clinical practice guidelines

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# Primary colon cancer: ESMO Clinical Practice Guidelines for diagnosis, adjuvant treatment and follow-up

R. Labianca[1], B. Nordlinger[2], G. D. Beretta[3], A. Brouquet[4] & A. Cervantes[5]
On behalf of the ESMO Guidelines Working Group*

[1]*Department of Medical Oncology, Ospedali Riuniti, Bergamo, Italy;* [2]*Department of Digestive Surgery, Ambroise Paré Hospital, Boulogne, France;* [3]*Department of Medical Oncology, Sant'Orsola–Fatebenefratelli Hospital, Brescia, Italy;* [4]*Department of Surgery, Ambroise Paré Hospital, Boulogne, France;* [5]*Department of Hematology and Medical Oncology, INCLIVA, University of Valencia, Valencia, Spain*

## general information

### incidence

Cancers of the colon and rectum altogether are the third most common tumour type worldwide. Cancer of the colon is more frequent than rectal cancer: in high-risk populations the ratio is 2: 1, while in low-risk countries rates are generally similar. In Europe ~250 000 new colon cancer cases are diagnosed each year, accounting for ~9 % overall. Rates increase with industrialization and urbanization and the incidence is slightly higher in western and northern than in southern and eastern Europe.

In general there have been increases in incidence in countries where the overall risk of large bowel cancer was low, while in high-risk countries there have been either stabilizations or decreases in incidence, particularly in younger age groups. About 70% of patients with colon cancer are >65 years of age and the disease is rare under the age of 45 (2 per 100 000/year).

### survival

In Europe the relative survival for adults diagnosed with colon cancer during 1995–99 was 72% at 1 year and 54% at 5 years. Five-year survival decreases from 63% to 49% from the youngest (15–45 years) to the oldest (≥75 years) age group of patients. There have been large improvements since the late 1970s in both genders and in all regions of the continent.

## aetiology and risk factors

### dietary factors

Colorectal cancer most commonly occurs sporadically and is inherited in only 5%–10% of cases. Migrant studies indicate that when populations move from a low-risk area (e.g. Japan) to a high-risk area (e.g. the USA), the incidence increases rapidly within the first generation of migrants. Diet is definitely the most important exogenous factor identified up to now in the aetiology of colorectal cancer. Recently, the World Cancer Research Fund and the American Institute for Cancer Research in their extensive report on diet, physical activity and prevention of cancer have concluded that colorectal cancer is mostly preventable by appropriate diet and associated factors [A].

### non-dietary factors

Established non-dietary factors of colon cancer include smoking tobacco, chronic use of non-steroidal anti-inflammatory drugs (NSAIDs) and some conditions and genetic predispositions.

- Smoking has consistently been associated with large colorectal adenomas, which are generally accepted as precursors for cancer. An updated review suggested a temporal pattern consistent with an induction period of three to four decades between genotoxic exposure and the diagnosis of colorectal cancer. In the USA one in five colorectal cancers may be potentially attributable to tobacco use.
- A systematic review was conducted to determine the effect of NSAIDs for the prevention or regression of colorectal adenomas and cancer: there is evidence from three randomized trials that aspirin significantly reduced the recurrence of sporadic adenomatous polyps [I, A] whereas there was evidence from short-term trials to support regression, but not elimination or prevention, of colorectal polyps in familial adenomatous polyposis.
- Inflammatory bowel diseases (Crohn's disease and ulcerative colitis) increase the risk of colon cancer: a recent meta-analysis reported an increased risk of developing colon cancer in people affected by Crohn's disease (relative risk: 2.59; 95% confidence interval 1.54–4.36). Another systematic review found a heavier relationship between ulcerative colitis and colorectal cancer: the risk exists for ulcerative colitis by decade of disease and is higher in pancolitis.

*Correspondence to:* ESMO Guidelines Working Group, ESMO Head Office, Via L. Taddei 4, CH-6962 Viganello-Lugano, Switzerland;
E-mail: clinicalrecommendations@esmo.org

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- Patients who have had previous malignant disease are also at great risk of developing a second colorectal tumour.
- The metabolic syndrome (high blood pressure, increased waist circumference, hypertriglyceridaemia, low levels of high-density lipoprotein cholesterol or diabetes/hyperglycaemia) had a modest, positive association with colorectal cancer incidence among men, but not among women and there was a clear relationship with the number of components present.
- Based on significant evidence, postmenopausal oestrogen plus progesterone hormone use decreased the incidence of colorectal tumour but a non-comparable benefit was demonstrated for oestrogen alone.

