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# Early colorectal cancer: diagnosis, treatment and survivorship care

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ABSTRACT

CRC is the third most commonly diagnosed malignancy and the fourth leading cause of cancer-related death in the world. With advances in treatment, colorectal cancer is being transformed from a deadly disease to an illness that is increasingly curable. With this transformation has come increased interest in the unique problems, risks, needs, and concerns of survivors who have completed treatment and are cancer-free. They often suffer late/long-term side effects of therapies that may compromise their QoL such as fatigue, sleep difficulty, fear of recurrence, anxiety, depression, negative body image, sensory neuropathy, gastrointestinal problems, urinary incontinence, and sexual dysfunction. In this review, we discuss what is known about early colorectal diagnosis, staging, treatments and their long-term effects on quality of life and survivorship care.

## 1. CRC incidence and epidemiology

Colorectal cancer (CRC) is the third most commonly diagnosed malignancy and the fourth leading cause of cancer-related death in the world, accounting for about 1.4 million new cases and almost 700.000 deaths in 2012. Its burden is expected to increase by 60% to more than 2.2 million new cases and 1.1 million cancer deaths by 2030. The distribution of CRC burden varies widely, with more than two-thirds of all cases and about 60% of all deaths occurring in countries with a high or very high human development index (HDI) (Ferlay et al., 2015). Rapid increases in both CRC incidence and mortality are now observed in many medium-to-high HDI countries particularly in Eastern Europe, Asia and South America. In contrast, CRC incidence and mortality rates have been stabilising or declining in a number of the highest indexed HDI countries: the USA, Australia, New Zealand and several Western European countries (Center et al., 2009a, b). The declining trends in incidence in these countries are thought to be a result of cancer prevention and earlier diagnosis through screening. Together with the factors that have brought about declines in incidence, improvements in perioperative care, as well as chemotherapy and radiotherapy, will have contributed to the uniformly decreasing trends in CRC mortality in many high income settings (Siegel et al., 2017). Despite the observed improvements in the overall colorectal cancer incidence rate, a retrospective cohort study of the SEER and data from Western registries found that the incidence of colorectal cancer in patients younger than 50 years has been increasing with a decrease in patients aged over 65 years (Arnold et al., 2016).

## 2. CRC risk assessement

The risk of developing colorectal cancer depends on different variables which can be classified into lifestyle or behavioural factors and genetically determinant factors. Approximately 20% of cases of CRC cancer are associated with familial clustering, and first-degree relatives of patients with colorectal adenomas or invasive colorectal cancer are at increased risk for colorectal cancer (Hemminki and Chen, 2004; Quintero et al., 2016). Genetic susceptibility to colorectal cancer includes well-defined inherited syndromes, such as Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer) and familial adenomatous polyposis (FAP) (Hampel et al., 2008). Lynch syndrome is the most common hereditary syndrome, accounting for 1–4% of all colon cancer, whereas FAP accounts for < 1% of cases. FAP in usually caused by mutations in the adenomatous polyposis coli tumor suppressor gene, whereas Lynch syndrome is associated with germline mutations in the mismatch repair genes: MLH1, MSH2, MSH6, PMS1 and PMS2. The Amsterdam criteria and Bethesda guidelines are commonly used to identify patients at risk of developing Lynch syndrome (Lynch and de la Chapelle, 2003; NCCN, 2017).

The risk of CRC is increased in the presence of other conditions, sush as inflammatory bowel disease (ie, ulcerative colitis, Crohn's disease); other possible risk factors for the development of colorectal cancer include smoking, the consuption of red and processed meats and alcohol,

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diabetes mellitus, low levels of physical activity, metabolic syndrome, and obesity/high body mass index (BMI) (Johnson et al., 2013; Lutgens et al., 2013; Alexander et al., 2011; Esposito et al., 2013; Fedirko et al., 2011; Cheng et al., 2015; Ma et al., 2013; Yuhara et al., 2011).

Large cohort studies and meta-analyses suggest that consumption of dairy (only for colon cancer in men), fish and legumes may lower risk for the development of colorectal cancer (Orlich et al., 2015; Yu XF and Dong, 2014). Furthermore, the use of aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) may also decrease the risk left side colorectal cancer (Cao et al., 2016; Rothwell et al., 2010). Prospective study have suggested that vitamine D deficiency may contribute to colorectal cancer incidence and that its supplementation may decrease colorectal cancer risk (Ma et al., 2011).

## 3. CRC diagnosis and staging procedures

Clinical presentation of CRC depends on the location and stage of the primary tumor: 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. Both right and left colon lesions occasionally cause hematochezia, but more often bleeding is occult, causing anemia and fatigue. Instead rectal lesions always cause hematochezia, bleeding and tenesmus (Labianca et al., 2013).

