Colon cancer

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Generalities

Definition

The colon is upstream of the rectosigmoid junction, located more than 15 cm from the anal margin on rectoscopy and above the body of the 3rd sacral vertebra (lateral view above the promontory of the sacrum).

For choice of therapy, cancers of the upper part of the rectum are considered tumors of the colon because of their similar risk of progression (level of evidence D)

Pretherapeutic explorations

Extension tests

— Clinical examination
— Ultrasound or abdominopelvic spiral CT with contrast (if doubt on ultrasound or obesity: spiral CT with contrast or MRI)
— Frontal and lateral lung x-ray (if doubt: CT)
— Colonoscopy (if incomplete before surgery, it must be planned in the 3–9 months after surgery)
— Radiological opacification only if acute occlusion, incomplete colonoscopy or identification problem (Gastrographin enema, barium enema, or virtual colonoscopy depending on the case and availability)

Search for genetic predisposition

Questioning:
• search for cancers that are epidemiologically related: endometrium, ovary, stomach small intestine, ureter, or excretory renal cavities
• search for familial cancer antecedents

HNPPC (LYNCH SYNDROME):
PRESENCE OF ALL AMSTELAND II CRITERIA

At least three subjects with cancers (colorectum, endometrium, ovary, stomach small intestine, ureter excretory renal cavities), one first-degree relative of the two others;

At least two successive generations concerned;

At least one cancer diagnosed before the age of 50 years; diagnosis validated by pathologist.

Incomplete forms are frequent and certain criteria should instigate a search for HNPPC. In particular, the French Expert Collective Conference retained the expanded clinical criteria requiring prescription of immediate oncogenetic consultation, (i) for patients having two relatives instead of three with cancer of this spectrum, one of whom before the age of 50 years, (ii) for patients with a personal antecedent of cancer, and (iii) for patients under 40 years of age.

In other cases, the search for microsatellite instability phenotype (MSI+) present in tumor cells using molecular biology techniques will identify potentially predisposed forms. At least three of the five microsatellite marker tests should be positive to retain the microsatellite instability phenotype. Presence of microsatellite instability therefore requires oncogenetic consultation.

In addition, immunohistochemistry looking for extinction of one or the other repair proteins, (MMR) MSH2, MLH1, MSH6, will orient the search of the causal genetic alteration toward one or the other gene. This alteration should be looked for in a blood sample.

Indications for search for unstable MSI+ phenotype are simple

• patient with HNPPC spectrum cancer who is less than 60 years of age
• patients with first-degree familial antecedent of HNPPC spectrum cancer whatever their age

FAMILIAL ADENOMATOUS POLYPOSIS

Characterized by the presence of more than 100 colon adenomas.

On the genetic level, the alterations of the two genes have been recognized as responsible for the phenotype: the APC gene, which is responsible for the autosomal dominant transmission of the disease, and the MYH gene, which is responsible for the recessive autosomal transmission of the disease. It both cases, attenuated forms of polyposis can exist, with more
difficult diagnosis. In both cases, there are benign and malignant manifestations exist outside the colon, which can be responsible for substantial morbidity (desmoid tumor and duodenal tumor).

Direct genetic diagnosis is possible in both cases, allowing screening for at-risk families and prophylactic surgery when necessary.

**UICC classification**

The Dukes and Astler-Coller classifications, which can be confusing, should be abandoned.

**TNM (UICC 2002)**

- **Tis**: carcinoma in situ: intraepithelial or invasion of lamina propria
- **T1**: tumour invades submucosa,
- **T2**: tumour invades muscularis propria,
- **T3**: tumour invades through muscularis propria into subserosa or into non-peritonealized pericolic tissues
- **T4**: tumour directly invades other organs or structures and/or perforates visceral peritoneum.
- **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
- **M0**: no distant metastasis
- **M1**: distant metastases (including subclavicular lymph nodes)

Examination of at least 12 regional lymph nodes is recommended by the UICC and the AJCC and a minimum of eight is necessary for proper assessment of the lymph node status (1998 consensus, FFCD and SNFGE [1]). Whatever the stage, the prognosis is increasingly good as the number of lymph nodes removed and analyzed increases [2].

