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TOPIC HIGHLIGHT

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Treatment of colorectal cancer in the elderly

Monica Millan, Sandra Merino, Aleidis Caro, Francesc Feliu, Jordi Escuder, Tani Francesch

Monica Millan, Aleidis Caro, Francesc Feliu, Jordi Escuder, Colorectal Surgery Unit, Department of Surgery, Joan XXIII University Hospital, 43005 Tarragona, Spain

Sandra Merino, Department of Medical Oncology, Joan XXIII University Hospital and St. Joan de Reus University Hospital, 43005 Tarragona, Spain

Tani Francesch, Department of Geriatrics and Palliative Care, Joan XXIII University Hospital (GiPSS), 43005 Tarragona, Spain

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Correspondence to: Monica Millan, MD, PhD, Colorectal Surgery Unit, Department of Surgery, Joan XXIII University Hospital, Rambla Francesc Macia 2, Esc D, 2-3, 43005 Tarragona, Spain. monica.millan@ymail.com
Telephone: +34-638-107948
Fax: +34-977-505277

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Abstract

Colorectal cancer has a high incidence, and approximately 60% of colorectal cancer patients are older than 70, with this incidence likely increasing in the near future. Elderly patients (> 70-75 years of age) are a very heterogeneous group, ranging from the very fit to the very frail. Traditionally, these patients have often been under-treated and recruited less frequently to clinical trials than younger patients, and thus are under-represented in publications about cancer treatment. Recent studies suggest that fit elderly patients can be treated in the same way as their younger counterparts, but the treatment of frail patients with comorbidities is still a matter of controversy. Many factors should be taken into account, including fitness for treatment, the wishes of the patient and family, and quality of life. This review will focus on the existing evidence for surgical, oncologic, and palliative treatment in patients over 70 years old with colorectal cancer. Careful patient assessment is necessary in order to individualize treatment approach, and this should rely on a multidisciplinary process. More well-designed controlled trials are needed in this patient population.

Key words: Colorectal cancer; Surgery; Chemotherapy; Radiotherapy; Elderly; Palliative care

Core tip: With the rise in the incidence of colorectal cancer and in the population > 70 years of age, the need to decide what type of treatment is most appropriate for patients > 70 with colorectal cancer will become more frequent. Age in itself should not be an exclusion criterion for radical treatment, but there will be many elderly patients that will not tolerate or respond well to standard therapies. These patients need to be properly assessed before proposing treatment, and a tailored, individualized approach should be offered in a multidisciplinary setting.

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INTRODUCTION

Colorectal cancer (CRC) is one of the most common cancers worldwide, and its incidence is increasing[1]. The choice of treatment is based on several factors, including stage at presentation, location, and the conditions of the patient. Current treatment in general for CRC includes surgery for CRC stage Ⅰ or Ⅱ; surgery followed by adjuvant chemotherapy for stage Ⅲ colon cancer; and in cases of metastatic CRC (mCRC), systemic chemotherapy alone or in combination with targeted biologics. mCRC requires multidisciplinary management, where surgical resection of metastatic disease is considered wherever possible. The treatment of rectal cancer includes surgery alone in stage Ⅰ or short-course radiotherapy or chemoradiotherapy with surgical resection followed by adjuvant chemotherapy in selected stage Ⅱ and Ⅲ patients[2].

Approximately 60% of CRC patients are > 70 years of age at the time of diagnosis, and 43% are > 75[1]. These proportions will likely continue to increase in the near future. Many of these older patients will have problems of frailty and comorbidity that demand careful patient assessment, and, if necessary, individualized treatment approaches[3].

Aging may be defined as a progressive decline in the functional reserve of multiple organ systems. This process is highly individualized, and poorly reflected in chronological age. The treatment of cancer should be based on the assessment of the physiological age, the patient's life expectancy, and tolerance to treatment[4]. Older patients risk being undertreated, and, therefore, presenting a worse oncologic outcome. If they are over treated, however, there is an increased risk of morbidity and mortality[5].