Endoscopy is the main procedure for diagnosis and can be carried out by either sigmoidoscopy or (preferably) a complete colonoscopy up to the cecum. Tumours with distal extension to 15 cm (as measured by rigid sigmoidoscopy) from the anal margin are classified as rectal, while more proximal tumours are classified as colonic. This exam, coupled with biopsy for histopathological examination, is considered the gold standard to diagnose colorectal lesions, in view of its high diagnostic performance (III, A) (Barret et al., 2013; Kaminski et al., 2010). However, a substantial proportion of patients will have an incomplete colonoscopy due to poor bowel preparation, poor patient tolerance, obstruction or other technical difficulties. In these cases, additional computed tomography-colonography (CT or CTC) can contribute to the CRC diagnosis (Graser et al., 2009; Pickhardt et al., 2011), as a potential alternative to the endoscopy. However, CTC does not offer the opportunity of taking biopsies or immediate polypectomy and the patient needs to return for a colonoscopy, in case of detected lesions (V, B). In any case, if not carried out before, a complete colonoscopy should be carried out within 3–6 months after surgery (Pullens et al., 2015). Once a colorectal cancer is diagnosed, clinical examination (including digital rectal examination DRE, for rectal cancer), full blood count, liver and renal function tests, serum carcinoembryonic antigen (CEA) and computed tomography (CT) scan of thorax and abdomen should be carried out to define functional status and presence of metastases (III, A). Imaging plays a crucial role in the diagnosis, staging assessment for specific therapy and follow-up of patients with colon and rectal cancer with the main function of defining the locoregional extent, identifying synchronous lesions and distant metastases. CRCs are classified according to local invasion depth (T stage), lymph node involvement (N stage) and presence of distant metastases (M stage) (Edge and Compton, 2010; Kekelidze et al., 2013). These stages are combined into an overall stage definition, which provides the basis for therapeutic decisions. Specifically, classification according to tumour, node and metastases (TNM) and Union Internationale Contre le Cancer (UICC) stage offers valuable prognostic information and guides therapy decisions. The most used imaging modalities for staging of CRC are chest/abdomen/pelvis CT (Leufkens et al., 2011; Verhoef et al., 2012; Floriani et al., 2010) and magnetic resonance imaging (MRI) (III, A). CT has a sensitivity of 74–84% and a specificity of 95–96% in detection of CRC liver metastases (Floriani et al., 2010). However, CT has shown to be poor in identifying nodal disease (Dighe et al., 2010a,b), with specificity for lymph node staging of 55% and sensitivity of 76% (Mitry et al., 2010). If the CT of the abdomen and pelvis is inadequate or if CT with IV contrast is controindicated, an abdominal/pelvic MRI with contrast plus a non-contrast chest CT should be considered. In preoperative imaging of rectal cancer, MRI is recommend for local staging (III, A) (Schmoll et al., 2012; Glimelius et al., 2011) and whole body CT for detection of distant metastases (van de Velde et al., 2013; Torkzad et al., 2010; Poston et al., 2011). MRI is able to accurately define the local extension of rectal tumour, the mesorectal fascia involvement, circumferential resection margin (CRM) (Schmoll et al., 2012) and the relationship of the tumour to the sphincter complex. Moreover, MRI represents the most accurate imaging tool for identifying nodal disease with a sensitivity of 85% and specificity of 97%, not by a size criteria but better with a definition of border irregularity and heterogeneity. MRI therefore is essential to accurately stage patients with rectal cancer in order to select the indication to a preoperative treatment or defining the extent of radical surgery. Endoscopic rectal ultrasound (ERUS) is another well established modality for the evaluation of the integrity of the rectal wall layers and T staging (III, A); it may define treatment for the earliest tumours. T1 tumours appropriate for transanal endoscopic microsurgery (TEM) can be selected by determining whether a lesion is limited to the mucosa or submucosa (sm). ERUS may also detect regional adenopathy, with a lower accuracy to identify nodal involvement compared to both CT and MRI. Therefore, the combination of MRI with ultrasound improves diagnostic accuracy; they are both recommended for the preoperative staging of rectal cancer, together with CT scans of the chest, abdomen and pelvis (Swartiling et al., 2013). If abnormalities are seen on CT or MRI scan and are considered suspicious but inconclusive for metastases, a PET/CT scan may be considered to further delineate that abnormality, if this information will change management of disease (Niekel et al., 2010). However, current evidence is not considered strong enough to recommend the use of PET in all patients (V, C). Levels of evidence and grades of recommendation are reported below in Table 1.

## 4. Surgical management of invasive nonmetastatic colon cancer

Primary colon cancers without systemic disease are treated mainly by surgery with complete mesocolic excision (CME) (Hohenberger et al., 2009; Sehgal and Coffey, 2014) with arteries and veins ligated as close as possible to the main vascular trunk to have lower local recurrence rate and improved survival (Søndenaa et al., 2014; Siani and

**Table 1**
Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System).
Source: Dykewicz CA. Summary of the guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. Clin Infect Dis 2001; 33: 139–144.

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|---|---|
| **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 |

Pulica, 2014). The concept of CME is similar to the total mesorectal excision (TME) for rectal cancer and allows an excellent oncological outcome with a 5-year cancer specific survival rate of 91.4% in stage II, and 70.2% in stage III CC (Sagar, 2011). Colonic segmental resection is performed according to the site of the tumour; right hemicolectomy transverse colectomy, left hemicolectomy or total colectomy are the most common surgical procedures and it is always indicated in absence of metastases. In the emergency setting, when presenting symptoms of obstruction, perforation and bleeding, segmental colectomy for resection of the tumour, with or without fecal diversion, is indicated (NCCN, 2017).

