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Early colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

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general information

incidence and epidemiology

Colorectal cancer (CRC) is the third most common tumour in men and the second in women, accounting for 10% of all tumour types worldwide. Incidence is higher in males (ratio: 1.4) and for both genders there is a 10-fold difference in incidence between several regions. With 608 000 deaths estimated each year (~8% of all cancer deaths), CRC is the fourth most common cancer-related cause of death in the world [1].

As a general observation, there has been an increasing incidence in countries where the overall risk of large bowel cancer was low, while in historically high-risk countries either a stabilisation (Western Europe and Australia) or a decrease (USA, Canada and New Zealand) in incidence was reported [2]. A gradient of incidence and mortality between North Western and South Eastern Europe has been observed: new CRC cases increased in historically low-risk areas such as Spain and Eastern Europe [3]. This growing incidence reflects modifications in lifestyle behaviours and their consequences related with 'westernisation' such as obesity, physical inactivity, heavy alcohol consumption, high red meat consumption and smoking.

Mortality has declined progressively in many Western countries: this can be attributed to cancer screening programmes, removal of adenomas, early detection of cancerous lesions and availability of more effective therapies, chiefly for early stage disease. Mortality rates for CRC in the European Union (EU) vary between 15 and 20 of 100 000 males and between 9 and 14 of 100 000 females and have decreased in both Western and Northern Countries, particularly in females. In 10 years (1997–2007), EU mortality declined by 6% per quinquennium in men and 8% per quinquennium in women. The analysis updated to 2007 showed a greater reduction of the mortality rate in the young population (aged 30–49 years) with ~10% per quinquennium [4]. In Europe, the 5-year survival for colon cancer in different geographical settings ranged from 28.5% to 57% in men and from 30.9% to 60% in women: the pooled estimation for 51 registries of 23 countries is 46.8% in men and 48.4% in women [5].

The risk of developing colon cancer depends on factors which can be classified into lifestyle or behavioural factors (such as smoking, high red meat consumption, obesity, physical inactivity) and genetically determinant factors. According to international guidelines [6, 7], screening tests are stratified according to the personal risk of disease. Age is considered the major unchangeable risk factor for sporadic colon cancer: nearly 70% of patients with colon cancer are over 65 years of age, and this disease is rare before 40 years even if data from SEER and Western registries show an increased incidence in the 40–44 years group and a decrease in the oldest groups [8].

Individuals with:

(i) a personal history of adenoma, colon cancer, inflammatory bowel disease (Crohn's disease and ulcerative colitis),
(ii) significant family history of CRC or polyps,
(iii) an inherited syndrome (5–10% of all colon cancers) such as familial adenomatous polyposis coli and its variants (1%), Lynch-associated syndromes [hereditary non-polyposis colon cancer (3–5%)], Turcot-, Peutz-Jeghers- and MUTYH-associated polyposis syndromes,

are considered at high risk of colon cancer and must be actively screened and, in cases of inherited syndromes, also referred for genetic counselling [7, 9].

screening principles

The aim of screening is to detect a pre-cancer condition in a healthy population, as well as very early-stage malignancies which can be treated with a clearly curative intention.

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For average-risk populations, the European Guidelines for quality assurance in CRC screening and diagnosis [10] provide '*guiding principles and evidence-based recommendations on quality assurance which should be followed when implementing CRC screening using the various modalities currently adopted in publically mandated programmes in EU member States*'.

The recommendations are:

Only the faecal occult blood test (FOBT) for men and women aged 50–74 (or 70) years has been recommended to date. In average-risk populations, the guaiac (g) FOBT reduced mortality from CRC by ∼15% [I] in different age groups [I, V]. The benefit from annual screening appears to be greater than for biennial screening and the test interval should not exceed 2 years [II, B].

Faecal immunochemical testing appears to be superior to gFOBT with respect to the detection rate and positive predictive value for adenomas and cancer [III]; the test interval should not exceed 3 years [V].

Flexible sigmoidoscopy (FS) reduces CRC incidence and mortality when carried out in an organised screening programme [II]; the optimal interval should not be <10 years and may even be extended to 20 years [IV, C]. The preferred age range is likely to be between 55 and 64 years [III, C]. After age 74, average risk FS screening should be discontinued, given the increasing co-morbidity in this population [V, D].

Colonoscopy: limited evidence exists on the efficacy in reducing CRC incidence and mortality [III]. A note of caution is the observation that colonoscopy screening may not be as effective in the right colon as in other segments of the large bowel [IV]. The age range is 50–74 years [V, D] with the optimal age for a single colonoscopy being around 55 years [IV, C]. The optimal interval should not be <10 years and may even be extended up to 20 years [III, C].