The challenge in this group of patients comes from the physiological heterogeneity of the older patient population, with frequent discrepancies between physiological and chronological age, coupled with the additional complications of coexisting medical conditions and potential psychological and social care issues[6].

The treatment of those at the upper extreme of life often presents significant clinical dilemmas. A critical appraisal is needed of the costs and benefits of treatment, and a better selection of patients who can benefit from available therapies is warranted. There is a paucity of controlled trials including this group of patients, and, therefore, evidence-based decision-making is difficult. Many elderly patients will benefit from radical treatment approaches, but others will not, and in some cases, non-operative "palliative" management should be offered, even though the cancer is "curable". This review aims to focus on the existing evidence to aid in the decision-making process for treatment of CRC in elderly patients.

GERIATRIC ASSESSMENT

The patient's biological age should ideally be established through a comprehensive geriatric assessment in order to aid therapeutic decisions.

There is a paucity of clinical trial data in these patients who, in many cases, have poor functional reserves, major comorbidities, and frailty. In older patients, functional levels vary widely- from robust and able to tolerate cancer treatments to frail and unable to tolerate even minor interventions without life-threatening consequences. At either end of this spectrum, treatment decisions are clear, but the identification of individuals at risk for functional decline and frailty, where interventions or treatment modifications are needed, is where geriatrics could have the biggest impact on oncology[7].

By distinguishing the fit from the vulnerable older patients, treatment can be adjusted to maximize its effectiveness, avoid complications, and better meet the individual requirements of the older patient. When choosing between various treatment options, quality of life and function may be at least as important for the elderly as the cancer-specific or surgical outcome[6].

The main difficulty for individualizing treatment in elderly patients is the capacity to evaluate vulnerability to treatment. Several aspects should be taken into account[8], which include: (1) an estimation of life-expectancy based on functional evaluation and co-morbidities; (2) an estimation of the risk of cancer-related morbidity: a: Tumor stage at diagnosis; b: Risk of recurrence and tumor progression; and c: Tumor aggressiveness; (3) an evaluation of the conditions that could interfere in the cancer treatment and tolerance; a Comprehensive Geriatric Assessment[7] (CGA), which includes: a: undernutrition (recent loss of > 5% weight/body mass index < 19); b: polypharmacy (more than 10 medications); c: social isolation; d: depression; e: cognitive disorder; f: risk of falls; g: side effects of neoplasia: sensory deterioration, urinary incontinence, sexual dysfunction; h: comorbidities (number and severity of co-existing illnesses); and (4) an evaluation of the goals of the patient (what the patient expects from treatment). An important aspect of this evaluation is quality of life (subjective evaluation of life as a whole). The instruments that can be used to measure quality of life include, at least three of the following 10 aspects[9,10]: Pain and other somatic symptoms, functional capacity, social and family well-being, emotional well-being, spirituality, satisfaction with care, future hopes and wishes, sexuality, body image, and social and work-related function.

Elements of the CGA, especially comorbidity, functional status, cognitive dysfunction, and frailty, are consistently associated with adverse treatment outcomes in relation to both toxicity and mortality[11-13].

A complete CGA is time-consuming. For now, it might be beneficial for all elderly patients with cancer

to receive a complete geriatric assessment[14], although recent publications show promise in the use of frailty screening methods to select which patients will benefit from a complete CGA or further assessment: (1) test Timed Up and Go: Patients who require more than 10 s to perform the exercise, need to use their arms to get up, or perform an erroneous trajectory will need a full CGA[15,16]; (2) seven-item physical performance: this test takes 10 min to perform. If the total result is less than 20, a CGA would be beneficial. It has been demonstrated to be more sensitive than the Karnofsky Performance Status in recognising patients with a higher risk of functional decline[16]; and (3) the Vulnerable Elderly Survey 13 (VES-13)[17]: when the scores are equal or above 3 it indicates a higher risk of functional deterioration, and a 4-fold increased probability of death in the next 2 years, and, therefore, a complete CGA is indicated[18-21].