**UICC 2002-AJCC classification stages [3, 4]**

- **Stage I** = pT1-T2 N0 M0 = subserosa intact with no lymph node metastases
- **Stage IIA** = pT3 N0 M0 = tumour directly invades other organs or structures and/or perforates visceral peritoneum with no lymph node metastases
- **Stage IIB** = pT4 N0 M0 = tumour invades through muscularis propria into subserosa or into non-peritonealized pericolic tissues with no lymph node metastases
- **Stage IIA** = pT1, T2, N1 M0 = lymph node invasion
- **Stage IIB** = pT3, T4, N1 M0 = lymph node invasion
- **Stage IIC** = any T, N2 M0 = lymph node invasion
- **Stage IV** = any T, any N, M1 = distant metastases

**Operability and resectability criteria**

Tests depending on whether anesthesia consultation favors operability.

Local extension (T) and metastases (M) condition resectability:

- if M0: first resection except if there is local invasion at the descending part of the duodenum or posterior invasion preventing R0 “en bloc” resection of the cancer and the organs and structures invaded; preoperative treatment in this case could be discussed to make this lesion resectable (level of evidence D).
- if nonresectable M1: no formal indication for initial treatment of the primary cancer except in cases of occlusion or perforation syndrome. Primary chemotherapy can be discussed (cf metastatic colon) (level of evidence C).
- if resectable M1, resection of the primary tumor and the metastases in one or two operations depending on the symptoms and locations with or without interval chemotherapy between the two operations depending on extension (5: expert conference on liver metastases; January 2003), (expert opinion).

**Surgical treatment**

Principle: excision of the cancer with a minimum of 5 cm for the distal and proximal margins, a healthy circumferential margin, and “en bloc” excision of the adjoining mesocolon with identification of the vascular pedicle (for tumors of the rectosigmoid junction, 5 cm of mesorectum under the lower pole of the tumor must be removed). The no-touch technique and preliminary ligation of the vessels are optional (level of evidence C). Celsioscopic resection is possible (level of evidence A).

When there is doubt on the existence of liver metastases, intraoperative ultrasound is recommended.

Types of resections:

- right colon: right hemicolecctomy with ileotransverse anastomosis
- sigmoid and left colon: segmentary colectomy and colorectal anastomosis
- rectosigmoid junction: resection with colorectal anastomosis
- for HNPCC syndromes: systematic total colectomy should be discussed

**Adjuvant treatment**

**GENERALITIES**

Examination of a minimum of 12 lymph nodes is recommended.

TNM typing is recommended. The number of lymph nodes examined and the number of lymph nodes invaded have a prognostic value.

In the TNM classification (UICC 2002) the severity of the lymph node invasion is taken into account: N1 = 1–3 N+ ; N2 = 4 or more N+. The respective importance of T and N is more accurately accounted for in the UICC’s and AJCC’s new classification by stages [3, 4].

Studies on the advantage of analyzing the sentinel lymph node(s) are in progress.

Molecular biology studies should be encouraged. To facilitate such studies, a sample should be taken for freezing, formalin used as a fixative or a tumor fragment should be preserved in ethanol [1].
STAGE I = T1-T2-N0 = SUBSEROSA INTACT

Reference
• surgery alone.

STAGE II = T3-T4-N0 = SUBSEROSA INVOLVED (T3) OR EXCEEDED (T4)

The consensus is not absolute, but a high level of heterogeneity exists for stage II patients [4, 6]. Stage II cases cover very different prognostic and potential benefit situations for adjuvant chemotherapy. For example, T4 tumors have a poor prognosis in multivariate analysis [4]. Any analysis of the literature should consider this stage.

The interaction tests on the NSABP C01-4 trials showed that stage II patients benefit from a relative reduction in mortality identical to stage III mortality (negative interaction test) [7].

The different meta-analyses are not conclusive because of their contradictory results. Two have shown therapeutic benefit of adjuvant chemotherapy in stage II patients [8, 9]. One study reported a minimal difference (+2% in 5-year overall survival; p=0.06; 10, 11) with the use of a combination of 5FU–folinic acid monthly with a modest statistical power; the last was negative with a methodology open to criticism [12].