### genetic factors

Genetic vulnerability to colon cancer has been attributed to either polyposis or non-polyposis syndromes. The main syndrome of the first group is the familial adenomatous polyposis (FAP), which is associated with mutation or loss of FAP (also called the adenomatous polyposis coli—APC) gene. Hereditary non-polyposis colorectal cancer (HNPCC) syndrome is associated with germ-line mutations in six DNA mismatch repair genes. The cumulative incidence of HNPCC-related cancers was determined in gene carriers in the Finnish Cancer Registry: by age 70 years, the percentage developing colorectal cancers was 82%.

## screening

The identification of the adenomatous polyp as a well-determined premalignant lesion, together with the good survival associated with early disease, makes colorectal cancer an ideal candidate for screening. The major aim is to detect the 90% of sporadic cases of cancer, most of which occur in people above the age of 50 years. Up to now two strategies have been available: faecal occult blood test (FOBT) and endoscopy. The most extensively scrutinized method, FOBT, has been shown in three randomized trials to reduce mortality from colorectal cancer by up to 25% among those attending at least one round of screening [I, A]. Within its recommendations, the Advisory Committee on Cancer Prevention in the European Union has suggested that if screening programmes for colorectal cancer are implemented they should use the FOBT, whereas colonoscopy should be used for the follow-up of test-positive cases. Screening should be offered to men and women aged 50 years until ~74 years [A], the screening interval should be 1–2 years and the strategies should be implemented within organized programmes.

## diagnosis

Colon cancer may be diagnosed when a patient presents with symptoms or as the result of a screening programme. Because early cancer produces no symptoms and because many of the symptoms are non-specific (change in bowel habits, general abdominal discomfort, weight loss with no apparent cause, constant tiredness), aggressive efforts at detection through screening programmes are essential. Endoscopy is the main tool for diagnosis and it can be performed to varying lengths using either a sigmoidoscope or a colonoscope. The only provision is that a few patients who are very difficult to study with colonoscope for anatomical reasons may be best examined by combining limited left-sided colonoscopy (much more accurate than double contrast barium enema in the sigmoid colon) with barium enema to demonstrate the proximal colon. Also, in a few very high-risk patients, such as those with numerous adenomas, it may be justified to combine a double contrast barium enema with colonoscopy for extra accuracy. Additional investigations might improve the results: virtual colonoscopy or CT colonography, even though they are not yet standard procedures, could be valuable to precisely locate the tumour, which is particularly useful for the surgical approach especially in patients who are candidates for a laparoscopic resection. They could also help to detect other synchronous colonic lesions or polyps if colonoscopy could not explore the whole colon due to obstructive tumour [IV]. Although positron emission tomography with the glucose analogue 18-fluoro-2-deoxy-D-glucose (FDG-PET) can be useful to detect recurrent colorectal cancer, its routine use is not recommended at the time of initial diagnosis because this method does not alter the treatment approach in most cases [II]. Early detection of peritoneal carcinomatosis on imaging remains a challenge and performance of the different diagnostic tools is poor. A great deal of effort has been spent in search of serological markers that would allow the early detection and diagnosis of colorectal cancer. The most widely studied marker, carcinoembryonic antigen or CEA, may be useful in the preoperative staging and postoperative follow-up of patients with large bowel cancer but has a low predictive value for diagnosis in asymptomatic patients due to its relatively low sensitivity and specificity. The sensitivity for Dukes' A and B lesions is 36%, compared with 74% for Dukes' C and 83% for Dukes' D disease when 2.5 mg/ml is used as the upper limit of normal.

## staging

Treatment decisions are usually made in reference to the older Dukes or the Modified Astler–Coller (MAC) classification schema. Stages should preferably be defined by the TNM classification.

### TNM classification

TNM (UICC 2002) is a dual system that includes a clinical (pretreatment) and a pathological (postsurgical histopathological) classification.The clinical classification is designed as cTNM, the pathological pTNM. Generally, cTNM is the basis for the choice of treatment and pTNM for prognostic assessment (Table 1).

### staging procedure

*history*. In addition to the personal medical history, the family history of colorectal cancer, polyps and other cancers should be obtained.