Combination of FOBT and sigmoidoscopy: there is no current evidence for extra benefit from adding a once-only sigmoidoscopy to FOBT screening [II].

New screening technologies are still under evaluation: computed tomography (CT) colonography, stool DNA testing and capsule endoscopy should therefore not be used for screening in the average-risk population [V, D].

diagnosis

symptoms

Colon cancer arises from the mucosa of the bowel, generally growing towards the lumen and/or spreading to adjacent organs. Symptoms are associated with relatively large tumours and/or advanced disease stages, and are generally not specific for colon cancer. Change in bowel habits, general or localised abdominal pain, weight loss without other specific causes, weakness, iron deficiency and anaemia are the most common symptoms, and depends on the location and stage of the primary tumour; they are associated with worse prognosis and their number (but not their duration) is inversely related to survival [11]. A systematic review and meta-analysis of the published literature were carried out to assess the diagnostic accuracy (sensitivity, specificity, and positive and negative ratios) of alarm features in predicting large bowel cancer, resulting in a pooled prevalence of CRC of 6% (95% CI: 5% to 8%) in >19 000 cases, and only dark red rectal bleeding and abdominal mass had a specificity of >95%, suggesting that the presence of either characteristic strongly indicates a diagnosis of CRC [12]. Colon cancer can occur as multiple or synchronous (2.5%) with identical or different histological patterns and stages of development.

Patients with synchronous primary tumours have the same prognosis as patients with single site colon cancers. Metachronous primary tumours arise in up to 3% during 5 years after surgery, and the incidence increases up to 9% after several decades in long-term survivors.

diagnostic procedures

Endoscopy is the main procedure for diagnosis and can be carried out by either sigmoidoscopy (as >35% of tumours are located in the rectosigmoid) or (preferably) a total colonoscopy. The advantages of endoscopy are many, e.g. determination of the exact localisation and biopsy of the lesion, detection of (further) synchronous precancerous or cancerous lesions and removal of polyps. Before surgery, if a complete colonoscopy cannot be carried out for whatever reason, the rest of the colon should be visualised by combining limited left-sided colonoscopy with barium enema in order to study the proximal colon. Virtual colonoscopy or CT colonography are not yet standard investigations, but are valuable instruments to identify with precision the location of the tumour or to detect synchronous lesions or polyps, and they are potentially helpful for patients eligible for laparoscopic resection. In any case, if not carried out before, a complete colonoscopy should be carried out within 3–6 months after surgery [V, B].

pathology

The standard assessment should include the morphological description of the specimen, surgical procedure carried out, definition of tumour site and size, presence or absence of macroscopic tumour perforation, histological type and grade, extension of tumour into the bowel wall and adjacent organs (T stage), distance of cancer from resected margins (proximal, distal and radial), presence or absence of tumour deposits, lymphovascular and/or perineural invasion, presence of tumour budding, site and number of removed regional lymph nodes and their possible infiltration by cancer cells (N stage), and finally the possible involvement of other organs (e.g. liver) if submitted for removal or biopsy (M stage) [13].

The pathological stage must be reported according to the American Joint Cancer Committee (AJCC)/ Union for International Cancer Control (UICC) TNM classification, 7th edition (Table 1).

staging and risk assessment

staging procedures

Once a colon cancer is diagnosed, clinical examination, laboratory tests and instrumental screening should be carried out in order to detect or to exclude metastatic disease. Clinical examination may show visceromegaly (hepatomegaly or lymphadenopathy), ascites and/or synchronous tumours (chiefly in women: ovarian, endometrial and breast cancers). Liver enzymes are generally obtained preoperatively, even if they can be normal in the presence of metastases. Ultrasonography of the liver and the whole abdomen may be useful, but a CT scan is usually more appropriate, in order to detect a metastatic spread to the liver or complications related to the tumour (perforation, fistula, obstruction…) [V, B]. However, sensitivity of the CT scan in detecting peritoneal implants is relatively poor (and influenced by lesion size). Magnetic resonance imaging might be useful for locally advanced tumours and could also be the preferred first-line investigation for evaluating liver metastases in patients who have not previously undergone therapy [14]. The clinical benefit of routine chest CT scan is controversial and its use is not generally recommended [III, D]. Similarly, the routine use of positron emission tomography (PET) with the glucose analogue 18-fluoro-2-deoxy-D-glucose (FDG-PET) is not recommended at the time of initial diagnosis, as it does not modify the treatment approach in the vast majority of patients [15].

