preoperative liver metastasis, then intra-operative ultrasound and/or liver biopsies are needed.

Options:

- “No-touch” technique and first vessel ligation (*grade C*).

### 5.2. Endoscopic treatment (Fig. 1)

Endoscopic mucosectomy resection (EMR) or endoscopic submucosal dissection (ESD) have emerged as optional and safe treatments for early CC [21,22]. Early CC is defined as neoplasia that does not involve the colonic wall beyond the mucosal and submucosal layers (carcinoma in situ [Tis] or T1). Resection of early CC should be performed by an experienced endoscopist using the appropriate technique, especially considering the size of the lesion. ESD should be considered for *en bloc* resection of colonic lesions with suspicion of limited submucosal invasion, particularly if the lesions are > 20 mm. Endoscopic evaluation of the depth of invasion of early CC is imperative in establishing an optimal endoscopic resection [23]. A colonic lesion classified as Tis does not invade the submucosa and lacks the potential for regional nodal metastasis. A colonic lesion classified as T1 infiltrates the submucosa with risk of LN metastasis (1%–25%) correlated with the depth of submucosal invasion. Before deciding on additional surgical resection of an endoscopically resected early CC, the case should be discussed in a multidisciplinary team meeting and then discussed with the patient. No additional surgery is required if the early CC has been completely resected and has favorable pathological features as mentioned above.

When early CC is removed (pTis or pT1), four criteria must be specified:

1. Macroscopic appearance using the Paris classification (sessile, pedunculated, and flat);
2. Choice and quality of the resection (cold forceps polypectomy, EMR, ESD, *en bloc* or *piecemeal* resection; macroscopically complete resection or not);

3. Risk of positive LNs according to the depth of invasion (1%–25% if the submucosa is invaded);
4. The surgical morbidity risk depending on the patient.

Endoscopic removal of a Tis colonic lesion is enough and better if it is a monobloc resection (*grade A*). When the superficial submucosa is invaded (T1), endoscopic removal (EMR or ESD) is curative if all the following criteria are fulfilled: complete endoscopic resection with negative lateral and deep margins, well-differentiated or moderately differentiated adenocarcinoma, absence of lymphatic or vascular invasion, depth of submucosal invasion less than 1000 µm, and the absence of grade 2 or 3 tumor budding. In other cases, due to the risk of local residual lesion and/or positive LNs, an additional surgery should be discussed in a multidisciplinary team meeting and with the patient.

### 5.3. Adjuvant chemotherapy

The choices for adjuvant chemotherapy for patients with resected non-metastatic CC depend mainly on the stage of cancer, reflecting the recurrence rates and survival outcomes. Indeed, the 5-year overall survival (OS) rate after surgical resection alone is estimated at 85%–95% for stage I disease, 60%–80% for stage II disease, and 30%–60% for stage III disease. Patients with stage I (T1–2 N0 M0) CC do not require adjuvant chemotherapy.

#### 5.3.1. Stage II (T3–T4 N0 M0)

This group includes different tumor types with a heterogeneous prognosis. Indeed, 5-year OS varies between 58.4% for stage IIc disease (T4b N0) and 87.5% for stage IIa disease (T3 N0) [24]. The benefit of adjuvant chemotherapy for patients with stage II CC is debated. The data come mainly from subgroup analyses of trials including patients with stage II and III CC and from meta-analyses [25–30]. The International Multicentre Pooled Analysis of B2 Colon Cancer Trials (IMPACT) included 1016 patients with stage II CC from five similarly designed randomized trials. The combined analysis showed a 2% non-significant difference in 5-year OS when adjuvant bolus 5-fluorouracil (5-FU)/folinic acid (FA) chemotherapy was compared with postoperative observation [26]. There were contradictory results with the subgroup analysis of patients with

stage II CC enrolled in the NSABP C01–4 trials, with a similar benefit of adjuvant fluoropyrimidine for patients with stage II and III CC [25]. There are some opposite conclusions of the different published meta-analyses [25–30]. In contrast to the results from most other trials, the QUASAR study reported a small but statistically significant benefit in patients with stage II CC for adjuvant chemotherapy in terms of relative risk of recurrence, which decreased by 29% (hazard ratio [HR] 0.71, 95% confidence interval [CI] 0.54–0.92,  $p = 0.01$ ) and with a trend for better OS (HR 0.83, 95% CI 0.65–1.07, not significant [NS]) [31]. However, in the patients included in the QUASAR trial, the median number of LNs examined was only 6, indicating that the QUASAR study certainly had a large population of undiagnosed patients with stage III disease who were wrongly considered to be stage II. Finally, the absolute 5-year OS benefit of adjuvant fluoropyrimidine was only 2.9%, leading to an absence of consensus regarding whether to treat these patients. Moreover, there was no benefit of adjuvant chemotherapy in patients > 70 years old in the QUASAR study. In addition, the most important issue is to identify patients with stage II CC and a high risk of recurrence. The results of the MOSAIC and C-07 trials and of a large population-based study support the lack of benefit of the addition of oxaliplatin to 5-FU/FA in adjuvant therapy for patients with stage II CC in terms of disease-free survival (DFS) and OS even in patients with relatively poor prognostic factors such as T4 stage, bowel perforation, and/or < 10 LNs examined [32–35].