**Table 1.** TNM classification

| | |
|---|---|
| **Primary tumour (T)** | |
| TX | Primary tumour cannot be assessed |
| T0 | No evidence of primary tumour |
| Tis | Carcinoma *in situ*: intraepithelial or invasion of the lamina propria[a] |
| T1 | Tumour invades submucosa |
| T2 | Tumour invades muscularis propria |
| T3 | Tumour invades through the muscularis propria into the subserosa, or into the non-peritonealized pericolic tissues |
| T4 | Tumour directly invades other organs or structures and/or perforates the visceral peritoneum.[b,c] |
| **Regional lymph nodes (N)** | |
| NX | Regional nodes cannot be assessed |
| N0 | No regional lymph node metastases |
| N1 | Metastases in 1–3 regional lymph nodes |
| N2 | Metastases in ≥4 regional lymph nodes |
| **Distant metastases (M)** | |
| MX | Presence of distant metastases cannot be assessed |
| M0 | No distant metastases |
| M1 | Distant metastases |
| **Stage grouping** | |
| Stage 0 | Tis N0 M0: (carcinoma *in situ*) |
| Stage I | T1 N0 M0, T2 N0 M0; stage I equivalent to Dukes' A or MAC A or B1 |
| Stage IIA | T3 N0 M0 |
| Stage IIB | T4 N0 M0; stage II equivalent to Dukes' B or MAC B2 or B3 |
| Stage III (A, B, C) | Any T1–2, N1, M0 (IIIA)any T3–4, N1 M0 (IIIB) any T N2 M0 (IIIC); stage III equivalent to Dukes' C or MAC C1–C3 |
| Stage IV | any T, any N, M1 |

[a]This includes cancer cells confined within the glandular basement membrane (intra-epithelial) or lamina propria (intramucosal) with no extension through the muscularis mucosae into the submucosa.
[b]Direct invasion in T4 includes invasion of other segments of the colon by way of the serosa; for example, invasion of the sigmoid colon by a carcinoma of the caecum.
[c]Tumor that is adherent to other organs or structures, macroscopically, is classified T4. However, if no tumour is present in the adhesion microscopically, the classification should be pT3. The V and L substaging should be used to identify the presence or absence of vascular or lymphatic invasion.

*physical examination*. Check for hepatomegaly, ascites and lymphadenopathy. In women, rule out synchronous breast, ovarian and endometrial cancer.
*laboratory data*. Blood count, CEA and liver chemistry.
*intestinal evaluation*. Full colonoscopy or proctosigmoidoscopy and air-contrast barium enema (in the absence of obstruction or perforation).
*instrumental work-up*. A preoperative chest radiograph and liver ultrasonography could be adequate even though CT scan (chest and abdomen) is more appropriate. Nuclear magnetic resonance tomography (MRI) might be useful for locally advanced cases, but its use is generally restricted to rectal cancer. PET and immunoscintigraphy are methods under evaluation and are currently mainly proposed for differentiating scar and tumour tissue after surgery and/or radiotherapy. PET should be considered also in metastatic disease, chiefly in the liver, suitable for salvage surgery in order to exclude other metastatic sites.
*surgical staging*. Includes an assessment of liver metastases, nodal spread of disease and extension of tumour through the bowel wall and onto adjacent structures. For proper pN-staging at least 12–14 nodes should be removed: this is particularly important for stage II patients whose prognosis is much better if this number of nodes has been removed. It is not clear, however, whether this is a surgical (resecting more nodes) or a pathological (finding more nodes) issue. Intraoperative 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; during resection of liver tumours intraoperative ultrasonography can be used to exclude multifocal tumour development or satellite metastases and to precisely plan the resection and the appropriate safety margin.

## prognosis

Disease relapse (local recurrence and/or distant metastases) following surgery is a major problem and is very often the ultimate cause of death. The prognosis of colon cancer is clearly related to the degree of penetration of the tumour through the bowel wall and the presence or absence of nodal involvement. Additional important parameters are grading, lymphatic or venous or perineural invasion, lymphoid inflammatory response and involvement of resection margins, all characteristics that Dukes' and TNM classifications do not take into account. Many other potentially prognostic factors such as p53, k-ras and bcl-2 expression, TGF-α, EGF, proliferation index and aneuploidy are under evaluation for their single or combined value in high-risk conditions. Bowel obstruction and perforation are clinical indicators of a poor prognosis. Elevated pretreatment serum levels of CEA and/or carbohydrate antigen 19-9 (CA19-9) have a negative prognostic significance. Some retrospective studies have suggested that perioperative blood transfusions could impair the prognosis but this finding was not confirmed by a large, multi-institutional, prospective randomized trial which demonstrated no benefit for autologous blood transfusions as compared with allogeneic transfusions.