The preoperative evaluation of the serum marker carcinoembryonic antigen (CEA) is useful for postoperative follow-up of CRC patients (or for use in the treatment of metastatic disease), while it has a low predictive value for diagnosis in asymptomatic patients due to its relatively low sensitivity and specificity [16]. The CEA level may have a prognostic value in the preoperative setting (>5 ng/dl suggests a worse prognosis). An increased preoperative value not normalised after 1 month following surgical resection may indicate persistent disease.

Table 1. The TNM staging system, AJCC/UICC 7th edition

Primary tumour (T)	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma *in situ*: intraepithelial or invasion of lamina propria[a]
T1	Tumour invades submucosa
T2	Tumour invades muscularis propria
T3	Tumour invades through the muscularis propria into the pericolorectal tissues
T4a	Tumour penetrates into the surface of the visceral peritoneum[b]
T4b	Tumour directly invades or is adherent to other organs or structures[b,c]
Regional lymph nodes (N)[d]	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in one to three regional lymph nodes
N1a	Metastasis in one regional lymph node
N1b	Metastasis in two to three regional lymph nodes
N1c	Tumour satellite deposits in subserose or in non peritonealised tissues
N2	Metastases in ≥4 regional lymph nodes (a: 4–6, b: ≥7)
Distant metastases (M)	
M0	No distant metastases
M1	Distant metastases
M1a	Metastases confined to one organ or site (for example liver, lung, ovary, nonregional node)
M1b	Metastases in more than one organ/site or the peritoneum

continued

Table 1. *Continued*

Stage	T	N	M	Dukes	MAC[e]
Anatomic stage/prognostic groups					
0	Tis	N0	M0	–	–
I	T1	N0	M0	A	A
	T2	N0	M0	A	B1
IIA	T3	N0	M0	B	B2
IIB	T4a	N0	M0	B	B2
IIC	T4b	N0	M0	B	B3
IIIA	T1-T2	N1/N1c	M0	C	C1
	T1	N2a	M0	C	C1
IIIB	T3-T4a	N1/N1c	M0	C	C2
	T2-T3	N2a	M0	C	C1/C2
	T1-T2	N2b	M0	C	C1
IIIC	T4a	N2a	M0	C	C2
	T3-T4a	N2b	M0	C	C2
	T4b	N1-N2	M0	C	C3
IVA	Any T	Any N	M1a	–	–
IVB	Any T	Any N	M1b	–	–

[a]This includes cancer cells confined within the glandular basement membrane (intraepithelial) or mucosal lamina propria (intramucosal) with no extension through the muscularis mucosae into the submucosa.

[b]Direct invasion in T4 includes invasion of other organs or other segments of the colorectum as a result of direct extension through the serosa, as confirmed on microscopic examination (for example, invasion of the sigmoid colon by a carcinoma of the caecum) or, for cancers in a retroperitoneal or subperitoneal location, direct invasion of other organs or structures by virtue of extension beyond the muscularis propria (that is, a tumour on the posterior wall of the descending colon invading the left kidney or lateral abdominal wall; or a mid or distal rectal cancer with invasion of prostate, seminal vesicles, cervix or vagina).

[c]Tumour that is adherent to other organs or structures, grossly, is classified cT4b. However, if no tumour is present in the adhesion, microscopically, the classification should be pT1-4a depending on the anatomical depth of wall invasion. The V and L classifications should be used to identify the presence or absence of vascular or lymphatic invasion, whereas the PN site-specific factor should be used for perineural invasion.

[d]A satellite peritumoural nodule in the pericolorectal adipose tissue of a primary carcinoma without histologic evidence of residual lymph node in the nodule may represent discontinuous spread, venous invasion with extravascular spread (V1/2) or a totally replaced lymph node (N1/2). Replaced nodes should be counted separately as positive nodes in the N category, whereas discontinuous spread or venous invasion should be classified and counted in the site-specific factor category Tumour Deposits.

[e]MAC is the modified Astler–Coller classification.

Edge et al. [17]. Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, IL. The original source for this material is the AJCC Cancer Staging Handbook, 7th edition (2010) published by Springer Science and Business Media LLC, www.springer.com.