The International Duration Evaluation of Adjuvant Chemotherapy (IDEA) collaboration conducted a pooled and pre-planned analysis of four trials that included 3273 patients with high-risk stage II CC defined as one or more of the following features: T4 tumors, < 12 LNs examined, poorly differentiated tumors, bowel obstruction, perforation, or vascular/perineural/lymphatic invasion. Of these patients, 2019 received CAPOX and 1254 received FOLFOX [36]. The 3-year DFS results were consistent with those obtained for patients with stage III CC with unconfirmed non-inferiority for a 3-month treatment for stage II CC regardless of the specific regimen (80.3% for 3 months versus 83.9% for 6 months; HR 1.17, 95% CI 1.05–1.31,  $p = 0.38$ ). As for stage III, the type of chemotherapy appears to be a determining factor, as the results suggest equivalence between 3 and 6 months of CAPOX regimen (3-year DFS of 81.7% for 3 months versus 82.0% for 6 months). Conversely, 3-year DFS was superior with 6 months of FOLFOX versus 3 months (3-year DFS of 79.2% for 3 months versus 86.5% for 6 months). Therefore, if oxaliplatin-based chemotherapy is discussed for a patient with stage II CC at high “relative” risk of recurrence, then 3 months of CAPOX is an alternative to 6 months of FOLFOX: It is associated with fewer adverse events, especially oxaliplatin-induced peripheral neuropathy.

Considering the 2%–5% improvement in OS with adjuvant chemotherapy in stage II CC, the treatment decision should be based on tumor-related prognostic factors, but also according to patient co-morbidities and life expectancy. The relatively poor prognostic factors that influence decision-making for stage II adjuvant chemotherapy are as follows: pT4 tumors, poorly differentiated grade, lymphovascular invasion, perineural invasion, bowel obstruction, tumor perforation, < 12 LNs examined, and isolated tumor cells in a regional LN. For some experts, lymphovascular or perineural invasion alone is not considered a high-risk factor for recurrence. The presence of isolated neoplastic cells in a LN–T3NO(iCTI)—is a rare situation that is considered by some to be a high-risk factor for recurrence [37]. In addition, tumor budding (especially grade 3) and emergency surgery are also considered high-risk factors for recurrence.

The dMMR/MSI status is a good prognostic marker with improved outcomes in patients with stage II and III CC [38–40]. The dMMR/MSI phenotype is more frequent in older patients and is

also associated with a better prognosis in older patients [6,41]. The dMMR/MSI phenotype is important information to consider adjuvant chemotherapy in stage II CC. Consequently, for patients with dMMR/MSI stage II disease, adjuvant chemotherapy is not recommended (*grade C*). Nevertheless, bowel obstruction, vascular emboli, and stage T4 are independently associated with dMMR/MSI CC recurrence [42].

Stage II CC should be distinguished into three groups:

- Low risk of recurrence including a dMMR/MSI or pMMR/MSS tumor with the following good prognostic factors: pT3; > 12 LNs analysed; no venous, perineural, or lymphatic invasion; well or moderately differentiated tumor; and no bowel perforation/obstruction at presentation.
- Intermediate risk of recurrence including pMMR/MSS tumor with one of the following poor prognostic factors: venous, perineural, or lymphatic invasion; poorly differentiated tumor; bowel perforation at presentation; bowel obstruction at diagnosis; and isolated tumor cells in regional LN. dMMR/MSI tumor with one of these poor prognostic factors are included in the group with a low risk of recurrence.
- High risk of recurrence including tumor with one or more of the following poor prognostic factors: pT4; < 12 LNs analysed; multiple prognostic risk factors from intermediate-risk group.

For adjuvant treatment decision-making, it is also important to consider whether there is only one poor prognostic or several prognostic features. A study reported that patients with high-risk stage II dMMR/MSI CC showed better outcomes with oxaliplatin-based adjuvant chemotherapy compared with surgery alone [43]. dMMR/MSI pT4b stage II cancer can be considered for adjuvant oxaliplatin-based chemotherapy (*grade C*).

The current definition of high-risk stage II CC is subject to debate, as the majority of patients with this disease have a good prognosis, and the potential benefit of adjuvant chemotherapy is minimal. Therefore, the decision-making process regarding the use of adjuvant chemotherapy for patients with high-risk stage II CC should involve personalized discussions between the patient and physician. This discussion should encompass an explanation of the specific characteristics of the disease, its prognosis, and the potential efficacy and associated toxicities of adjuvant chemotherapy, with a focus on the patient's preferences.

Several other markers have been evaluated to provide prognostic and predictive information to help make decisions regarding adjuvant chemotherapy for CC, such as allelic loss at chromosome 18q, SMAD4 protein expression, the Coloprint® signature, the Oncotype DX® signature, loss of CDX2 expression, the Immunoscore®, and circulating tumor DNA (ctDNA) [44–53]. All these very promising markers need to be confirmed in clinical trials with integrative approach including clinical, pathological, biological, and molecular features to identify which factors remain independently associated with recurrence in multivariate analysis. It is important to find predictive markers of the benefit of adjuvant chemotherapy for daily practice. To date, no robust predictive markers for adjuvant chemotherapy efficacy has been identified. A ctDNA-guided approach to adjuvant chemotherapy for stage II CC seems to be the most promising [54].

Recommendations:

- Low risk of recurrence: no adjuvant chemotherapy.
- High-risk or intermediate risk of recurrence: no standard recommendations.