## adjuvant treatment

Adjuvant therapy is a systemic treatment administered after primary tumour resection with the aim of reducing the risk of relapse and death. Every treatment option, including observation alone, needs to be discussed with patients according to their characteristics (performance status, age, comorbidities and patient preference…) and to cancer features (pathological stage, grading, overall risk of relapse…).

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

is: for stage I 85%–95%, stage II 60%–80%, stage III 30%–60%. The wide ranges reflect major differences in prognosis depending upon stage subset, tumour grading, and the other biological characteristics discussed below. The question therefore remains: who should be treated and by what.

*stage subset*. Penetration of cancer through the serosa is generally considered the cut-off separating high- versus low-risk patients. In general, stages I and IIA can be considered low-risk while stages IIB and III are widely felt to deserve adjuvant treatment. T4 lesions carry a much worse prognosis than T1–T3 lesions; within the stage III group the 5-year survival drops to half (26%) if more than four lymph nodes are involved.

*tumour grading*. Grade 1 carcinomas are less aggressive than the others and the 5-year survival ranges between 59% and 93%, while it drops to 33%–75% and 11%–56% in grade 2 and 3 tumours, respectively.

Among the other biological characteristics, blood vessel invasion, microscopic tumour budding around the primary lesion, DNA content and thymidine labelling index are recognized parameters accounting for the different prognosis of patients with cancers at the same stage and of the same grade. Several newer predictors have been examined recently, including microsatellite instability (MSI), 18q deletion, k-ras mutations, TP53, TGFBR2, DCC and TS gene expression. The most promising risk factors at the present time are represented by allelic loss of chromosome 18q (negative for prognosis) and MSI (positive for prognosis). Furthermore, fluoropyrimidine-based chemotherapy seems useless or even detrimental in MSI+ patients, even though other data did not confirm this observation and the effect of irinotecan-based treatment appeared favourable in one study. The ultimate practical value of these factors still needs confirmation by large-scale prospective studies, but it is recommended that the evaluation of MSI status be performed in patients eligible for adjuvant fluoropyrimidine monotherapy.

The general consensus suggests that patients with stage II are at high risk if they present at least one of the following 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].

Another important problem is tailoring the decision to each individual patient. In this context, the most debated issue is the impact of patient age on decision making. The median age of patients presenting with colorectal cancer is 72 years whereas the median age of patients in clinical trials is 63 years, and <10% of patients above age 70 are accrued in the studies. When facing an elderly patient (>70) with a resected high-risk colorectal cancer 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 to that in the general population [II]; (iv) recent data from pooled analysis suggest caution in treating elderly patients with novel chemotherapy drugs (chiefly, oxaliplatin) in the adjuvant setting.

Recently, nomograms have been developed and are available for resected colon cancer. These statistically based tools attempt to provide all proven prognostic factors and to quantify the risk of 5- and 10-year death as precisely as possible.

## strategy of treatment by stage

### treatment of malignant polyps

Complete endoscopic polypectomy should be performed 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, like involvement of submucosa (sm1, sm2, sm3, involves the superficial, middle and deep thirds of the submucosa, respectively), invasion into the stalk and absolute thickness of the invasive tumour beyond the muscularis mucosae. When unfavourable histological features are present in a polyp from a patient with an average operative risk, resection is recommended. The pedunculated polyp with invasive carcinoma confined to the head with no other unfavourable factors carries minimal risk of an adverse outcome. The consensus is that endoscopic polypectomy is adequate treatment with proper follow-up examination. Invasion of the stalk but with clear margins of excision and favourable histological features may be treated with endoscopic polypectomy with a similar risk to that of 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 usually should be interpreted as having level 4 invasion. Consequently, standard surgical resection is recommended in patients with average operative risk.

### localized disease

The goal of surgery is a wide resection of the involved segment of bowel together with 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.

The laparoscopic approach has now received wide acceptance for several types of surgical procedure of major abdominal surgery. Laparoscopic colectomy can be safely performed 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 [I]. Advantages of laparoscopy over the conventional approach are reduced pain, reduced length of hospital stay and reduced duration of ileus [II].