Surgical staging includes an assessment of liver metastases, nodal spread of disease and extension of the tumour through the bowel wall and onto adjacent structures. For adequate pN-staging, at least 12 nodes have to be examined [17]. This is particularly important for determination of stage II status, as it has been shown that patient prognosis is much better if at least 14 tumour-free nodes have been presented. It is not entirely clear, however, if this is a surgical (resecting more nodes) or a pathological (finding more nodes and preventing inaccurate classification of stage II) issue. Intra-operative ultrasound is a more accurate assessment for liver metastases: occult liver metastases can be found in 15% of patients; in 5% these are solitary and could easily be resected.

risk assessment

Although local failure rates are very low in colon cancer, systemic recurrence of the disease following surgery is frequent and is very often the ultimate cause of death. The prognosis of colon cancer is clearly related to the staging features of the TNM classification, including the degree of penetration of the tumour through the bowel wall and the presence, or absence, of nodal involvement. However, many additional parameters such as grading, lymphatic or venous or perineural invasion, lymphoid inflammatory response and involvement of resection margins, which are reflected by the Dukes' and TNM classifications, have been shown to have strong prognostic impact. Furthermore, factors such as p53, k-ras and bcl-2 expression, TGF-alpha, EGFR, proliferation index and aneuploidy are under evaluation for their single or combined value under high-risk conditions. Bowel obstruction and perforation are clinical indicators of a poor prognosis.

Elevated pre-treatment serum levels of CEA and/or carbohydrate antigen 19-9 (CA 19-9) have a negative prognostic significance. An age of >70 years at presentation is not a contraindication to standard therapies; acceptable morbidity and mortality, as well as long-term survival, are achieved in this patient population. Some retrospective studies suggested that perioperative blood transfusions could impair the prognosis, but these findings were not confirmed by a large, multi-institutional, prospective randomised trial which demonstrated no benefit for autologous blood transfusions when compared with allogeneic transfusions [18].

Risk assessment is particularly important in order to decide when to propose an adjuvant treatment to an individual patient. As it is well known, adjuvant therapy is a systemic treatment administered after primary tumour resection with the aim of reducing the risk of relapse and death. It is well established that in colon cancer, adjuvant therapy decreases the risk of death by absolute 3%–5% in stage II with single-agent 5-FU and by 10%–15% in stage III with fluoropyrimidines alone plus a further 4%–5% with oxaliplatin-containing combinations [I, A]. Each treatment option, including observation alone, should be thoroughly discussed with the patient, taking into consideration prognostic aspects of the tumour disease, non-disease-related characteristics (such as performance status, age, comorbidities, etc.) and the individual's preferences.

Notably, there is no evidence for a predictive marker regarding the benefit of adjuvant chemotherapy for early CRC, and therefore the use of any predictive marker information for decision making is not indicated [IV, C].

Generally, adjuvant treatment is recommended for stage III and 'high-risk' stage II patients [A]. The first issue is therefore how to define the risk. The 5-year survival after surgical resection alone is:

(i) stage I: 85%–95%,
(ii) stage II: 60%–80%,
(iii) stage III: 30%–60%.

The wide ranges reflect major differences in prognosis depending upon the stage subset, tumour grading and the other biological characteristics discussed below.

Several newer predictors have been recently examined, including microsatellite instability (MSI)/mismatch repair (MMR), 18q deletion, k-ras mutations, TP53, TGFBR2, DCC and thymidilate synthase gene expression.

The most promising risk factors at the present time are represented by allelic loss of chromosome 18q (negative for prognosis) and MSI/MMR (positive for prognosis). In particular, MSI/MMR may be useful to identify a small (10%–15%) subset of stage II patients who are at a very low risk of recurrence and in whom the benefits of chemotherapy are very unlikely. Beyond this prognostic information, the MSI/MMR status is not useful for guidance on treatment decisions, reflecting the heterogeneity of data for the potential predictive value [19–22]. In stage III, the role of MSI/MMR status is not clear: conflicting data exist on the potential benefit of treatment with 5-FU alone in the older studies and in the more recent analyses [23], whereas no conclusive data are available for oxaliplatin. Therefore, MSI/MMR does not need to be determined if an oxaliplatin combination is planned [IV, D].

The general consensus suggests that patients with stage II are considered at high risk if they present at least one of the following clinical characteristics: lymph nodes sampling <12; poorly differentiated tumour; vascular or lymphatic or perineural invasion; tumour presentation with obstruction or tumour perforation and pT4 stage [II].

During risk assessment, one must integrate all known tumour-related prognostic factors starting from the stage and grade and deriving a rough estimate of the chances of relapse. For example, a patient with a stage II G3 adenocarcinoma with blood vessel invasion, presence of tumour budding and high thymidine labelling index, is likely to have >70% chance of relapse, much higher in comparison to another patient with a stage IIIA G1 lesion but with opposite pathological and biological parameters.

Another important problem is tailoring the decision to each individual patient's clinical characteristics. In this context, the most debated issue is the impact of age on decision making.