The QUASAR 2 [13] study (n = 3239), published only in abstract form, compared adjuvant chemotherapy using 5FU + folinic acid +−/− levamisole to an arm with no adjuvant chemotherapy in patients who had colorectal cancers (92% stage II in a mixed population of 71% colon cancer and 29% rectal cancer). The results showed an absolute gain of 2.9% in 5-year overall survival in favor of the chemotherapy group for the entire population (p=0.02 for stage II patients, p=0.04).

For high-risk patients with stage II cancer (T4 or occlusion or perforation or poorly differentiated tumor, venous or lymph node invasion, or number of lymph nodes examined <10), the MOSAIC study reported a 3% gain in disease-free survival (DFS) at 3 years, in favor of the FOLFOX4 chemotherapy compared to the LV5FU2 arm (hazard ratio: 0.72; [0.48–1.08], NS) [14].

In view of these results, the indication for adjuvant chemotherapy for patients with stage II cancer should be discussed on a case by case basis with evaluation of the risk-benefit ratio of this adjuvant chemotherapy. The potential gain should be weighed against the exposure to chemotherapy toxicity and the social cost. Since the benefit in terms of survival is modest (between 2% and 5% in absolute value depending on the risk of recurrence), practitioners should be encouraged to stage II patients according to the risk of recurrence:

• low or moderate risk of recurrence (tumors well or moderately differentiated, T3, absence of venous, perineural, and lymphatic embolism, analysis of at least 12 lymph nodes, and no perforation);
• high risk (poorly differentiated tumors, T4, presence of venous, perineural, and lymphatic embolism, analysis of less than 12 lymph nodes, perforation and for some revealing occlusion).

Stage II patients must be included in therapeutic trials specifically evaluating the advantages of adjuvant treatments, with a surgery alone control group for low- or moderate-risk forms.

The recommendations of the American Society of Clinical Oncology (ASCO) are a useful aide in the discussion with the patient [15]. Biological factors such as microsatellite instability (MSI) and the absence of a deletion of certain chromosomes (LOH 18q) are now prognostic factors validated by retrospective studies [35, 36]. Their validation by prospective investigations will probably modify our therapeutic indications for stage II cases.

For oral chemotherapies, the equivalence demonstrated between the Mayo Clinic protocol and capecitabine (16) for stage III patients, and that reported with the UFT compared to the weekly Roswell Park protocol of 5FU–folinic acid, for stages II and III [17], associated with the Japanese meta-analysis (Meta-Analysis Group of the Japanese Society) are arguments in favor of the use of an oral fluoropyrimidine as a replacement for a chemotherapy combining 5FU and folinic acid when this is chosen (expert opinion).

Reference
• When there are no recognized poor prognosis factors: no chemotherapy
• When there are poor prognosis factors: no reference

Alternatives
— In case of recognized poor prognosis factors (T4, perforation, poorly differentiated tumor, venous, lymphatic, or perineural invasion, or number of lymph nodes examined <12): chemotherapy can be proposed to patients with no co-morbidity who are in good general health. In the absence of level of evidence A for efficacy and consensus in this situation, caution is key as well as explaining to patients the risk-benefit balance in their case. The protocols proposed should have little toxic risk: LV5FU2, oral fluoropyrimidines, even FOLFOX4. When the FOLFOX4 protocol is used, oxaliplatin should be interrupted as soon as persistent grade 2 neurotoxicity appears (see below).

Trials:
• PETACC 4–FFCD: stage II cases with low or moderate risk: FOLFIRI (6 months) vs observation (+ biochemical tests). Coordinator in France: Prof. JF Seitz, Hôpital La Timone, Marseille; activated in July 2004 closed June 2006.
• AVANT study (ROCHE - GERCOR): Randomization between FOLFOX4 (6 months), FOLFOX4 (6 months) + Avastin (12 months) and XELOX (6 months) + Avastin (12 months). Coordinator in France: Prof. T André, Paris; activated in December 2004.

STAGE III = ANY PT –N1 OR N2 = LYMPH NODE INVASION

Adjuvant chemotherapies with FUFOX for 6 months: high-dose 5FU–folinic acid (FFCD 8802-IMPACT trial [18, 19, 20]) or low-dose FUFOX [21, 23, 24]) reduced the absolute risk of death at 5 years by 12%–16% [19, 22]. The 5FU–folinic acid–levamisole combination had no advantage.