Options:

- Adjuvant chemotherapy could be considered for patients with a good performance status and without severe co-morbidities and poor prognostic factors:

- In the absence of poor prognostic factors or one poor prognostic factor except pT4, < 12 LNs examined, and except the dMMR/MSI tumor status: consider capecitabine or LV5FU2s for 6 months (*expert opinion*).
- In the presence of one major poor prognostic factor (pT4a tumor, < 12 LNs examined, poorly differentiated grade, tumor perforation or multiple other prognostic risk factors from intermediate-risk group): capecitabine or LV5FU2s for 6 months (adjuvant chemotherapy with fluoropyrimidine alone is not recommended for tumors with dMMR/MSI status); an oxaliplatin-based regimen (CAPOX for 3 months or sFOLFOX-4 for 6 months) can be considered for a fit patient (*expert opinion*).
- In the presence of more than one major poor prognostic factors, especially for tumors with pMMR/MSS status, an oxaliplatin-based regimen (CAPOX for 3 months or sFOLFOX-4 for 6 months) can be used (*expert opinion*).
- pT4b tumor, including those with the dMMR/MSI status: adjuvant sFOLFOX-4 for 6 months or CAPOX for 3 months (*expert agreement*).

### 5.3.2. Stage III (any T N1–N2 M0)

Adjuvant chemotherapy is recommended for all patients with stage III CC in the absence of contraindications (*grade A*). Fluoropyrimidine monotherapy decreases the risk of death by 10%–15%; the addition of oxaliplatin reduced the risk of death by 20%–22%.

Since the 1990s, 5-FU-based adjuvant chemotherapy has been associated with longer survival versus observation after surgical treatment of stage III CC [55]. The FUFOL regimen decreased the 5-year death rate from 12% to 16% [56–61]. The LV5FU2 regimen was preferred over the FUFOL regimen because of its similar efficacy but better tolerance [62,63]. Addition of oxaliplatin to 5-FU and FA has been evaluated in two main trials: MOSAIC and NS-ABP C07 [64,33]. In the stage III population of the MOSAIC trial, addition of oxaliplatin to LV5FU2 significantly improved the 3-year DFS rate from 73% to 78% and the 10-year OS rate from 67.1% to 71.7% [35]. This OS improvement was greater in the N2 population, with an absolute 10-year OS increase of 12.9%. There were comparable results in the NSABP C07 trial, where oxaliplatin in addition to 5-FU significantly improved the 3-year DFS rate from 67.0% to 73.2% [33]. The NO16968 trial reported the superiority of CAPOX (capecitabine and oxaliplatin) over bolus 5-FU/FA as an adjuvant treatment for stage III CC, with a significant improvement in the 3-year DFS rate from 67% to 71% and the 7-year OS rate from 67% to 73% [65,66]. A meta-analysis of randomized trials confirmed that addition of oxaliplatin to fluoropyrimidine had a significant positive impact on DFS and OS in patients with stage III CC [67]. These gains in survival are balanced by an increase in treatment-related toxicities—in particular, 12.5% of grade 3 neuropathy induced by oxaliplatin at the end of 6 months of adjuvant therapy and 3.5% of grade 2 or 3 neuropathy at 4 years [33]. Both the FOLFOX and CAPOX regimens are currently considered standard adjuvant treatments for fit patients with stage III CC.

The IDEA collaboration study, which pooled data from six prospective trials, tried to determine whether 3 months of adjuvant chemotherapy was as effective as 6 months [68–74]. The primary endpoint of these six trials was non-inferiority in terms of DFS for 3 versus 6 months of adjuvant treatment. A total of 12,834 patients were randomized. CAPOX was administered to 39.5% of the patients, and 41.3% of the patients had T4 and/or N2 disease. With a median follow-up of 41.8 months, non-inferiority of 3 months of therapy versus 6 months was not confirmed in the overall population (HR 1.07, 95% CI 1.00–1.15). The 3-year DFS rate was slightly lower with 3 months of chemotherapy than with 6 months of chemotherapy (74.6% versus 75.5%). There was non-inferiority of the shorter CAPOX regimen (3-year DFS: 75.9% versus 74.8%; HR

0.95, 95% CI 0.85–1.06) but not for the shorter FOLFOX regimen (3-year DFS: 73.6% versus 76.0%; HR 1.16, 95% CI 1.06–1.26). Among the patients with T1–3 and N1 CC, 3 months of therapy was non-inferior to 6 months, with a 3-year DFS of 83.1% and 83.3%, respectively (HR 1.01, 95% CI 0.90–1.12). Among patients with cancers that were classified as T4, N2, or both, the DFS rate for 6 months of therapy was superior to 3 months of therapy (64.4% versus 62.7%; HR 1.12, 95% CI 1.03–1.23,  $p = 0.01$  for superiority). Neurotoxicity of grade  $\geq 2$  at the end of the adjuvant therapy was substantially lower in the 3-month therapy group (16.6% with FOLFOX and 14.2% with CAPOX) than in the 6-month therapy group (47.7% with FOLFOX and 44.9% with CAPOX).

Non-inferiority of 3 versus 6 months of adjuvant chemotherapy for patients with stage III CC was not confirmed in terms of OS, and updated DFS results confirmed the previous findings [74]. With a median follow-up of 72.3 months, 5-year OS was 82.4% with 3 months of therapy versus 82.8% with 6 months of therapy (HR 1.02, 95% CI 0.95–1.11,  $p = 0.058$  for non-inferiority). For patients treated with CAPOX, 5-year OS was 82.1% versus 81.2% (HR 0.96, 95% CI 0.85–1.08,  $p = 0.033$  for non-inferiority), and for patients treated with FOLFOX, 5-year OS was 82.6% and 83.8% (HR 1.07, 95% CI 0.97–1.18,  $p = 0.34$  for non-inferiority). A shorter duration of adjuvant therapy with the CAPOX regimen is associated with a significant reduction in inconveniences and costs (fewer clinic visits, no need to place a venous access device for most patients, and less oxaliplatin-induced neuropathy). These results support the use of 3 months of adjuvant CAPOX for patients with low-risk stage III CC and 6 months of adjuvant FOLFOX or CAPOX for patients with high-risk stage III CC.