## 5. Adjuvant chemotherapy for resectable colon cancer

Adjuvant systemic chemotherapy is currently recommended for stage III CRC patients (any T, N1-2, M0) and for high risk stage II (T3-T4, N0, M0), defined as those with poor prognostic features, including T4 tumors (stage IIB/IIC), poorly differentiated histology (exclusive of those cancers that are MSI-H), inadequate number of lymph nodes analyzed (< 12 lymph nodes), vascular, lymphatic and/or perineural invasion, clinical presentation with perforation or occlusion (NCCN, 2017; Labianca et al., 2013). Results from a 2015 meta-analysis of 25 high-quality studies showed that 5-year DFS for stage II patients operated without subsequent adjuvant chemotherapy was 81.4% (95% CI, 75.4–87.4) whereas for stage II patients treated with adjuvant chemotherapy the 5-year DFS was 79.3% (95% CI, 75.6–83.1). For patients with stage III patients, the 5-year DFS was 49.0% (95% CI, 23.2–74.8) and 63.6% (95% CI, 59.3–67.9) in those treated without and with adjuvant chemotherapy (Bockelman et al., 2015). The impact of adjuvant chemotherapy for patients with high-risk stage II and III colon cancer has been addressed in several clinical trials and practice-based study (Andre et al., 2004, 2009; Andre et al., 2015; Kuebler et al., 2007; Haller et al., 2011; Schmoll et al., 2007; Twelves et al., 2005; Anon., 1995; Andre et al., 1999; Haller et al., 2005; Wolmark et al., 1999; Compton et al., 2000; Benson et al., 2004; Saltz et al., 2007; Van Cutsem et al., 2009; Allegra et al., 2011; de Gramont et al., 2012; Alberts et al., 2012; Taieb et al., 2014; Sobrero et al., 2017; Shi et al., 2017). In patients with stage III disease is recommended adjuvant chemotherapy with oxaliplatin and 5-FU/LV (Andre et al., 2004, 2009; Andre et al., 2015; Kuebler et al., 2007) or oxaliplatin and capecitabine (Haller et al., 2011; Schmoll et al., 2007), single-agent capecitabine (Twelves et al., 2005) or 5-FU/LV in patients for whom oxaliplatin therapy is believed to be inappropriate (Anon., 1995; Andre et al., 1999; Haller et al., 2005; Wolmark et al., 1999). Patients with high-risk stage II disease can be considered for adjuvant chemotherapy with 5-FU/LV or capecitabine (Compton et al., 2000; Benson et al., 2004). Patients with stage I disease and patients with MSI-high (MSI-H), low-risk stage II disease do not require any adjuvant therapy. Patients with low-risk stage II disease microsatellite-stable (MSS) can be enrolled in a clinical trial, observed without adjuvant therapy or considered for chemotherapy with capecitabine or 5-FU/leucovorin (LV). The adjuvant chemotherapy regimens are based on therapies that have proven their effectiveness in the advanced setting. Conversely, not all treatments commonly used in metastatic disease have maintained their effectiveness when used in the adjuvant setting. The combination of fluoropyrimidine (5-FU/LV or capecitabine) and oxaliplatin is the adjuvant treatment recommended by the current international guidelines (NCCN, 2017; Labianca et al., 2013). The benefit of combinations with oxaliplatin has been demonstrated in three landmark trials. In the MOSAIC study (Andre et al., 2009), the addition of oxaliplatin to 5-FU/LV (FOLFOX4 schema), demonstrated a significantly increased disease-free survival (DFS) at 3 years 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 (Andre et al., 2015). Similar results were observed in a phase III trial (NSABP C-07) evaluating FLOX (bolus of 5-FU/LV plus oxaliplatin) vs 5-FU/LV alone (Roswell Park schedule) (Kuebler et al., 2007). The XELOXA international phase III study (Twelves et al., 2005) 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 demonstrated 3-year DFS rates to the i.v. fluoropyrimidine. In patients with non-optimal PS, monotherapy with fluoropyrimidine can be considered a viable alternative to the doublet chemotherapy and capecitabine has shown a similar efficacy and a better tolerability than intravenous 5-FU/LV (Bockelman et al., 2015). According to the efficacy demonstrated in patients with metastatic CRC, the irinotecan-based regimes were also assessed in the adjuvant setting, but the results failed to demonstrate any advantage. Two randomized trials (CALGB-89803, PETACC-3) comparing bolus 5-FU/LV plus irinotecan to only 5-FU/LV did not find differences in terms of DFS and OS (Saltz et al., 2007; Van Cutsem et al., 2009). There is currently no role for targeted agents associated with chemotherapy in the adjuvant setting for colon cancer. Bevacizumab reached negative results in the adjuvant setting as in the NSABP C-08 trial and in the AVANT study (Allegra et al., 2011; de Gramont et al., 2012). Similarly, both NCCTG NO147 (Alberts et al., 2012) and PETACC-8 trials (Taieb et al., 2014) demonstrated a detrimental effect of cetuximab in the adjuvant setting. Therefore, both irinotecan-based regime combinations and biological targeted agents should be ruled out in the adjuvant setting of primary CRC. About duration of treatment, six months of oxaliplatin-based treatment has been the standard of care as adjuvant therapy for stage III colon cancer and an accepted option for high-risk stage II. Given the cumulative neurotoxicity associated to oxaliplatin, a shorter duration of therapy has been investigated with some trials. In Italy, the TOSCA trial demonstrated an absolute difference in RFS of less than 3% at 5 years between the two treatment durations (Sobrero et al., 2017). Moreover, the IDEA pooled analysis supported the non-inferiority of 3 months treatment duration only for XELOX adjuvant cohort and for certain substages (T1-3 N1) (Shi et al., 2017). An open question about adjuvant treatment is the validation of prognostic/predictive factors. Additional information that may influence adjuvant therapy decisions in stage II and/or stage III disease are MSI, multigene assays and patient age but only research into additional possible markers may allow for more informed decision making in the next future (Dalerba et al., 2016; Tie et al., 2016).

## 6. Adjuvant chemotherapy in elderly patients

In clinical practice, elderly patients are less likely to receive adjuvant chemotherapy than younger patients because of the concern for toxicity (Schrag et al., 2001; Jessup et al., 2005). 5-FU/LV adjuvant chemotherapy seems to be as beneficial in older patients as it is in younger patients in terms of progression-free survival (PFS), disease-free survival (DFS), and overall survival (OS). The oral fluoropyrimidine capecitabine can be an effective alternative to 5-FU/LV in the adjuvant setting because of equivalent capecitabine DFS versus 5-FU/LV and its fewer adverse events (Iwashyna and Lamont, 2002; Sargent et al., 2001). In an adjuvant setting the benefit of adding oxaliplatin to 5-FU/LV (FOLFOX) for elderly patients is controversial. Infact subset analyses of major adjuvant therapy trials also show no benefit of adding oxaliplatin for older patients (Yothers et al., 2011; Tournigand et al., 2012), while a recent pooled analysis of individual patient data from pooled adjuvant trials containing oxaliplatin found that DFS and OS were improved with adjuvant XELOX or FOLFOX over 5-FU/LV in patients 70 years of age or older (Sanoff et al., 2012; Haller et al., 2015). However, with no data from prospective randomized studies demonstrating a clear benefit from the addition of oxaliplatin to 5-FU/LV in patients aged 70 years and older, the use of adjuvant oxaliplatin-containing regimens needs to be considered on an individual basis for these patients (NCCN, 2017; Labianca et al., 2013).