In 2012[22], an algorithm was proposed to evaluate an elderly cancer patient that uses the frailty criteria, the VES-13 scale and the CGA. All patients diagnosed with cancer would be tested using VES-13. If the score is < 3 the patient can receive the standard treatment recommended for adult patients according to tumor stage. If the score is > 3, a full CGA is recommended, and further recommendations can be made according to the possibilities of treatment of the patient's comorbidities or functional dependence; palliative or standard treatment could be recommended.

The concept of frailty is still under construction and has many common aspects with the definition of aging. Fried *et al*[23] criteria include an assessment of weight loss, physical exhaustion, physical activity level, grip strength, and walking speed. Any degree of frailty measured by the Hopkins Frailty Score[24] has been linked to a worse postoperative outcome after surgery for CRC. Core features of frailty include impairments in multiple, interrelated systems, resulting in a reduced ability to tolerate stressors. This is associated with an increase in vulnerability to severe complications with cancer treatment, which translates into an increase in global mortality[25,26].

The CGA should include the following determinations[27]: (1) functional status: Evaluation of dependency in daily activities using scales such as Barthel and Lawron, the TITAN scale, and Karnofsky index. Functional decline in elderly patients is a predictor of short- and medium-term mortality, independent of the disease process[28]; (2) coexisting illness (Comorbiditiy): The Charlson comorbidity index[29] predicts 1-year mortality in patients with comorbidities. Sarcopenia (skeletal muscle depletion) in older patients is related to infection, requirements for rehabilitation following surgery, and length of hospital stay[30]; (3) socio-economic evaluation: the elderly population is at a greater risk of social deprivation[28]. The social situation of the elderly patient should always be evaluated, and the detection of social isolation should lead to the application of the necessary social resources; (4) nutritional status: Mini Nutritional Assessment[31]. An albumin < 2.5 g/dL + CT < 156 mg/dL + weight loss of 10% indicates terminal illness; (5) cognitive status: Mental Status Questionnaire-Pfeiffer and Mini Mental State Examination. The impact of depression and dementia on oncologic treatment is not well known[32,33], but it has been identified as one of the determinant factors in receiving inadequate treatment[34,35]; (6) geriatric syndromes: sleep disturbances, incontinence, risk of falls, *etc*. The presence of geriatric syndromes is an indicator of frailty. An assessment of the cognitive and emotional state is especially important in older cancer patients. Polypharmacy is common in older patients, and the possibility of drug interactions and the delicate clinical situation in a geriatric cancer patient should be considered; (7) surgical risk: The American Society of Anesthesiologists (ASA) classification continues to be one of the most reliable predictors of postoperative morbidity and mortality[34,35]. Multiple studies have shown that the presence of comorbidities increases the risk of postoperative complications, and this is more evident in patients over 70 years of age[35]; and (8) An evaluation of the patient's views on the goals of treatment (what does the patient expect and want?). Optimal treatment of the older adult patient who has cancer starts with a careful delineation of goals through conversation. There is a general tendency to think that geriatric patients do not want to be informed about the diagnosis and prognosis of their disease; however, several studies refute this hypothesis[36,37]. In reality, there does not seem to be any difference with respect to age regarding the wish of cancer patients to receive information[38].

Multidisciplinary cooperation involving oncologists, gastroenterologists, radiotherapists, anesthetists, radiologists, pathologists, and surgeons has become essential in elderly patients. Geriatricians are not typically members of MDTs, but there is clear evidence that older CRC patients should be treated in centers where the expertise is available to provide the most favorable surgical and oncologic treatment and care[21,39].

Balducci[40] studied the role of CGA in the selection of oncologic treatment and divided patients into three groups depending on the severity of frailty symptoms and signs: Type Ⅰ: Functionally independent patient without important comorbidities: these patients would be candidates to receive onco-specific treatment in standard conditions; Type Ⅱ: Functionally dependent patient with two or less comorbidities: these patients could benefit from a modified onco-specific treatment with standard intention; and Type Ⅲ: Partially dependent patient with three or more comorbidities or the presence of a geriatric syndrome: these patients would be candidates for symptom treatment exclusively (palliative care).