In patients treated with 6 months of oxaliplatin-based chemotherapy for stage III CC, early discontinuation of all treatment is associated with poorer oncological outcomes, but it is not the case for early discontinuation of oxaliplatin. These data favor discontinuing oxaliplatin while continuing fluoropyrimidine in individuals with significant neurotoxicity who have received > 50% of the planned 6 months of chemotherapy [75].

For patients with high-risk stage III CC, prognostic biomarkers including immune scores; tumoral molecular markers such as dMMR/MSI, KRAS, BRAF, or the methylator phenotype; tumor budding; and/or ctDNA as a marker for minimal residual disease may help in the future to define the best duration of adjuvant therapy [50,76–80]. For patients with stage III CC, the dMMR/MSI status is associated with a better prognosis [35,39,40,42,43,47]. Moreover, adding oxaliplatin to fluoropyrimidine adjuvant chemotherapy improves survival in patients with dMMR/MSI stage III CC, similarly to patients with pMMR/MSS stage III CC [81,82]. As for stage II CC, ctDNA analysis after surgery is a promising predictive biomarker of the adjuvant chemotherapy efficacy in stage III CC.

The relatively poor survival in the high-risk subgroup of stage III CC and the good results of FOLFIRINOX in metastatic CRC suggest that this regimen may be particularly interesting in this setting. These factors served to justify the rationale and the design of the IROCAS study [83].

Based on clinical trials, the combination of irinotecan and 5-FU (bolus or infusion) in the adjuvant setting is not superior [84–86]. In addition, there is currently no role for raltitrexid and targeted agents (i.e., bevacizumab and cetuximab) associated with chemotherapy in the adjuvant setting for CC [86–90].

#### Recommendations:

- Adjuvant sFOLFOX-4 for 6 months or CAPOX for 3 or 6 months for high or low risk, respectively (*grade A*) (Table 3).
- For elderly patients, LV5FU2s or capecitabine for 6 months (*grade B*).

#### Options:

- CAPOX for 3 months in high-risk stage III (T4 and/or N2).



**Table 3**

Recommendations for adjuvant oxaliplatin-based chemotherapy (sFOLFOX-4 or CAPOX) in stage II and III colon cancer depending on the regimen, treatment duration, and prognostic risk factors.

Stage	Regimen	
	CAPOX	sFOLFOX-4
Stage III low-risk (T1–3 N1)	3 months	6 months (option: 3 months)
Stage III high-risk (T4 and/or N2)	6 months (option: 3 months)	6 months
Stage II pMMR/MSS high-risk and dMMR/MSI pT4b N0	3 months	6 months

- sFOLFOX-4 for 3 months in low-risk stage III (T1–3 N1).
- LV5FU2s or capecitabine for 6 months if oxaliplatin is contraindicated.
- Oxaliplatin-based chemotherapy for fit patient older than 70 years.

#### 5.4. Chemotherapy optimization and other adjuvant treatments

##### 5.4.1. Timing of adjuvant chemotherapy

If adjuvant chemotherapy is indicated, then it should be administered as soon as the patient is medically able. In patients with stage III disease, adjuvant chemotherapy started after 8 weeks beyond surgical resection seems to be associated with a worse prognosis [91]. Adjuvant chemotherapy must be delivered earlier than 8 weeks after surgery to reduce the relative risk of death [92]. It might still be useful even with a longer interval, with a maximum of 6 months [93]. When it is delayed beyond 3 months after surgery, adjuvant chemotherapy must be discussed after a reassessment of the disease-free status (CT scan) (*expert agreement*).

##### 5.4.2. Dihydropyrimidine dehydrogenase deficiency screening

The main origin of early hematological and digestive fluoropyrimidine-related toxicities is a deficiency in dihydropyrimidine dehydrogenase (DPD), the rate-limiting enzyme of 5-FU catabolism. The performance of DPD phenotyping and *DPYD* genotyping has been poorly documented, and there is no worldwide consensus on the best approach to identify patients with a DPD deficiency. DPD phenotyping approaches based on plasma analysis of uracil are recommended for DPD deficiency screening, with fluoropyrimidine dose adjustment in the case of partial DPD deficiency and fluoropyrimidine contraindication in the case of complete DPD deficiency (*expert opinion*) [94]. A cut-off of 150 ng/mL uracilemia has been identified as a warning signal associated with complete deficiency and risk of toxic death. Patients with uracilemia between 16 and 150 ng/mL are considered partially DPD deficient.

##### 5.4.3. Management of oxaliplatin-induced peripheral neurotoxicity

Oxaliplatin-induced peripheral neurotoxicity is a frequent, severe, and potentially permanent side effect of cancer treatment, mostly with the onset of acute symptoms, but also with the establishment of chronic sensory loss. No treatment can be suggested for its prevention, and there is no curative treatment of oxaliplatin-induced neuropathy. Dose and schedule modification of oxaliplatin-based chemotherapy represent the most effective approach to limit the severity of oxaliplatin-induced neuropathy (stop oxaliplatin if there is grade 3 neuropathy). A randomized study to assess the therapeutic interest of donepezil to treat severe oxaliplatin-induced peripheral neuropathy is ongoing (DONEPEZOX trial) [95].