## 7. Surgical management of invasive nonmetastatic rectal cancer

Rectal cancers can be divided into 4 groups: very early (some cT1), early (cT1-2, some cT3), intermediate (most cT3, some cT4) and locally advanced (some cT3, most cT4) but, for cancer staging are also relevant other important factors other than T stage, as distance from the anal verge, circumferential margin (crm), nodal (cN) stage, vascular and nerve invasion. A variety of surgical approaches, depending on the location and extent of disease, are used to treat primary rectal cancer lesions (Guillem and Cohen, 1999; Lindsetmo et al., 2008).

These methods include local procedures, such as polypectomy, transanal excision, and transanal endoscopic microsurgery (TEM), and more invasive procedures involving a transabdominal resection (low anterior resection, LAR), proctectomy with TME and coloanal anastomosis, abdominoperineal resection (APR) (Sgourakis et al., 2011; Valentini et al., 2009). In the very early most favourable cases and for the malignant polyps (Haggitt 1–3, T1 sm 1 (-2?) N0), a local procedure can be considered, using the traditional transanal endoscopic excision or microsurgery (TEM) technique (Sgourakis et al., 2011). In early, favourable cases (cT1-2, some early cT3, N0 [cT3a(-b) and clear crm (crm-) according to MRI], good group) above the levators, surgery alone, meaning a sharp radical dissection using the TME technique is appropriate, since the risk of local failure is very low. However, the role of TME in tumours situated in the upper third of the rectum has been much discussed and no strong evidence supporting TME in those cases has been reported. TME involves an en bloc removal of the mesorectum, including associated vascular and lymphatic structures, fatty tissue, and mesorectal fascia as a “tumor package” through sharp dissection and in designed to spare the autonomic nerves (Baxter and Garcia-Aguilar, 2007; Heald et al., 1982).

## 8. Neoadjuvant therapy for rectal cancer

Neoadjuvant therapy of rectal cancer includes long term preoperative radiotherapy, long-term preoperative concurrent chemoradiotherapy (concurrent radiotherapy, CRT) and short-term preoperative radiotherapy. It allows radical surgery with TME in intermediate and also locally advanced rectal cancer. Preoperative chemoradiotherapy can reduce the tumor mass, block the tumor invasion, increase the tumor resection rate, and anus retention rate, reduce iatrogenic dissemination during operation, and reduce the local recurrence rate (Schrag, 2013; Schrag et al., 2014; Maas et al., 2010a; Fisher et al., 1988; Gastrointestinal Tumor Study Group, 1985). The German Rectal Cancer Trial randomized 823 patients with cT3–4 N + rectal cancer to either preoperative or postoperative CRT and demonstrated that the rate of local recurrence was lower in the preoperative CRT group than in the postoperative CRT group and DFS and OS rates were similar between the groups (Fernandez-Martos et al., 2014). Another trial, the NSABP R-03 study, also supported the advantages of preoperative CRT with a trend toward better OS (Roh et al., 2009). The neoadjuvant approach led to consistent tumor down-staging, with 15–27% of patients achieving a pathologically complete response (pCR) defined as no residual cancer found on histological examination of the specimen (Maas et al., 2010b; Pucciarelli et al., 2004). These patients enjoyed better longterm outcomes with organ preservation, decreased likelihood of developing both local and distant recurrence and improved DFS (Ro¨del et al., 2005; Valentini et al., 2002; Vecchio et al., 2005). There are potential scenarios in which preoperative treatment may not necessarily be the best option. These include patients who present with either very small or proximal T2-T3 tumors where chemoradiation may in fact represent over-treatment exposing patients to associated side effects and potential longterm morbidity. Of these patients, who do have nodal involvement or have positive surgical margins, there is evidence from the German Rectal Cancer Trial that postoperative chemoradiation can be safely administered (Garcia-Aguilar et al., 2015; Schrag, 2013; Sauer et al., 2012). In intermediate cases [most cT3 (cT3(b)c + without threatened and involved crm (crm-) according to MRI], some cT4a (with limited peritoneal involvement only), N+, bad group), preoperative radiotherapy is recommended followed by TME, since this reduces local recurrence rates. This preoperative therapy could be given either as short-course radiotherapy, 25 Gy, 5 Gy/fraction during 1 week followed by immediate surgery (< 10 days from the first radiation fraction) (Sebag-Montefiore et al., 2009; Folkesson et al., 2005; van Gijn et al., 2011) or as 45–50.4 Gy, 1.8–2 Gy/fraction without or preferably with 5-fluorouracil (5-FU; bolus, continuous infusion or oral) (Bujko et al., 2006; Gérard et al., 2006; Bosset et al., 2006; Ngan et al., 2012). Short-course radiotherapy with delayed surgery is also a useful alternative to conventional short-course RT, with immediate surgery offering similar oncological outcomes and lower post-operative complications (Sebag-Montefiore et al., 2009; Folkesson et al., 2005; van Gijn et al., 2011). In locally advanced, sometimes non-resectable cases [cT3 crm+, cT4 with overgrowth to organs not readily resectable (cT4b)], preoperative chemoradiotherapy (CRT) with concomitant 5-FU-based therapy should be used (Glimelius et al., 2008; Braendengen et al., 2008). This should be followed by radical surgery 6–8 weeks later. Standard preoperative chemoradiotherapy means a dose of 45–50.4 Gy, 1.8 Gy/fraction, or alternatively 50 Gy, 2 Gy/fraction together with a fluoropyrimidine, as trials have shown that chemoradiotherapy provides better local control than the same radiotherapy alone. The fluoropyrimidine may be 5-FU given either as bolus injections with leucovorin (at 6–10 times during the radiation) (Gérard et al., 2006; Bosset et al., 2006; Glimelius et al., 2008; Braendengen et al., 2008) or as prolonged continuous infusion (which is likely better than bolus) or oral capecitabine (Hofheinz et al., 2012). In very old patients (≥80–85 years) and in patients not fit for CRT, 5 × 5 Gy with a delay of ~8 weeks before surgery is an option (Radu et al., 2008; Pettersson et al., 2012). Recently, combinations of 5-FU with other cytotoxics such as oxaliplatin or irinotecan or targeted biologic drugs have been extensively explored, in attempts to improve on the outcomes achieved with neoadjuvant 5-FU/RT or capecitabine/RT, minimizing micro-metastatic disease. Several large randomized phase III trials (ACCORD 12, STAR-01, R-04, CAO/ARO/AIO-4 and FOWARC) addressed the addiction of oxaliplatin to the 5-FU/capecitabine regimens. These trials demonstrated that the addition of oxaliplatin did not improve clinical outcomes including the endopoints of locoregional events, DFS, OS, pathologic complete response, sphincter-saving surgery, and surgical downstaging, while it increased toxicity (Aschele et al., 2011; O'Connel et al., 2014; Allegra et al., 2015; Gerard et al., 2012; Rodel et al., 2012, 2015; Deng et al., 2016). However, the German CAO/ARO/AIO-04 trial, in contrast to STAR-01, R-04 and ACCORD 12, demonstrated higher rates of pathologic complete response in the oxaliplatin arm (17% vs 13%, P = .038) (Janssen-Heijnen et al., 2010) with the 3-years DFS rate of 75.9% in the oxaliplatin arm versus 71.2% in the control arm (P = .03) (Rodel et al., 2012, 2015). In line with CAO/ARO/AIO-04, the Chinese FOWARC phase III trial found that FOLFOX-RT resulted in higher rates of pathologic complete response and downstaging than the other regimens (Deng et al., 2016). Many phase II trials have been conducted or have begun to assess the effects of adding irinotecan, bevacizumab, cetuximab or panitumumab to neoadjuvant regimens, with controversial results. Moreover, at this time the use of the above mentioned drugs or oxaliplatin to neoadjuvant chemo-RT is not recommended (NCCN, 2017; Labianca et al., 2013). Following short-course radiotherapy or chemoradiotherapy, a clinical complete response (cCR), defined as absence of clinically detectable residual tumour after CRT, can be obtained in 10–40% of patients when assessed after an interval of 12 weeks from the start of treatment. The likelihood of achieving a cCR will depend partly on initial stage and currently unknown molecolar factors. cCR has only a partial concordance with pCR. Investigators have since explored definitive CRT and careful follow up, also called nonoperative management (NOM), as a curative approach for these selected patients, with surgery reserved as salvage therapy. Substantially more follow-up and larger