The median age of patients presenting with CRC is 72 years, whereas the median age of patients in clinical trials is 63 years and <10% of patients >70 years are accrued in the studies. When facing an elderly patient (>age 70) with a resected high-risk CRC, one must keep in mind that:

(i) the life expectancy of a 70-year old otherwise healthy individual is ~8 years for men and 14 years for women; (ii) toxicity of chemotherapy is similar below and above age 70 [II]; (iii) the efficacy of adjuvant treatments is similar in elderly

people compared with that in the general population [II]; (iv) data from pooled analyses indicate that patients >70 years may not benefit significantly from oxaliplation-based combinations in the adjuvant setting. However, they may have a similar benefit to younger patients from 5-FU-based chemotherapy [24]. A subset analysis of the MOSAIC trial also confirms that patients over 70 years may not further benefit from the addition of oxaliplatin [25].

Recently, nomograms have been developed and are also available for CRC. These statistics-based tools attempt to provide all proven prognostic factors and to quantify the risk of 5- and 10-year death as precisely as possible [26].

management of local/locoregional disease

treatment of malignant polyps

Complete endoscopic polypectomy should be carried out whenever the morphological structure of the polyp permits. The presence of invasive carcinoma in a polyp requires a thorough review with the pathologist for histological features that are associated with an adverse outcome. Making the decision to undergo surgical resection for a neoplastic polyp that contains invasive carcinoma involves the uncertainties of predicting and balancing adverse disease outcome against operative risk. Unfavourable histological findings include lymphatic or venous invasion, grade 3 differentiation, level 4 invasion (invades the submucosa of the bowel wall below the polyp) or involved margins of excision. Although level 4 invasion and involved margins of excision are two of the most important prognostic factors, their absence does not necessarily preclude an adverse outcome. Several staging systems to stratify the aggressiveness of polyps have been proposed such as involvement of submucosae (sm1, sm2, sm3: involves the superficial, middle and deep thirds of the submucosa, respectively), invasion into the stalk, absolute thickness of the invasive tumour beyond the muscolaris mucosae. When unfavourable histological features are present in a polyp from a patient with an average operative risk, resection is recommended [IV, B]. The pedunculated polyp with invasive carcinoma confined to the head, with no other unfavourable factors, has a minimal risk for an adverse outcome. The consensus is that endoscopic polypectomy is adequate treatment with proper follow-up examination [IV, B]. Invasion of the stalk but with clear margins of excision and favourable histological features may be treated with endoscopic polypectomy with a similar risk as level 2 invasion (invades the muscularis mucosa but is limited to the head and neck of the stalk). Pedunculated polypoid carcinomas can be treated using the same criteria as other pedunculated polyps with invasive carcinoma. Invasive carcinoma in a sessile polyp should usually be interpreted as having level 4 invasion. Consequently, standard surgical resection is recommended in patients with average operative risk [IV, B].

localised disease

The goal of surgery is a wide resection of the involved segment of bowel together with the removal of its lymphatic drainage. The extent of the colonic resection is determined by the blood supply and distribution of regional lymph nodes. The resection should include a segment of colon of at least 5 cm on either side of the tumour, although wider margins are often included because of obligatory ligation of the arterial blood supply [IV, B].

To clearly define stage II versus III and to identify and eradicate potential lymph node metastases, at least 12 lymph nodes must be resected [IV, B].

Laparoscopic approach has now received wide acceptance for several types of surgical procedures of major abdominal surgery. Laparoscopic colectomy can be safely carried out for colon cancer, particularly for left-sided cancer [I]. For right-sided colonic cancers, the benefit is less obvious since anastomosis must be hand sewn, which requires a laparotomy [IV]. The long-term oncological results of laparoscopic colectomy are similar to those of the conventional approach [27] [I]. Advantages of laparoscopy over the conventional approach are reduced pain, reduced length of hospital stay and reduced duration of ileus [28] [II]. It is recognised that a laparoscopic approach should only be carried out if the following criteria are met:

(i) technically experienced surgeons,
(ii) lack of serious abdominal adhesion due to prior major abdominal surgery,
(iii) no locally advanced disease and/or acute bowel obstruction or perforation.

Obstructive colorectal cancers can be treated in one or two stages. Two-stage procedures can include colostomy followed by colonic resection, or Hartmann's procedure followed by colostomy closure and anastomosis. An alternative is a one-stage procedure with either subtotal colectomy and ileorectal anastomosis or, in selected cases, segmental resection after intraoperative colonic lavage [III]. Endoscopic stenting can be used to relieve obstruction from rectosigmoid cancer and allow subsequent one-step resection. Obstructive right-sided cancers can be treated by colonic resection and immediate anastomosis [IV].

treatment by stage

Stage 0 (Tis N0 M0)

Treatment options are:

(i) Local excision or simple polypectomy.
(ii) Segmentary en-bloc resection for larger lesions not amenable to local excision.