The LV5FU2 protocol is also effective and better tolerated than high-dose FUFOX [25, 26]. The FFCD-PETACC 2 protocol compared LV5FU2 and low-dose 5FU–folinic acid (closed trial, 1600 stage III patients, results expected).

The FOLFOX 4 (LV5FU2 + LOHP (oxaliplatin, Eloxatine®) 85 mg/m²/14 days) for 6 months showed a significant therapeutic effect in the MOSAIC trial, which included 2246 patients (stage II, 40% and stage III, 60%) compared to the LV5FU2 protocol on 3-year relapse-free survival (RFS) (77.8% vs 72.9%; p=0.01) [27], confirmed at 4 years [28]. The results on overall survival are not known and the decrease in the number or
recurrences was 5% in absolute terms, the majority of which were stage III [27]. The C06 investigation of the NSAPBP confirmed the advantages of oxaliplatin combined with the weekly Roswell Park protocol, showing a 4.9% improvement in 3-year disease-free survival (DFS) [29]. These results are recognized as significant because the analysis pooling many trials (having used 5FU and not oxaliplatin) showed an excellent correlation between DFS and overall survival [30].

The combinations of irinotecan and 5FU did not demonstrate their efficacy as clearly in two phase III trials: the IFL protocol is toxic and does not increase recurrence-free survival (31); the LV5FU2-irinotecan protocol, used in high-risk stage III patients (N2, T4, perforation, etc.), and compared to the LV5FU2 protocol, did not show an improvement in recurrence-free survival (ACCORD 02-FFCD 9802 trial; 32). However, the PETACC 3 trial, which tested the LV5FU2-irinotecan protocol compared to the LV5FU2 protocol in stage III disease (and stage II disease in an associated V307 study) showed a nonsignificant benefit in DFS-free survival, including second, noncolorectal cancers (DFS for stage III patients, the main objective of the trial, p=0.091), but significant disease-free survival when second and noncolorectal cancers were not included (RFS for stage III disease, a secondary objective of the study; p=0.045), which corresponded to the definition of disease-free survival used in the MOSAIC trial [33].

Adjuvant chemotherapy based on 5-Fluorouracil for selected patients over 70 years of age produced the same benefit as for patients under 70 years of age without a significant increase in toxicity [34].

Stage III: Reference
Postoperative chemotherapy with FOLFOX 4 administered for 6 months, and begun if possible before the 42nd day after surgery (level of evidence B).

Cessation of oxaliplatin is recommended as soon as persistent grade II neuropathy appears (persistent painful paresthesias between two cycles) and is mandatory in cases of functional difficulties (grade III) or an allergic reaction.

Fixation in formalin of samples and if possible freezing of healthy and tumor samples for later immunohistological and biochemical studies given the importance of certain biological characteristics such as the MSI phenotype [35, 36].

Alternatives
In patients who do not accept the probability of increased toxicity related to oxaliplatin, or who are not candidates for this chemotherapy: Chemotherapy of the 5FU-folinic acid combination (level of evidence A), for example, standard or simplified LV5FU2 (expert agreement) or FUFO.

oral 5FU, capecitabine, or UFT, (level of evidence B)

or LV5FU2-CPT 11 combination (expert opinion).

On-going trials
— AVANT study (ROCHE - GERCOR):
Randomization between FOLFOX4 (6 months) FOLFOX4 (6 months) + Avastin (12 months) and XELOX (6 months) + Avastin (12 months). Coordinator in France: T André, CHU Tenon, 75020 Paris (activated in December 2004).

— PETACC 8 (FFCD plus intergroup EORTC-GI, AIO, etc.): FOLFOX 4/6 months vs FOLFOX 4 + cetuximab / 6 months: (launch, end 2005) Coordinator: J Taieb, CHU Pitié-Salpêtrière, 75013 Paris.

FOLFOX = folinic acid 200 mg/m²/day or L-folinic acid 100 mg/m²/day in 10-min IV bolus, then 30-min 5FU 375 mg/m²/day in 250 ml of 5% isotonic glucose solution from D1 to D5 every 28 days.

Option: increase 5FU to 400 mg/m² if good tolerance at first cycle.

Low-dose FUFO = folinic acid 20 mg/m²/day or L-folinic acid 10 mg/m²/day in 10-min IV bolus, then 5FU 425 mg/m²/day in 3-min IV bolus in isotonic solution from D1 to D5 every 28 days.