numbers of patients treated within properly controlled prospective studies are needed to validate this 'watch-and-wait' approach (Glynne-Jones and Hughes, 2012; Martens et al., 2016).

## 9. Adjuvant therapy for rectal cancer

Although mortality and local recurrence rates have improved dramatically over the past decades as a result of more accurate preoperative staging modalities [magnetic resonance imaging (MRI), endoscopic ultrasound] and surgical techniques (TME), the rate of systemic relapse is still unacceptably high and contributes significantly (Bosetti et al., 2011). About a third of patients with advanced rectal cancer will eventually develop distant metastases (Sauer et al., 2004). In order to prevent this, postoperative adjuvant chemotherapy has been employed in the management of locally invasive treatment of rectal cancer and is now incorporated into most treatment protocols in the west. Various national and international guidelines (National Comprehensive Cancer Network, American Society of Clinical Oncology, European Society of Medical Oncology, National Institute of Clinical Excellence) recommend postoperative chemotherapy with either capecitabine or 5-FU, alone or combined with oxaliplatin for a total of 6 months for stage II and III rectal cancers (taking into account the risk of relapse) (Poulsen et al., 2015). Despite the widespread use of this approach, the evidence for beneficial effects of postoperative chemotherapy is conflicting. Many trials have failed to show an improvement in OS or DFS with adjuvant therapy with a fluoropyrimidine alone in this setting (Poulsen et al., 2015; Bosset et al., 2014; Sainato et al., 2014; Breugom et al., 2015). Other trials have investigated the use of more modern agents in the adjuvant setting. Result from the phase III ECOG E3201 trial in patients with stage II/III rectal cancer after either preoperative or postoperative chemoRT, indicated that adjuvant FOLFOX can be safely used in this patient population (Benson et al., 2006). The phase II ADORE trial (Hong et al., 2014) and the CAO/ARO/AIO-04 trial found an improvement in 3-years DFS when oxaliplatin was added to 5-FU as adjuvant treatment (Rodel et al., 2012; Glimelius et al., 2013). Although conclusive data on the use of adjuvant chemotherapy in patients stage II/III rectal cancer are lacking, it is reasonable to consider adjuvant chemotherapy in rectal cancer patients after preoperative CRT/RT with yp stage III (and 'high-risk' yp stage II). Hence, the decision on postoperative chemotherapy (fluoropyrimidine alone or combined with oxaliplatin) should be risk-balanced, taking into account both the predicted toxicity for a particular patient and the risk of relapse, and should be made jointly by the individual and the clinician. Postoperative chemoradiotherapy with concomitant fluoropyrimidine-based chemotherapy could be used in patients with positive crm, perforation in the tumour area, defects in the mesorectum, or in other cases with high risk of local recurrence if preoperative radiotherapy has not been given (NCCN, 2017; Glimelius et al., 2013).