SURGERY

There is no consensus about the optimal surgical

management of elderly people, who are a heterogeneous group of patients, ranging from very fit to very frail individuals. This population is undertreated compared with younger patients, with a lower percentage of patients operated on; a lower rate of curative surgery, and more emergency surgery. Elderly patients are generally recruited to clinical trials less often than younger patients and are under-represented in publications about cancer treatment[41].

A comprehensive geriatric assessment is a major consideration when assessing operative risk, treatment decision making, and adapting perioperative care, if surgery is undertaken.

Surgical risk stratification remains one of the most important aspects of management in elderly patients[42]. Age is associated with increased mortality following elective colorectal resection, up to 15.6% in patients > 80 years of age. Elderly patients with higher levels of comorbidity might be expected to have significantly higher rates of complications, longer hospital stays, and higher mortality[43].

Elderly patients deemed to be optimized for surgery through traditional clinical and biochemical markers may still have poor outcomes. The concept of frailty can be used to identify a group of patients for further investigation before surgery[23]. Patients who were positive for frailty had 4 times higher risk of developing major complications (OR = 4.083; 95%CI: 1.433-11.638)[43]. Decreased survival in older (> 75 years) patients post-surgery has mainly been attributed to differences in early mortality[44-48]. The rate of cardiovascular complications increases significantly with age. Pulmonary complications are also twice as common. Postoperative complications are more severe in elderly patients[49-52]. The occurrence of a complication was associated with a significantly increased risk of 6 mo mortality. Overall, 6 mo mortality was 4 times higher in elderly patients than in younger patients (14% *vs* 3.3%; $P < 0.0001$) as was the 1-year mortality rate (20.1% *vs* 5.1%)[53]. Progressive loss of stress tolerance with aging exacerbates the consequences in case of postoperative complications[54]. However, older patients with CRC who survived the first year after surgery had the same overall cancer-related survival as younger patients[53].

Therefore, the focus should be on survival and minimizing postoperative complications during the first postoperative year. Pre-habilitation programs could be of great importance in elderly patients: Correction of malnutrition, optimization of cardiovascular and pulmonary comorbidities, and medication use have been shown to reduce complications after elective surgery in elderly patients and are a promising area of future research[54].

Emergency surgery should be avoided if possible. The presence of obstruction or perforation increases the perioperative mortality rate in older patients. Several studies show the correlation between advanced age, mortality, and emergent surgery. Kurian *et al*[55] reported a postoperative 30 d mortality rate of 28% in emergent surgery compared to only 5% in elective surgery. Morse *et al*[56] found similar outcomes in 39 patients older than 80 in open colectomy for colon cancer. In the same way, Louis *et al*[57] observed the close correlation between advanced age, advanced ASA grade, and emergent surgery, and other authors found that no patients with an ASA grade of 3 or more survived more than 6 mo[58]. Modini *et al*[59] reported a 6 fold higher 30 d postoperative mortality in elderly patients > 80 years of age with respect to others. They noted that although morbidity and mortality rates in elderly patients could be similar to that of younger patients, it would rise up to 9 fold higher in cases of emergent surgery[60,61]. Patients over 70 years of age after emergency surgery have been shown to have a higher rate of postoperative myocardial infarction, and this complication is associated with a 6 times higher rate of mortality in the postoperative period[62]. Other common complications are pulmonary failure, acute renal failure, and sepsis; anastomotic leakage also occurred more frequently in elderly patients after emergency colorectal surgery and presented a significant association with postoperative mortality[63].

A feasible alternative management to emergency surgery for colonic obstruction could be the endoscopic placement of stents, especially in acute left-sided colonic obstruction. Use of these self-expanding metallic stents would provide "extra time" to better study the patient's clinical situation and the tumor-stage, improve the nutritional status, optimize comorbidities, and, in some cases, allow a subsequent elective surgery. Consequently, it is an appealing option either for palliation or as a "bridge" to definitive surgery in the management of left-sided colonic obstruction for elderly patients. Nevertheless, the current data are controversial and the advantages in terms of early morbidity and mortality compared to emergency surgery are not as clear as originally described[64].