Stage I (T1-2 N0 M0)

(old staging: Dukes' A or modified Astler–Coller A and B1).
Wide surgical resection and anastomosis. No adjuvant chemotherapy.

Stage II A, B, C (T3 N0 M0, T4 a-b N0 M0)

Standard treatment options:

(i) Wide surgical resection and anastomosis.
(ii) Following surgery, adjuvant therapy should not be routinely recommended for unselected patients. In high-risk patients who present at least one of the previously mentioned clinical high-risk features (see above), adjuvant therapy could be considered in clinical practice [II, B].

Stage III (any T, N1-N2, M0)

(i) Wide surgical resection and anastomosis.
(ii) Following surgery, the standard treatment is a doublet schedule with oxaliplatin and a fluoropyrimidine. Although all three combination regimens are superior to 5-FU/FA alone [I, A], FOLFOX4 or XELOX should be preferred to FLOX. When oxaliplatin is contraindicated, monotherapy with infusional or oral fluoropyrimidines should be preferred to bolus 5-FU FU/LV.

treatment options

The benefit of combinations with oxaliplatin has been demonstrated in three landmark trials. In the MOSAIC study [29], the addition of oxaliplatin to 5-FU/LV (FOLFOX schema), demonstrated a significantly increased disease-free survival (DFS) at 3 years, with a reduction in the risk of recurrence of 23% compared with the control arm (LV5FU2).The update at the 6-year follow-up confirmed the benefit in DFS of adjuvant treatment with FOLFOX4, and an advantage was also observed in overall survival (OS), but for stage III patients only [30].

The NSABP C-07 trial compared the efficacy of bolus FU/LV + oxaliplatin (FLOX) versus FU/LV alone (Roswell Park schedule); 3-year DFS was 76.5% versus 71.6% for FLOX and FULV, respectively [31], and the magnitude of reduction in the risk of recurrence was similar to that of the MOSAIC trial. The spectrum of toxicity between MOSAIC and NSABP-C07 was different: grade 3–4 diarrhoea occurred more often with FLOX than with FOLFOX, while grade 3 sensory neuropathy was observed in 12% with FOLFOX and 8% with FLOX. FLOX should probably not be used in clinical practice, due to its toxicity and also due to a lack of OS benefit. The XELOXA international phase III study [32] assessed the safety and efficacy of adjuvant capecitabine plus oxaliplatin (XELOX) versus bolus FU/LV (Mayo Clinic or Roswell Park regimen) in stage III patients: the arm including the oral compound was well tolerated and superior to the i.v fluoropyrimidine. As capecitabine does not require a central venous access, it may be preferred in many patients [IV, B].

In case a clinically relevant neurotoxicity occurs, oxaliplatin should be stopped and fluoropyrimidine continued, as it contributes to about two-third to the therapeutic effect of adjuvant FOLFOX/XELOX.

As stated before, in special situations monotherapy with capecitabine or 5-FU/LV in infusion can be an alternative approach. The X-ACT trial showed that capecitabine is an active agent with a favourable toxicity profile and may reduce overall costs compared with i.v. treatments [I]: after 4.3 years of follow-up, the data still confirm the equivalence in terms of DFS between capecitabine and 5-FU/LV [33] in stage III patients.

Negative trials are related to irinotecan in combination with 5-FU (bolus or infusional). The CALGB-89803 trial [34] compared 5-FU/LV + irinotecan (IFL) with the Roswell Park scheme in more than 1200 patients. The trial was prematurely closed because of an elevated rate of mortality in the IFL group with respect to the FL regimen (2.2% versus 0.8%). Efficacy results indicated no improvement in terms of either OS or event-free survival for IFL, when compared with FL. The PETACC-3 trial [35] compared LV5FU2 or AIO regimen plus irinotecan with LV5FU2 or AIO regimen alone. Results did not show any significant advantage for the regimen with irinotecan in terms of DFS.

There is currently no role for targeted agents associated with chemotherapy in the adjuvant setting for colon cancer. All trials evaluating bevacizumab, NSABP C-08 [36], AVANT [37] or cetuximab, NCCTG NO147 [38] and PETACC-8 [39] are negative, probably due to different biological characteristics in early when compared with advanced disease.