##### 5.4.4. Aspirin

Aspirin ( $\leq 100$  mg/day) used after surgery for stage II or III CRC was associated with a lower risk of CRC-specific and overall mor-

tality for people with a *PI3KCA* activating gene mutation in two trials and two meta-analyses [96–99]. About 10%–15% of CRCs have a *PI3KCA* activating gene mutation. A third trial did not show survival improvement with aspirin [100]. More studies are required to evaluate the use of aspirin for chemoprevention of CRC recurrence after curative surgery. A double-blind randomized phase III study to evaluate aspirin (100 mg/day for 3 years or until recurrence) versus placebo for high-risk stage II and stage III is ongoing (ASPIK trial) [101].

##### 5.4.5. Physical activity

Some studies have shown a positive interaction between moderate physical activity (3–9 h each week) and OS [102–107]. It is important to encourage patients to participate in post-cancer adapted physical activity programs.

##### 5.4.6. The simplified FOLFOX-4 regimen can replace the classical FOLFOX-4 regimen

The simplified FOLFOX-4 (sFOLFOX-4) regimen (oxaliplatin 85 mg/m<sup>2</sup> with FA 400 mg/m<sup>2</sup> for 2 h, then 5-FU bolus 400 mg/m<sup>2</sup> followed by 5-FU 2400 mg/m<sup>2</sup> for 46 h) is easier, less burdensome for patients, and less expensive than the FOLFOX-4 regimen (1 day versus 2 days the hospital). To date, no study has compared the sFOLFOX-4 regimen to the FOLFOX-4 regimen as adjuvant therapy. Nevertheless, in the NSABPC-08 and NCCTG N0147 trials, which evaluated sFOLFOX-4  $\pm$  bevacizumab or  $\pm$  cetuximab, the 3-year progression-free survival was identical to the FOLFOX arm of the NSABPC-07 trial and the FOLFOX-4 arm of the MOSAIC trial [64,89,108,109].

##### 5.4.7. Oral fluoropyrimidine

Capecitabine is as effective as the FUFOL regimen in adjuvant treatment and has fewer adverse events [110,111]. The standard posology in monotherapy is 2500 mg/m<sup>2</sup>/day. Moreover, the CAPOX regimen is more efficient than 5-FU/FA in stage III tumors and can be used without an implantable site [66,112]. In the IDEA trial, CAPOX seemed to be at least as effective as the FOLFOX regimen, with no increase in adverse events. The administration of oral chemotherapy can be difficult for elderly patients with greater toxicity risks (diarrhea). For elderly patients, it is recommended to begin with 2000 mg/m<sup>2</sup>/day and then to increase the dose if the treatment is well tolerated [113].

#### 5.5. Adjuvant chemotherapy in older patients

Many factors should be considered when determining whether to treat older patients with CC with adjuvant chemotherapy, including fitness for treatment, the wishes of the patient and family, and quality of life. There are limited specific data on adjuvant chemotherapy in patients > 80 years old, who are rarely included in adjuvant therapeutic trials. Besides, the few elderly patients included in these trials are probably highly selected.

Compared with patients < 70 years old, selected patients > 70 years old enrolled in clinical trial have a comparable benefit and safety profile of adjuvant 5-FU-based chemotherapy compared with surgery alone [114,115]. Addition of oxaliplatin does not appear to provide any benefit or minimal benefit in patients over 70 years old of age [33,116,117]. However, the pooled analysis of the NSABP C-08, XELOXA, X-ACT, and AVANT trials, including only stage III, has shown a survival benefit of adding oxaliplatin to fluoropyrimidine for patients > 70 years old [118]. More well-designed trials are required in this specific patient population, such as the ongoing PRODIGE34-ADAGE trial testing LV5FU2 versus no chemotherapy in frail patients and LV5FU2 versus FOLFOX in fit patients > 70 years old with stage III CC [119]. To decide on an adjuvant chemotherapy in an older patient, it is necessary to consider his/her co-morbidities, presumed life expectancy, performance status, and expectations. In difficult situations, an oncogeriatric evaluation should be requested. This approach allows balancing the risk/benefit ratio for each individual patient.

## 5.6. Neoadjuvant treatment

Various published or ongoing clinical trials have evaluated neoadjuvant therapy for patients with localized CC.

### 5.6.1. Neo-adjuvant chemotherapy in resectable pMMR/MSS localized CC

The phase III FOxTROT trial compared perioperative chemotherapy (FOLFOX, three preoperative cycles, then nine postoperative cycles) with the FOLFOX regimen for 12 adjuvant cycles, using 2:1 randomization in 1052 patients with localized cT3–4 cN0–2 cM0 CC. Patients with KRAS wild-type tumors were also randomized 1:1 to receive or not receive panitumumab 6 mg/kg for the first three cycles of treatment. Only the pilot phase of the study, evaluating the feasibility and safety of a neoadjuvant strategy, has been published [19]. Most patients (85.9%) had received the three cycles of neoadjuvant treatment, and all of them underwent surgery without an increase in postoperative morbidity. The ability to predict the pTN stage based on the baseline CT scan was evaluated in the control group: 50% of the tumors considered cT4 were pT4 and 44% of the tumors considered cN+ were pN-. These data are consistent with the literature, showing the poor value of a CT scan for the diagnosis of stage III CC (positive predictive value of 39%–70% and negative predictive value of 68%–91%) [120].