## 10. Cured patients

The possibility of early diagnosis of cancer, accompanied by progress in the treatment option, has led to a great reduction of cancer-related death risk. In recent decades the number of patients with a history of cancer in Italy has increased from about 2 million in 2006 to over 3 million in 2016 (AIRTUM, 2015). In 2020, 4.5 million cancer patients are expected. The Italian data on cancer survivors are in line with the rest of the world: the number of cancer survivors in the United States, for example, increased from 3 million in 1970 to about 15 million survivors in 2012, accounting for 5% of cancer survivors total population. Although there is an increase in patients suffering from colorectal cancer, a percentage are long term survivors. Colon carcinoma long term survivors represent 9.5% and occupy the third place, preceded only by patients with breast cancer and patients suffering from prostate cancer. Since the 1990s, the use of 5-fluorouracil adjuvant chemotherapy resulted in an improvement in survival of about 30%, while subsequent use of oxaliplatin in the adjuvant treatment of patients in Stage III an improvement of about 20% was added (Moertel et al., 1990). In addition, preoperative radio-chemotherapy combined treatment in rectal adenocarcinoma patients contributed to improved local disease control and survival (Sauer et al., 2004). In cancer patients, the risk for death from a specific neoplasm is highest in the initial years after diagnosis and decreases progressively thereafter, until a time at which the risk becomes negligible (Baade et al., 2011a; Ellison et al., 2011). The use of the term "cured" for some cancer patients refers to complete clinical remission of a cancer, regardless of the presence or absence of late sequelae of treatment, only when surviving patients reach a life expectancy that matches that of a sex- and age- matched general population. Moreover, the correct applicability of the word "cured" is influenced by some variables, such as cancer subtypes, its biologic characterization, stage and disease-free interval (Tralongo et al., 2015; Janssen-Heijnen et al., 2010; Småstuen and Aagnes, 2008). Data from a study population on 818,902 Italian cancer patients diagnosed at age 15–74 years in 1985–2005 with 26 cancer types provided estimates of indicators of long-term survival and cure, by cancer type, sex and age. In CRC patients group, cure fractions were higher (0 to 10%) in women than in men for all age groups, cure prevalence were 83% in men and 87% in women and time to cure in both men and women with CRC was reached in less than ten years (five to nine years). The proportion of CRC patients who reached five-year or ten-year CRS (conditional relative survival) > 95% was intermediate respect other cancer types (30% and 27% among 422/100,00 men; 40% and 36% among 352/100,00 women). Therefore, this study showed more favourable long-term survival for overall colorectal patients with cure fractions > 50% reached in eight years (Dal Maso et al., 2014). A longitudinal cohort study of 139.743 patients with colorectal cancer found that 95% of deaths from the disease occurred within the first 5 years after diagnosis. Colorectal cancer deaths were surpassed by cardiovascular deaths at 8 years post-diagnosis and by deaths from second primaries and neurologic diseases at 10 years post-diagnosis. Causes of death among patients surviving at least 5 years and the types of second primaries in the entire cohort appeared to be similar to those in the general population (Lewis, 2017).

## 11. Follow-up after curative resection of colorectal cancer

The principal aim for a follow-up program after completion of cancer therapy is to improve survival (*surveillance cancer oriented*). It requires that effective treatment be available for patients who experience recurrence and that the effectiveness of the treatment is superior when the recurrence is detected prior to the development of symptoms. In the case of colorectal cancer, the treatment is surgery for resectable recurrences and new primary tumors. Long-term survival data has been published for complete resection of local recurrences, regional recurrences (retroperitoneal and mesenteric) and metastatic recurrences, including the liver and lung. It is known that asymptomatic recurrences of colorectal cancer are more amenable to an R0 (margin negative) surgical resection.The common sites of recurrence following resection of colorectal cancer include the liver (33%), lung (22%), local (15% for colon, 35% for rectum) and regional lymph nodes (14%), with few second or metachronous new primaries (3%). As no single screening test is best suited for all sites of recurrent disease, the follow-up programe includes a combination of tests (clinic visits, serum CEA levels, liver imaging, colonoscopy) (Table 2). The incidence of recurrent disease is ˜50% following curative resection of primary colorectal cancer with 71% of recurrences occurring in the first 2 years following resection and 91% by 5 years. For this reason most follow-up studies have conducted frequent tests during the first 2–3 years with less frequent tests for years 4 and 5. The majority of screening strategies for recurrent colorectal cancer do not extend beyond 5 years. The incidence of a second colorectal cancer primary, however, occurs at a constant cumulative rate of ˜3% every 6 years and, as such, screening tests must be

**Table 2**
Recommended schedule of surveillance for colon and rectal cancer AJCC stage I (at increased risk for recurrence[a]), stage II, stage III.
Source: Steele SR, Chang GJ, Hendren S, Weiser M, Irani Buie D, et al. Practice Guideline for the Surveillance of Patients After Curative Treatment of Colon and Rectal Cancer. Dis Colon Rectum 2015;58:713-725.

| Colon | Rectum[b] |
|---|---|
| **Office visit and CEA**<br>Every 3-6 mo for 2 y, then every 6 mo until 5 y<br>**CT chest/abdomen/pelvis**[c]<br>Annually for 5 y[d]<br>**Colonoscopy**<br>1 y after preoperative colonoscopy (or 3–6 mo after surgery if colon not preoperatively "cleared")[e] | **Office visit and CEA**<br>Every 3-6 mo for 2 y, then every 6 mo until 5 y<br>**CT chest/abdomen/pelvis**<br>Annually for 5 y[d]<br>**Colonoscopy**<br>1 y after preoperative colonoscopy (or 3–6 mo after surgery if colon not preoperatively "cleared")[e]<br>**Proctoscopy (+/– ERUS)**<br>Every 6–12 mo[f] for patients who underwent resection with anastomosis or every 6 mo for patients undergoing local excision for 3–5 y |

[a] High risk of recurrence is defined by the treating provider. High-risk factors may include margin positivity (≤1 mm), Nx status (rectal cancer s/p local excision, higher-risk malignant polyps that do not undergo radical surgery, inadequate LN sampling), lymphovascular invasion, poorly differentiated tumors (grade 3 or 4), and T2 disease.

[b] For patients who receive neoadjuvant therapy, these guidelines refer to clinical rather than pathologic stage.

[c] PET-CT is not typically recommended, although PET-CT or MRI might be considered for imaging in a patient with contraindication to intravenous-contrast-enhanced CTscanning or to follow-up abnormalities seen on CT scans.