In the adjuvant setting many questions are still unanswered:

(i) The optimal duration of adjuvant treatment: 3 or 6 months? In Italy, the TOSCA trial investigates whether 3 months of FOLFOX4 or XELOX treatment are not inferior to 6 months with the same schedule in terms of recurrence-free survival (RFS) in stage II and III colon cancer patients. Together with other studies (SCOT, France, US, Greece, Japan…), this trial forms the backbone of a large international collaboration ('IDEA') which will give a definitive answer regarding the duration of adjuvant therapy in stage III patients.
(ii) The validation of prognostic/predictive factors: interesting and potentially positive data are expected from large subset analyses from large trials, such as PETACC-3, AVANT and PETACC-8.
(iii) The possible role of aspirin in this setting: from a large study [40], it appears that the regular use of this drug after diagnosis of CRC leads to an increase in cancer-specific survival and OS but only in patients with mutated PIK3CA cancer. Further studies on this topic are needed to confirm these exciting findings.

personalised medicine

In this disease setting, more research is needed to identify molecular markers which could lead to advances in personalised medicine.

follow-up and long-term implications

follow-up

Despite optimal primary treatment, with adequate surgery with or without adjuvant chemotherapy, 30%–50% of patients with colon cancer will relapse, and most of those patients will die from their disease.

Detecting relapse in advance is the main goal of surveillance after primary treatment, but this is clinically meaningful only if it improves survival. Furthermore, follow-up can be expensive and resource-consuming in terms of both money and procedures for a national health system, so intensive surveillance needs to be justified with a good level of evidence.

In the past, there was no strong evidence that regular follow-up could improve the outcome for patients radically resected for colon cancer. Several trials failed to demonstrate a benefit, and results of old meta-analyses were unfortunately based on nonrandomised data or mix of randomised and cohort studies.

In the last 10 years, four further systematic reviews [41–44] have been published. All of these studies demonstrated improved

survival in patients undergoing more intensive surveillance when compared with those with minimal or no follow-up. The estimated OS gain was between 7% and 13%. On the basis of these data, intensive follow-up should now be considered standard practice for colon cancer patients [I, A] [45].

The improvement in OS has been attributed to earlier detection of recurrent disease and in particular, to a higher rate of detection of isolated locoregional relapses. The same rate of recurrence for intensive and minimal follow-up was reported [46], but with an anticipation of 8.5 months in the intensive group. Detection of isolated local recurrences was increased in the intensive group (15% compared with 9%, with RR 1.61 and P = 0.011), and also a small non-significant increase in the detection of hepatic metastases was reported. Absolute reduction in mortality was 9%–13%, comparable with the benefit observed with adjuvant chemotherapy in stage III. In addition, trials included in this analysis were conducted before the modern multidisciplinary approach to metastatic disease, and therefore, the real benefit in clinical practice at the present time could be even more evident.

Despite these results, recent data still showed low adherence to follow-up recommendations. This could be due to difficulties in determining which is the best surveillance test.

Indeed, although pooled data suggest a survival advantage related to intensive follow-up, the heterogeneity of the studies included in these meta-analyses does not allow assessment of which kind of surveillance must be applied in clinical practice. It seems clear that more investigations are better than fewer, which in turn are better than no follow-up at all, but it is nearly impossible to recommend an optimal strategy with an adequate level of evidence. As a matter of fact, 'intensive' procedures in one trial can be similar to 'minimal' procedures in another trial, and surveillance intervals and duration of follow-up cannot be extrapolated by meta-analyses data. Only trials including CEA testing and/or liver imaging achieve significant improvements in survival, but all studies considering liver imaging also included blood CEA monitoring; CEA testing alone does not show benefit in individual studies and has demonstrated a reduction in mortality only in meta-analyses [47]. Despite this, CEA rise is often the first signal of recurrence: a positive value could be detected 1.5–6 months before clinical/instrumental detection with other test(s). There are false-positive rates of CEA elevation of 7%–16% and false-negative rates of up to 40%. CEA test monitoring is also effective in patients without elevation in the preoperative setting: in these patients, a subsequent elevation was observed in 44% of recurrent patients. There is no evidence that other laboratory tests can be useful.

As far as liver imaging is concerned, a CT scan has been shown to be more sensitive than ultrasonography (0.67 compared with 0.43), but a modern contrast enhancement ultrasound scan (CEUS) can substantially increase the sensitivity of ultrasonography. Chest recurrence could be detected by the CT scan: in colon cancer, lung is the first site of relapse in 20% of patients and pulmonary resection could determine a 30% 5-year survival. In contrast, there are no data in favour of regular use of chest X-rays.