The results of the FOxTROT trial were reported in 2019 but have not been published [121]. The study failed to meet its primary endpoint, with a non-significant reduction in the failure rate (recurrent or persistent disease) at 2 years (14% in the experimental arm versus 18% in the standard arm, HR 0.77,  $p = 0.11$ ). The rate of incomplete R1/R2 resection was 4.8% in the neoadjuvant arm, compared with 9.1% in the standard arm. The pathological response rate according to Dworak criteria was 59% in the experimental arm.

The randomized phase II PRODIGE 22 ECKINOXE trial evaluated in cT3, cT4, and/or cN2 CC surgery ± adjuvant FOLFOX for 6 months ( $n = 52$ ) or a perioperative strategy ( $n = 52$ ) with four preoperative cycles of FOLFOX and eight postoperative cycles [18]. The R0 resection rate was 94% and 93%, respectively. In the experimental group, 44% of patients had major pathological regression (TRG1–2). In the control group, 33% of patients had a low-risk stage II tumor. Three-year OS was similar in both arms (90.4%), and 3-year DFS was 76.8% in the experimental arm and 69.2% in the control arm (HR 0.94). To conclude, a perioperative FOLFOX strategy is feasible, but it does not alter the prognosis of the patients. Based on the available knowledge, neoadjuvant treatment of resectable localized CC is not recommended outside of clinical trials.

### 5.6.2. Neoadjuvant immunotherapy in resectable dMMR/MSI localized CC

Data are accumulating regarding the efficacy of neoadjuvant immune checkpoint inhibitors (ICIs) for patients with localized dMMR/MSI CRC, with approximately two thirds of patients achieving a pathological complete response (pCR). In the NICHE-1 study, among 21 patients with dMMR/MSI CC treated with one dose of ipilimumab and two doses of nivolumab 4 weeks prior to surgery, the major pathological response (MPR) rate ( $\leq 10\%$  viable residual tumor cells) was 95% and the pCR rate was 60% [8]. These data have been confirmed by the results of the NICHE-2 study (including data from NICHE-1), presented at the European Society for Medical Oncology (ESMO) Congress 2022 ( $n = 112$ , 95% MPR, 67% pCR), with no distant relapse (median follow-up 13 months) and an acceptable safety profile (95% of surgeries performed on time, 4% grade 3–4 immuno-mediated adverse events) [122]. It is noteworthy that the pCR rate appears to be equivalent across studies, regardless of the treatment type (anti-programmed cell death protein 1 [PD1] alone or in combination with an anti-cytotoxic T-lymphocyte-associated protein 4 [CTLA4]), the duration of treatment, and the tumor site (the NEONIPIGA trial) [123]. The IMHOTEP trial, which is currently enrolling patients in France, is evaluating neoadjuvant pembrolizumab for all resectable dMMR/MSI tumors [124]. A dual evaluation of dMMR/MSI status with both IHC and molecular assay is mandatory for inclusion in a clinical trial.

Recommendations:

- pMMR/MSS resectable stage I–II CC: no neoadjuvant therapy.
- pMMR/MSS resectable stage III CC: no neoadjuvant therapy.
- dMMR/MSI resectable stage II–III CC: no neoadjuvant therapy. Patients should be referred for clinical trials evaluating neoadjuvant immunotherapy given the pCR rate of about 70% (the IMHOTEP trial).

Options:

- Neoadjuvant chemotherapy may be discussed for patients with a good performance status and no DPD deficiency, notably for a pT4 tumor with potentially morbid surgery and/or a risk of incomplete R1/R2 resection.
- Neoadjuvant immunotherapy may be discussed for patients with dMMR/MSI CC not eligible for clinical trial enrollment at risk of morbid surgery and/or at risk of incomplete R1/R2 resection.

## 6. Therapeutic indications by stage

### 6.1. Stage I (T1–T2 N0 M0)

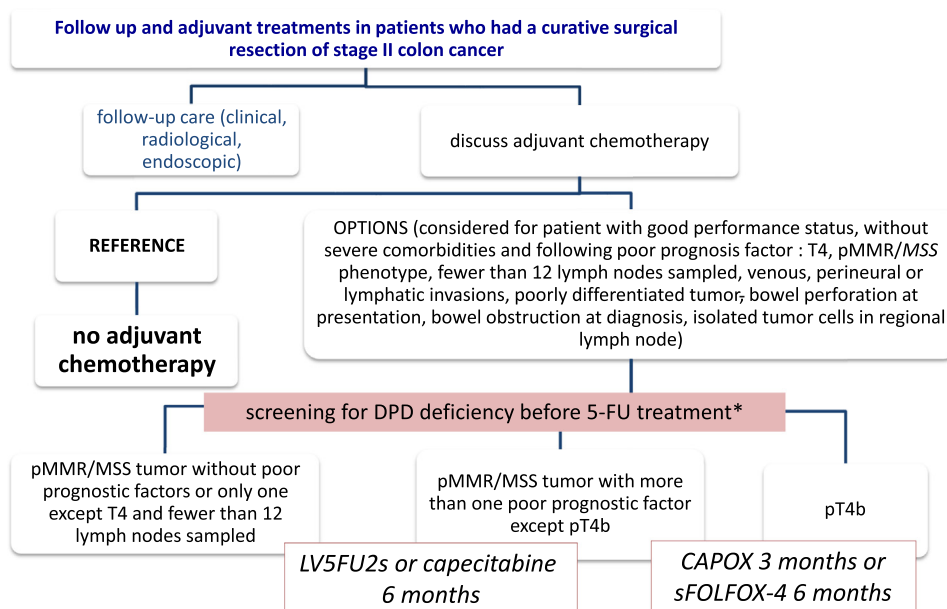
Recommendations:

- Surgical resection alone.
- Endoscopic resection alone for Tis and some pT1.
- No adjuvant treatment.