Option: reduce 5FU to 375 mg/m² in fragile or elderly patients (>75 years) for the first cycle.

LV5FU2 = folinic acid 200 mg/m² (or L-folinic acid 100 mg/m²) in 2 h in 250 ml 5% isotonic glucose solution, rinse, then 5FU 400 mg/m² in 10 min in 100 ml of 5% isotonic glucose solution, then 5FU 1200 mg/m² in continuous 44-h perfusion in 5% isotonic glucose solution in portable infuser (QSP 220 ml, 5 ml/h), pump or portable syringe pusher; on D2, clamp H24/H26 infuser to go from AF in 2 h and 5FU bolus same as D1; every 14 days.

Simplified LV5FU2 = folinic acid 400 mg/m² (or L-folinic acid 200 mg/m²) in 2 h in 250 ml 5% isotonic glucose solution, rinse, then 5FU 400 mg/m² in 10 min in 100 ml of 5% isotonic glucose solution then 5FU 2400 mg/m² in continuous perfusion for 44 h in 5% isotonic glucose solution with portable infuser (QSP 220 ml, 5 ml/h), pump or portable syringe pusher.

FOLFOX 4 = oxaliplatin (Eloxatine®) + LV5FU2 oxaliplatin 2-h 85 mg/m² in 250 ml of 5% isotonic glucose solution in Y IV of folinic acid on D1 of LV5FU2 every 2 weeks (12 cycles).

Capecitabine (Xeloda®) = 2500 mg/m²/day (1250 mg/m² morning and evening), 2 weeks out of 3 (8 cycles=24 weeks).

Tegafur-uracil (UFT®) = 300 mg/m² of Tegafur in 3 sessions (3-6 capsules/day depending on body surface), combined with 90 mg/day folinic acid, in 3 sessions (e.g., Osfolate® or Folinoral®, 25- and 5-mg capsule, Lederfoline 15-mg capsule). Treatment for 4 weeks out of 5.

Monitoring after curative treatment

In patients who can endure reoperation or chemotherapy

Reference

• Clinical examination every 3 months for 3 years then every 6 months for 2 years.
• Abdominal ultrasound every 3–6 months for 3 years then every 6 months for 2 years, (spiral angio-CT as option, in case of doubt or unsatisfactory ultrasound).
• Lung x-ray every year for 5 years.
• Colonoscopy: If incomplete or of poor quality before operation, do colonoscopy within 3–9 months after surgery. If complete and good quality after surgery, it should be redone at 2-3 years then every 5 years if normal. If there is doubt, follow-up at 1 year.

After complete excision of three adenomas or more than one adenoma at risk (size >1 cm, villous component, or high-grade dysplasia, or carcinoma in situ), follow-up at 1 year and 3 years (ANAES lower endoscopy, April 2004). If HNPCC, check-up every 2 years.
Alternatives
- ACE, advantage not completely demonstrated, can be closed 2-3 months the first 3 years with tests in case of high level (expert agreement).
- PET scan: when there is doubt on a possible recurrence or for an assessment of extension before treatment of recurrence (SOR)

After palliative treatment
- see metastatic colon cancer section

Screening for other cancers
In first-degree relatives of a patient with colon cancer before 60 years of age or two relatives whatever their age:
- Colonoscopy every 5 years starting at 45 years or every 5 years before the age of diagnosis of the index case

HNPCC (LYNCH SYNDROME)
Amsterdam II criteria (or Bethesda) section II-B
If Amsterdam criteria complete (or incomplete and RER phenotype) B oncogenetic consultation after information and patient agreement
- colonoscopy every 2 years beginning at the age of 20-25 years or every 5 years before the age of diagnosis of the earliest case in the family
- gastroscopy every 1 or 2 years in case of stomach cancer in family antecedents (expert opinion).
- annual gynecological examination after the age of 30 years, with endovaginal ultrasound and PAP smear

FAMILIAL ADENOMATOUS POLYPOSIS WITH MUTATION OF APC GENE
if mutation is found in one of the parents
- annual rectosigmoidoscopy beginning at puberty.
- duodenoscopy with lateroscope and biopsy of the papilla:
  - every year if adenoma
  - every 2 years if normal.
if mutation is not found
- screening B general population

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