Metachronous primary cancer could be detected with an incidence of 0.7% within the first 2 years after curative surgery, but there is no evidence favouring a survival benefit through the detection of intraluminal recurrent cancer, and therefore there is no indication of intensive endoscopic follow-up. If a colon without tumour or polyps is observed 1 year after resection, colonoscopy should be carried out after 3–5 years. In this field, specific recommendations are based mainly on level II and III evidence, particularly concerning timing intervals and duration of follow-up [48].

A recently reported analysis of individual patient data from large adjuvant colon cancer randomised trials including >20 000 patients indicated that 82% of stage III and 74% of stage II colon cancer recurrences are diagnosed within the first 3 years after primary cancer resection [49].

Suggested recommendations are as follows [50]:

(i) Intensive follow-up must be carried out in colon cancer patients [I, A].
(ii) History and physical examination and CEA determination are advised every 3–6 months for 3 years and every 6–12 months at years 4 and 5 after surgery [II, B].
(iii) Colonoscopy must be carried out at year 1 and every 3–5 years thereafter, looking for metachronous adenomas and cancers [III, B].
(iv) CT scan of chest and abdomen every 6–12 months for the first 3 years can be considered in patients who are at higher risk of recurrence [II, B].
(v) CEUS could substitute for abdominal CT scan [III, C].
(vi) Other laboratory and radiological examinations are of unproven benefit and must be restricted to patients with suspicious symptoms.

long-term implications: survivorship care plans

Follow-up is therefore standard practice after completing cancer treatment. It consists of periodic visits and investigations, which usually take place in a specialist cancer setting sometimes for prolonged periods after the treatment ends. However, there has been growing awareness in recent years that optimal cancer survivorship care involves more than surveillance tests. In this setting, the primary practitioner should have a significant role [51].

Survivors of CRC now represent the third largest group of long-term cancer survivors in Western countries, ~11% of the population.

Survivorship care plans are an increasing priority within the cancer system, and supporting colon cancer patients and their providers in staying on track with recommended follow-up is only part of helping patients to regain their health and stay well after treatment.

Data from the Tjandra surveillance meta-analysis [44] reported benefit in the intensive arm, but this benefit was less significant. In fact, in this systematic revision it was observed that, despite benefit in OS and in re-resection rate, the cancer-related mortality was not improved and the survival benefit was not due to early detection and treatment of recurrent disease. Other factors contributing to a survival advantage of surveillance in these patients might include the management of co-morbidities, promotion of beneficial dietary and lifestyle factors and increased psychosocial support.

Major elements in survivorship care are as follows [52]:

(i) Prevention of recurrent and new cancer (classic end-point of follow-up),
(ii) Intervention for cancer sequelae and their treatment (rehabilitation),
(iii) Assessment of medical and psychological late effects (modern end-point of follow-up),
(iv) Health promotion (lifestyle promotion, co-morbidity prevention, etc.).

Most long-term survivors of CRC report very good quality of life following their treatment, but several problems are still observed. Some patients can have bowel dysfunction: diarrhoea, constipation, bowel obstruction, pain. Hemicolectomy can lead to loose stools but this usually improves over time and surgery can also lead to adhesions. It is important to carry out dietary counselling and suggest use of over-the-counter medications (e.g., fibre laxative, stool softeners, antidiarrhoeals). Survivors who received oxaliplatin can experience numbness or painful sensations [53].

More than 76% of colon cancer survivorships are >65 years of age, so long-term employment is not a problem for a majority, but in young people employment and financial concerns should be an important issue to consider.

Despite colon cancer survivors often staying well, higher rates of psychological depression have been reported. Assessment of distress should be considered but evidence on the effectiveness of psychosocial interventions among survivors of CRC is limited.

The majority of colon cancer survivors die of other causes. Consequently, care for general medical and preventive health issues are equal in importance in the care of index cancer. This simple consideration is often not applied in clinical practice. A recent analysis [54] showed that survivors were overall less likely to receive recommended follow-up for chronic conditions, such as angina, congestive heart failure and chronic lung disease, and to receive less of some types of preventive care compared with matched controls. For example, diabetic cancer survivors were less likely to have preventive eye examinations, and the data showed a trend toward less intensive monitoring of HbA1c.

Even though at the present time, this issue can be considered still experimental, the development of Survivorship Care Plans will certainly be one of the major topics in the near future for gastro intestinal medical oncologists.

Table 2. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System[a])

Levels of evidence	
I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, experts opinions
Grades of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, …), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome never recommended

[a]Dykewicz CA. Summary of the guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. *Clin Infect Dis* 2001; 33: 139–144. By permission of the Infectious Diseases Society of America.

note

Levels of evidence and grades of recommendation have been applied using the system shown in Table 2. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty.

conflict of interest

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