Obstructive colorectal cancers can be treated in one or two stages. Two-stage procedures can include colostomy first followed by colonic resection, or Hartmann's procedure first followed by colostomy closure and anastomosis. An alternative is a one-stage procedure with either subtotal colectomy and ileorectal anasomosis 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].

*stage 0 (Tis N0 M0, T1 N0 M0)*. Treatment options are: (i) local excision or simple polypectomy; (ii) segmentary resection for larger lesions not amenable to local excision.

*stage I (T2 N0 M0) (old staging: Dukes' A or MAC A and B1)*. Wide surgical resection and anastomosis.

*stage II (T3 N0 M0, T4 N0 M0) (old staging: Dukes' B or MAC B2 and B3)*. Standard treatment options: (i) wide surgical resection and anastomosis; (ii) following surgery, in high-risk patients (who present at least one of the previously mentioned features) adjuvant therapy could be considered in clinical practice [II, B]. Even better, all patients should be considered for entry into randomized clinical trials evaluating new options for adjuvant treatment.

*stage III (any T, N1 M0, any T, N2 M0) (old staging: Dukes' C or MAC C1–C3)*. (i) Wide surgical resection and anastomosis; (ii) following surgery the standard treatment is a doublet schedule with oxaliplatin and 5FU/folinic acid (LV) (FOLFOX4 or FLOX) [I, A]. When oxaliplatin is contraindicated monotherapy with FU/LV, mostly with infusional schedules (DeGramont, AIO regimen), or oral fluoropyrimidines (capecitabine) can be employed) [I, A].

The benefit of the doublet schedule with oxaliplatin and 5FU/LV has been demonstrated in two recent trials. In the MOSAIC study, the addition of oxaliplatin to 5-FU/LV (FOLFOX schema), showed 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 6-year follow-up confirmed the benefit in DFS of adjuvant treatment with FOLFOX4 and an advantage was also observed in OS (absolute gain of 4.2%), but for stage III patients only.

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, and the magnitude of reduction in the risk of recurrence was similar to that of the MOSAIC trial.

Spectrum of toxicity between MOSAIC and NSABP-C07 was different: grade 3–4 diarrhoea resulted higher with FLOX, while grade 3 sensory neuropathy was observed in 12% with FOLFOX and 8% with FLOX. As a result of these studies FOLFOX for 6 months has been adopted worldwide as the standard of care in stage III colon cancer patients [A].

The X-ACT trial showed that in stage III capecitabine in monotherapy 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 5FU/LV.

Capecitabine and oxaliplatin in combination have been evaluated in a range of different schedules and doses. The XELOXA international phase III study assessed the safety and efficacy of adjuvant capecitabine plus oxaliplatin (XELOX) versus bolus FU/LV (Mayo Clinic or Roswell Park regimen). The toxicity profile was different: patients receiving XELOX experienced less all-grade diarrhoea, alopecia, and more neurosensitive toxicity, vomiting and hand–foot syndrome. Preliminary data of efficacy, presented at the moment only as an abstract, indicated a benefit in DFS for XELOX.

Also, the NSABP C-06 trial demonstrated the equivalence of oral treatment (UFT/LV) to 5FU/LV in stage II/III colon cancer patients but the drug is not approved in the adjuvant setting and therefore these data have no practical implication.

Negative trials are related to irinotecan in combination with 5FU (bolus or infusional).

The CALGB-89803 trial compared 5-FU/LV + irinotecan (IFL) with the Roswell Park scheme in >1200 patients. The trial was prematurely closed due to an elevated rate of mortality for IFL as compared with the FL regimen (2.2% versus 0.8%). Preliminary results indicated no improvement in terms of either OS or event-free survival for IFL, as compared with FL. The PETACC-3 trial compared the LV5FU2 or AIO regimen plus irinotecan with the LV5FU2 or AIO regimen alone. Results did not show an advantage for the regimen with irinotecan in terms of DFS.

Also, the ACCORD trial, performed in high-risk stage III patients, did not report any significant benefit with irinotecan-based chemotherapy.

In the adjuvant setting many questions are still unanswered.