[d] More frequent imaging may be considered for patients at particularly high risk for recurrence, including those with N2 disease, previous liver resection for metastasis, etc.

[e] Further colonoscopy frequency depends on the results of the 1-year colonoscopy, with repeat examination in 3 years for patients without adenomas and 1 year for patients with adenomas. Annual colonoscopy is generally recommended for patients with confirmed or suspected familial cancer syndromes that have not undergone total proctocolectomy.

[f] Patients at higher risk for local recurrence may be considered for the more frequent intervals, and for ERUS in addition to proctoscopy. Higher-risk patients may include those with poorer-risk tumors (eg, T2 or poor differentiation) who underwent local excision, those with positive margins (≤1 mm), and those with T4 or N2 rectal cancers.

done at regularly spaced intervals for life (NCCN, 2017; Labianca et al., 2013; Glimelius et al., 2013).

As a result of improved survival of patients with colorectal cancer, new scenarios have been opened, as the survival benefit has led to a potential load of late or long-term side effects may compromise the QoL of colorectal cancer patients with colorectal cancer (*surveillance all inclusive*).

## 12. Late and long-term effects of treatments

### *12.1. Chemotherapy-induced peripheral neuropathy (CIPN)*

Cumulative dose is the most important risk factor for platinum-based drugs, > 850 mg / $m^2$ for oxaliplatin (Beijers et al., 2014a) and > 200–300 mg / m2 for cisplatin (Glendenning et al., 2010). Previous treatments, anemia, hypoalbuminemia, hypomagnesemia and alcohol consumption have been identified as risk factors for peripheral neuropathy induced by oxaliplatin (Vincenzi et al., 2013). Several studies have also assessed genetic predisposition or protection against CIPN (chemo-induced peripheral neuropathy), mainly through polymorphisms that affect the pharmacokinetics of platinum-based anticancer drugs. Single-nucleotide polymorphisms (SNPs) that affect GSTP1 and GSTM1 genotypes were significantly associated with a higher incidence of CIPN associated with oxaliplatin (grade 2) (Kumamoto et al., 2013). Single-nucleotide polymorphisms (SNPs) affecting cyclin H and BCRP were significantly associated with higher risk of severe peripheral neuropathy induced by oxaliplatin (Custodio et al., 2014). Platinum compounds reach peripheral nervous system neurons and induce various types of toxic effects, including nucleic, mitochondrial, oxidative stress and ion channel disorders. In particular, oxaliplatin treatment has been shown to increase protein carbonylation and lipid peroxidation in both the sciatic nerve and spinal cord; silibinin and α-tocopherol (Di Cesare Mannelli et al., 2012) are able to reduce this oxidative stress; MnL4, a mimetic compound of superoxide dismutase, reduced the production of superoxide anions, lipid peroxidation and intracellular calcium induced induction by oxaliplatin in vitro; in addition, was able to reduce mechanical hyperalgesia and mechanical and cold allodynia induced by oxaliplatin in rats. Oxaliplatin has a neurotoxicity other than other neurotoxic anti-tumor drugs. It is responsible for acute neuropathic disorders (dysesthesia of the hands, feet and perioral area caused by cold stimuli) occurring in the hours or days following the infusion of chemiotherapy. At the beginning of chemotherapy, this acute neuropathy usually resolves alone within a week and disappears by the beginning of the next cycle of chemotherapy. The cyclicity of chemotherapy treatment induces the onset of chronic and disabling CIPN for several patients (Balayssac et al., 2011). It is associated with paresthesia, numbness, sensory ataxia, and can lead to functional deficiencies (Zedan et al., 2014). It can be aggravated by cold outside temperatures, as in the Nordic countries (Altaf et al., 2014; Stefansson and Nygren, 2016). Oxaliplatin is probably the most neurotoxic drug since more than 90% of patients develop acute neuropathy and 30–50% of patients develop chronic neuropathy (Tofthagen, 2010). The degree of severity and duration of symptoms vary between studies. Although the symptoms decrease over time, long-term clinical trials seem to show persistence of neuropathy after 24 months (Beijers et al., 2014b): 25 months, 37.5% grade 1, 29.2% grade 2, and 0.7% Grade 3 (Park et al., 2011); 48 months, 11.9% grade 1, 2.8% grade 2, and 0.7% grade 3 (52); 8 years, 30.4% grade 2 + (78). Consequently, the reversibility of this CIPN remains equivocal. In addition, some authors suggest that peripheral neuropathy induced by oxaliplatin may be more frequent and more severe in the longer term than expected, which lasts more than 12 months (Vatandoust et al., 2014). In a retrospective study involving 57 patients with stage III colon cancer and treated for adjuvant chemotherapy with oxaliplatin, it was observed that, acute peripheral neuropathy, occurring on the first day within 24 h of infusion of oxaliplatin, was predictive of persistent peripheral neuropathy induced by oxaliplatin (Tanishima et al., 2017). In survivors of colorectal cancer, oxaliplatin-induced neuropathy has a strong negative impact on HRQOL, associated with depression and sleep disorders (Mols et al., 2013; Tofthagen et al., 2013). About 12% of the long-treated patients previously treated with oxaliplatin developed persistent neurologic symptoms up to 4 years after the last chemotherapy cycle. As far as CIPN treatment is concerned, a total of 42 RCTs have been identified that have studied the efficacy of pharmacological agents, including

**Table 3**
Lifestyle interventions.

- Reduction of caloric intake and weight loss
- Targeted interventions on food education
- Prefer a diet rich in fruits, vegetables and fish
- Increase in physical activity

anticonvulsants, antidepressants, vitamins, minerals and other chemoprotectors. A review that took into consideration 5 Trials, with 694 evaluable patients, showed that calcium and magnesium infusion did not have any beneficial effect on the prevention of peripheral neuropathy induced by oxaliplatin (Jordan et al., 2016). Unfortunately, there are no effective strategies to prevent neurotoxicity, except for the accurate collection of anamnestic data useful in identifying possible risk factors for its development. To date, no definitive medicines are known to treat this form of toxicity and its control is based on the reduction in the dosage, the substitution or the suspension of the drug involved; only duloxetine showed a moderate symptomatic effect on pain in a meta-analysis published by the ASCO (Hershman et al., 2014). As for lifestyles, in a review of 22 articles it has been showed how supplements such as antioxidants and herbal extracts, as well as physical activity, and complementary therapies such as acupuncture can have a beneficial effect on the prevention and reduction of the symptoms of peripheral neuropathy induced by chemotherapy. Given the limitations of some revised articles such as group heterogeneity, small sample testing, it is not possible to draw strong conclusions about the role of lifestyle-related factors in the management of peripheral neuropathy in colorectal cancer patients(Derksen et al., 2017).