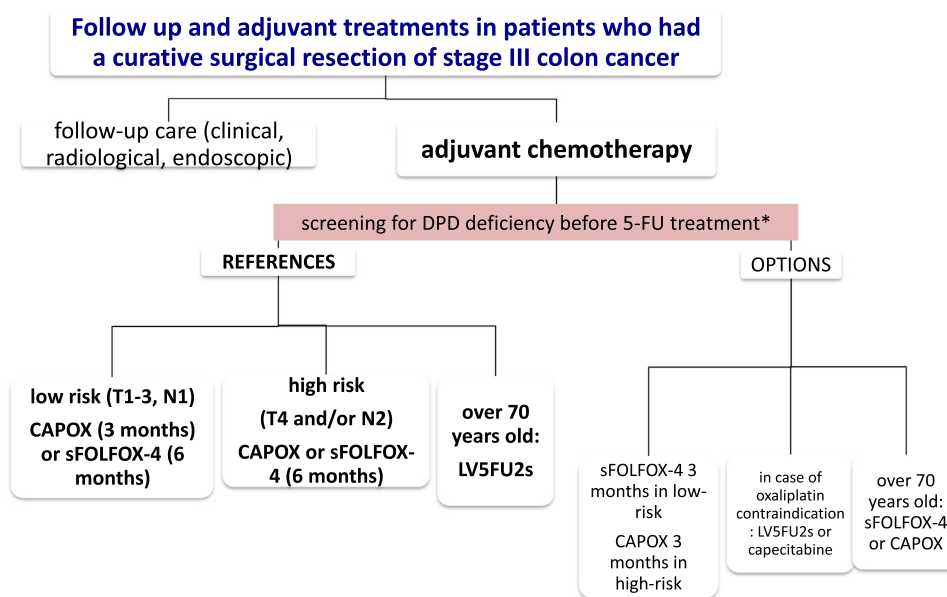
### 6.2. Stage II (Fig. 2)

Recommendations:

- Surgical resection.
- Patients with a pMMR/MSS tumor:
  - Low risk of recurrence (as defined in Section 5.4.1): no adjuvant chemotherapy.
  - High or intermediate risk of recurrence (as defined in Section 5.4.1): no standard recommendations.
- Patients with a dMMR/MSI tumor: no adjuvant chemotherapy.
- Screening for DPD deficiency before 5-FU or capecitabine treatment is mandatory (grade C).



**Fig. 2.** Algorithm for the treatment of stage II colon cancer. \*: dose adjustment in case of partial DPD deficiency and fluoropyrimidine, contraindication in case of complete DPD deficiency.



**Fig. 3.** Algorithm for the treatment of stage III colon cancer. \*: dose adjustment in case of partial DPD deficiency and fluoropyrimidine contraindication in case of complete DPD deficiency; option in case of complete DPD deficiency: raltitrexed-oxaliplatin.

- Physical activity is recommended (*grade C*).

**Options:**

Adjuvant chemotherapy could be considered for patients with a good performance status and without severe co-morbidities and poor prognostic factors:

- Patients with a pMMR/MSS tumor:
  - In the absence of poor prognostic factors or one poor prognostic factor except pT4, < 12 LNs examined, poorly differentiated grade, and tumor perforation: consider capecitabine or LV5FU2s for 6 months (*expert opinion*).
  - In the presence of one major poor prognostic factor (pT4a tumor, < 12 LNs examined, poorly differentiated grade or tumor perforation or multiple other prognostic risk fac-

tors from intermediate-risk group): capecitabine or LV5FU2s for 6 months; an oxaliplatin-based regimen (CAPOX for 3 months or sFOLFOX-4 for 6 months) can be used for fit patients (*expert opinion*).

- In the presence of more than one major poor prognostic factors, an oxaliplatin-based regimen (CAPOX for 3 months or sFOLFOX-4 for 6 months) can be used (*expert opinion*).
- pT4b tumor: adjuvant sFOLFOX-4 for 6 months or CAPOX for 3 months (*expert agreement*).
- Patients with dMMR/MSI tumors: adjuvant chemotherapy (sFOLFOX-4 for 6 months, or CAPOX for 3 months) could be considered for pT4b tumor or in the presence of at least one major poor prognostic factor; adjuvant chemotherapy with fluoropyrimidine alone is not recommended (*expert agreement*).

### 6.3. Stage III (Fig. 3)

#### Recommendations:

- Surgical resection.
- Adjuvant sFOLFOX-4 for 6 months or CAPOX for 3 or 6 months according to high or low risk, respectively (*grade A*) (Table 3).
- Adjuvant chemotherapy is recommended for dMMR/MSI and pMMR/MSS tumors.
- Start adjuvant chemotherapy before 42 days post-surgery.
- Stopping oxaliplatin is recommended if there is grade 2 neurotoxicity and is mandatory if there is grade 3 neurotoxicity.
- For elderly patients, LV5FU2s or capecitabine is recommended for 6 months (*grade B*).
- Screening for DPD deficiency before 5-FU or capecitabine treatment is mandatory (*grade C*).
- Physical activity is recommended (*grade C*).