- The role of targeted agents associated with chemotherapy. At the present time the AVANT study (bevacizumab + FOLFOX or XELOX versus FOLFOX) and the PETACC-8 trial in k-ras wild-type patients (cetuximab + FOLFOX versus FOLFOX) are exploring this question. At ASCO Meeting 2009 disappointing results were presented for the NSABP C-08 trial evaluating the addition of bevacizumab to FOLFOX: 3-year DFS was not improved by the biologic drug. Other ongoing trials in this field are the QUASAR 2 and E5202 (with bevacizumab) and the INT NO 147 (with cetuximab) trials.
- The 'optimal duration' of adjuvant treatment: 3 or 6 months? In Italy, the TOSCA trial is investigating whether 3 months of FOLFOX4 treatment are not inferior to 6 months with the same schedule in terms of RFS in stage II and III colon cancer patients. Together with other studies, this trial is the backbone of a large international collaboration ('IDEA') which will give a definitive answer regarding the duration of adjuvant therapy in stage III patients.
- The validation of prognostic/predictive factors: data are expected from large subset analysis in the context of international trials, such as PETACC-3, AVANT and PETACC-8.

## follow-up

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

In the past there was no strong evidence that regular follow-up could improve the outcome for patients radically resected for colon cancer. As follow-up can be expensive and resource consuming in terms of both money and procedures for a national health system, an intensive surveillance needs to be justified with a good level of evidence and generally was not strongly recommended even in the recent past. Several randomized controlled trials have addressed this issue but failed to demonstrate a benefit due to insufficient statistical power. In the last decade of the past century two meta-analyses were published, but unfortunately one was based entirely on non-randomized data and the other one included a mix of randomized trials and cohort studies.

In the last few years four further systematic revisions have been published. All of these demonstrated an improved survival for patients undergoing more intensive surveillance as 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 a new standard in colon cancer patients [I].

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. Renehan reported the same rate of recurrence for intensive and minimal follow-up, 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 detection of hepatic metastases was reported. Absolute reduction in mortality was 9%–13%, comparable to 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.

Similarly, Figueredo reported an improvement of 7% in 5-year survival ($P = 0.002$) and also in the Cochrane meta-analysis there was a clear benefit in this parameter, with OR = 0.73, and the number of attempted curative surgical procedures was significantly higher in the intensively followed arm. A similar result, but with less benefit, was reported by Tjandra, who observed also 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 life-style factors and increased psychosocial support.

Although pooled data are suggestive for a survival advantage related to intensive follow-up, the heterogeneity of the studies included in these meta-analyses does not consent to assess which kind of surveillance must be applied in clinical practice: it is clear that more investigations are better than less, 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 furthermore 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 test alone does not produce benefit in individual studies and demonstrated a reduction in mortality only in meta-analyses. 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 ∼40%. CEA test monitoring is effective also in patients without elevation in the preoperative setting: in these patients a subsequent elevation in 44% of recurrent patients was observed. There is no evidence that other laboratory tests can be useful.

As far as liver imaging is concerned, CT scan has been shown to be more sensitive than ultrasonography (0.67 compared with 0.43), but modern contrast enhancement ultrasound scan (CEUS) can substantially increase the sensitivity of ultrasonography.

Chest recurrence could be detected by 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-ray.

Complete visualization of the colon is recommended before curative resection to identify synchronous lesions. If this was not possible (e.g. obstruction, perforation) a colonoscopy should be performed within 3–6 months after resection. 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 for intensive endoscopic follow-up. If a colon without tumour or polyps is observed 1 year after resection, colonoscopy should be performed after 3–5 years.

In this field, specific recommendations are based mainly on level II–III evidence**,** particularly concerning timing intervals and duration of follow-up. A recently reported analysis of individual patient data from large adjuvant colon cancer randomized 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.

Meta-analysis and guidelines consider surveillance only for patients at high risk of recurrence, but a recent study seems to the show the same benefit also in early stage.

Suggested recommendations are as follows.

- Intensive follow-up must be performed in colon cancer patients [I, A].

- 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].
- Colonoscopy must be performed at year 1 and thereafter every 3–5 years looking for metachronous adenomas and cancers [III, B].
- 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 for recurrence [II, B].
- CEUS could substitute for abdominal CT scan [III, C].
- Other laboratory and radiological examinations are of unproven benefit and must be restricted to patients with suspicious symptoms.

## note

Levels of evidence [I–V] and grades of recommendation [A–D] as used by the American Society of Clinical Oncology are given in square brackets. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty.

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