### *12.2. Bowel and urogenital dysfunction*

Patients with rectal carcinoma, compared with those with colon cancer, are more likely to report diarrhea (24% vs 10%, $p = 0.04$) (Gami et al., 2003). 13–50% of long term survivors patients report chronic diarrhea up to 10 aa after the end of treatment; those who have undergone anterior rectal surgery report an increase in the frequency of evacuation, urgency and difficulty evacuating. These symptoms are most important during the first year after resection (Guren et al., 2005). Pre and postoperative radiotherapy increases the risk of long-term intestinal dysfunction (Dahlberg et al., 1998). 30% of patients who have undergone a definitive treatment for rectal cancer present both urinary and the sexual dysfunctions. At 5 years of intervention, the main problems are urinary incontinence (38%), bladder bleeding problems (31%), need to empty the bladder frequently (70%), need to wear a diaper (57%). The severity of incontinence increases with time, from 18% after three months of intervention to 31% at 5 years (Lange et al., 2008). In a study, it has been evaluated the disorders of urination and sexual function before and after rectal resection. At baseline, of the 52 patients enrolled, 49 had a normal bladder function and only three had a post-void urine residue superior to 100 ml. After the intervention, 12 out of the 49 patients with normal baseline urinary function had mood disorders. So in about 90% of patients, urinary function returned normal after surgery and only 10% had urinary problems six months after surgery. 30% of patients who did not have baseline alterations in the baseline were having a disorder after surgery (Sterk et al., 2005). In a study it has been evaluated 250 patients treated for rectal cancer; 68% of patients answered to the questionnaire. Results: Urinary function was temporarily reduced by RT in men (International Prostatic Symptom Score: 7.8 vs 4.9; $p < 0.001$). Sexual activity was significantly reduced in women after radiotherapy ($p = 0.02$), and in all patients after surgery ($p < 0.001$). At 12 months, sexual activity in women declined from 59% to 36% ($p = 0.02$). In men, sexual activity (82% vs 57%), erection (71% vs 24%), and ejaculation (78% vs 32%) decreased compared to the baseline ($p < 0.001$) (Adam et al., 2016).

## 13. Lifestyles and cancer risk

Physical activity, sedentary behaviour, and diet are factors of cancer risk. More than ten types of cancer, including colorectal cancer are inversely associated with physical activity and positively associated with sedentary behavior (Kerr et al., 2017). In a meta-analysis, the consumption of red meat was linked with BMI, rate of overweight and obese, low physical activity, and smoking are inversely associated with rate of nonsmokers and high physically active individuals. On the other hand, high consumption of fruits and vegetables was positively associated with prevalence of non-smokers, high education and high physical activity (Grosso et al., 2017). The data concerning the effect of diet in long-term colorectal survivors are few; a western dietary pattern, resulted in a worse disease-free and overall survival (Meyerhardt et al., 2007). On the other hand a diet rich in fruits, vegetables and fish has not been significantly associated with recurrence of tumor and mortality. Obesity is a factor associated with cancer risk and mortality. A BMI 35 $Kg/m^2$ could be related to a mayor mortality and the risk of a colon cancer recurrence (Dignam et al., 2006). It is associated to poor prognosis after cancer diagnosis and could increase the risk of second primary tumors. Lifestyle intervention studies showed that the reduction in caloric intake, the increase in physical activity will benefit a better quality of life and a lower incidence of comorbidity (Ballard-Barbash et al., 2012). The American Society of Clinical Oncology, to reduce obesity, has established: 1) to fight lifestyle which determines the weight gain; 2) increasing education; 3) understand the pathophysiology of weight gain and provide long term cancer survivors effective eating habits (Ligibel et al., 2015). In a randomized trial, it has been showed that the increase of aerobic fitness, improved QoL, psychosocial distress compared to whose fitness decreased (Courneya et al., 2003). Physical activity reduces the risk of recurrence, the specific mortality and overall mortality of long term colorectal cancer survivors (Haydon et al., 2006). Several studies have shown an inverse correlation between physical activity and cancer mortality (Haydon et al., 2006; Meyerhardt et al., 2009; Baade et al., 2011b) The data collected in a systematic review of seven studies of colorectal cancer survivors, have highlighted that the physical activity performed before and after the diagnosis of colorectal cancer reduces the risk of mortality (Schmid and Leitzmann, 2014) In this context, a lifestyle modification action is important to maintain the state of health. Table 3.

## 14. Conclusion

Increasing survival in colorectal cancer patients as a result of early and accurated diagnostic evaluation and personalized treatment based on a better understanding of the biology and potential response to therapies of each individual cancer, has highlighted the importance of surveillance in long-term colorectal cancer patients. Long-term follow-up, health maintenance and lifestyle modifications remain important components of care for CRC survivors. Goals of survivorship care include surveillance for recurrence, management of late and long-term toxicities associated with multimodality treatment, encouragement of healthy diet and lifestyle behaviors, and adherence to recommended preventive care guidelines. A shared model of care is ideal for survivorship care and may be facilitated by a survivorship care plan. In this plan, late effects (those that may occur in the future) and long-term effects (residual effects from treatment not expected to improve) can be delineated. Moreover, further research evaluating issues specific to CRC survivorship and potential interventions need to be a priority.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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