#### Options:

- CAPOX for 3 months in high-risk stage III (T4 and/or N2).
- sFOLFOX-4 for 3 months in low-risk stage III (T1–3, N1).
- LV5FU2s or capecitabine for 6 months if oxaliplatin is contraindicated.
- Oxaliplatin-based chemotherapy for fit patients > 70 years old.

## 7. Follow-up after curative treatment

Despite optimal primary treatment, 30%–50% of patients with non-metastatic CC will relapse. After curative-intent treatment, 80% of cancer recurrences are diagnosed within the first 3 years after the primary cancer resection [125]. Approximately 25% of the recurrences are amenable to a curative treatment [126]. The tools used for follow-up include clinical exams, serum CEA measurements, various imaging techniques, and colonoscopy. The benefit of follow-up care on OS has not clearly been proved. The advantage of intensive follow-up of patients with stage II and/or III CC is supported by only a few studies [127,128]. More recent trials have reported no benefit in 5-year OS in favor of the more intensive surveillance program [129–132]. An intensive surveillance protocol with both a CEA assay and a CT scan every 3–6 months generally resulted in the detection of more recurrences and recurrences that could be treated with a curative intent than less intensive follow-up, but this approach did not affect OS [133]. The recent phase III PRODIGE 13 clinical trial, which compared 5-year OS after intensive postoperative surveillance (thoracic-abdominopelvic CT scan and CEA assay) with a less intensive program (abdominal ultrasound and chest X-ray) every 3 months the first 3 years and every 6 months the next 2 years in patients with stage II or III CRC, did not provide any benefit in 5-year OS. However, the more intensive follow-up allows more curative-intent surgeries of disease recurrence for patients [134]. Consequently, the recommendations are based mainly on expert opinions, with low adherence to follow-up recommendations [135].

Approximately 5% of CC recurrences will occur beyond 5 years after resection. There are currently no clear recommendations for follow-up after 5 years except for follow-up colonoscopy.

For patients who could be treated with chemotherapy or a new surgery, a follow-up program should be proposed. Surveillance colonoscopies aim to detect local recurrence, but also at diagnosis, and to remove metachronous lesions (cancer, adenoma) because patients have an increased risk of developing second CRC, particularly in the 2 years after resection (an incidence of 1%) [136,137]. It should be noted that use of colonoscopy surveillance after CRC resection has not been shown to improve survival. For patients with stage I CC, only follow-up colonoscopy is recommended.

#### Recommendations:

- Clinical examination every 3 months for 3 years (or every 6 months in low-risk stage II [*expert opinion*]) and every 6 months at years 4 and 5 after curative-intent surgery.
- Ultrasound imaging of the abdomen every 3 months for 3 years (or every 6 months in low-risk stage II [*expert opinion*]) and every 6 months at years 4 and 5 after curative-intent surgery.
- Chest X-ray every 6 months for 3 years and every year at years 4 and 5 after curative-intent surgery.
- Given the recent reports of controlled trials, monitoring CEA levels is not recommended in all patients (*grade B*). When the preoperative CEA level is available, if the value increases, then its normalization must be evaluated by an assay carried out within 6–8 weeks after surgery. Its persistent elevation indicates a possible residual tumor requiring morphological assessment.
- Colonoscopy must be carried out at years 1 and 3 and then every 5 years thereafter if colonoscopy is normal, looking for metachronous adenomas and cancers (*grade C*).
- In patients with a hereditary CC syndrome, specific and intensive endoscopic surveillance is recommended [17]. For example, in LS, colonoscopy with indigo carmine chromoendoscopy is recommended every 1 or 2 years, and esophagogastroduodenoscopy is recommended every 3–4 years.

#### Options:

- As an alternative to a follow-up every 3 months, a follow-up every 6 months particularly in patients with stage II or low-risk stage III CC is possible.
- An alternative to ultrasound imaging of the abdomen is thoraco-abdominopelvic CT scan every 3 months for 3 years and every 6 months at years 4 and 5 after curative-intent surgery, particularly in patient with high-risk stage III CC (T4 and/or N2)
- Thoraco-abdominopelvic CT scan can replace ultrasound and chest X-ray in patients with overweight.
- 18-FDG PET/CT is not recommended. However, 18-FDG PET/CT must be used for a patient presenting elevated CEA levels with no recurrent disease on the CT scan.

## Conflict of interest

- T. Lecomte: Amgen, Merck Serono, Pierre Fabre, and Servier.  
 D. Tougeron: Amgen, Merck Serono, Pierre Fabre, Servier, MSD, BMS, Astra Zeneca, Sanofi, and Roche.  
 F. Bibeau: Astellas, Astra-Zeneca, BMS, Incyte, MSD, Pierre Fabre, and Sanofi.  
 R. Cohen: MSD Oncology, Pierre Fabre, Bristol-Myers Squibb, Mylan Medical, Servier, Exelium Biosciences, and Enterome Bioscience.  
 T. Aparicio: MSD, Pierre Fabre, BMS, Servier, and Amgen.  
 O. Bouché: Amgen, Apromia Therapeutics Bayer, Grunenthal, Merck KGaA, MSD, Pierre Fabre, and Servier.  
 The other authors have reported no conflicts of interest.

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