Laparoscopic surgery has been shown to reduce postoperative pain, allowing a decreased use of narcotics and opioids, reduced postoperative ileus, and a reduced hospital stay[65]. Furthermore, elderly patients benefit from laparoscopic surgery because it reduces the risk of cardiovascular and pulmonary complications, reduces intraoperative blood loss, and seems to accelerate gastrointestinal recovery. Stocchi *et al*[66] found that the preoperative functional status of patients was more frequently maintained at the time of discharge in elderly patients operated on by laparoscopy. In a randomized trial including 553 patients, Frasson *et al*[65] similarly concluded that laparoscopy should be the first choice in elderly patients operated on for CRC because it increases preservation of functional status, allowing a higher rate of independence during the postoperative period and discharge and a faster postoperative recovery.

However, most trial protocols of laparoscopic surgery for CRC have been biased to exclude or under-

represent the elderly. Decision-making for such patients is, therefore, still based on inadequate evidence[67-69]. Clinical trials on laparoscopic surgery in the older population are lacking: 44% of trial protocols excluded elderly patients. Nevertheless, since a higher systemic inflammatory response to the surgical aggression and lower physiological reserve appear to be the origin of the high postoperative mortality in the elderly patient[70-73], laparoscopic surgery could be beneficial due to its decrease in inflammatory response and lower surgical stress[74-79].

The literature suggests that elderly patients benefit from multimodal rehabilitation programs or enhanced recovery programs after surgery (ERAS) in the same way as younger patients[80]. Initial studies by Senagore *et al*[75] and more recent studies by Keller *et al*[81] and Wang *et al*[82] showed better results in terms of length of stay, readmission rate, and reoperation rates for elderly people using ERAS programs. Elderly patients benefit from the avoidance of bowel preparation, opioid restriction, and early mobilization. There does not seem to be an increased risk of aspiration pneumonitis in elderly patients following early resumption of oral feeding, although overall complications are higher in elderly patients[80].

Delays in discharge of elderly patients can be attributable to inadequate levels of social support or resources in the community, even when the postoperative course has been uneventful. Liaison with elderly care physicians may minimize avoidable hospital stay by optimizing the management of geriatric syndromes and by pre-emptively addressing the psychosocial needs of older patients. Specialized, organized, and coordinated geriatric care in the hospital setting improves outcomes, such as survival and in their own home up to 1 year after surgery[83-85].

In spite of all of the above, the fact still remains that some elderly patients will do very well after curative surgery, and others will not[86,87]. It is quite clear from the literature that the risks and benefits of surgery for CRC in the elderly have not been clearly reviewed[86]. There is, therefore, still no common consensus on how actively we should treat the elderly and when not to push them into unnecessary surgery, which could lead to severe functional impairment and diminished quality of life. Over 74% of patients interviewed in a recent study stated that they would refuse, or be reluctant, to receive treatment leading to severe functional impairment[87]. Life-expectancy, higher rates of 60 d mortality, higher likelihood of impairment of physical and mental function, and the possibility of never returning home and needing permanent residential care, should ideally be considered and discussed with the patient and family before deciding on surgical treatment[88].

RECTAL CANCER

Older patients with rectal cancer undergoing surgery should receive the same treatment as their younger counterparts, but with an adjustment of treatment strategy in the case of comorbidity, limited physiologic reserves, and emergency situations. Complete mesorectal excision is considered the "gold-standard" surgical treatment for rectal cancer, but we continue to look for alternatives to avoid the high rates of postoperative morbidity[89]. Elderly patients are less frequently treated with neoadjuvant radiotherapy or chemotherapy, and non-restorative procedures are more frequently used. Anterior resection is performed less often in elderly patients, although tumor location and stage does not differ[90-92].

Population-based studies clearly show that older patients with rectal cancer are treated less often with RT[90-92]. Fewer older patients are likely to receive preoperative RT with proportionately more receiving palliative RT as an alternative[93]. Older patients with stage II or III rectal cancer who are fit enough for surgery are generally fit enough for preoperative neoadjuvant radiation therapy. Tolerability and response rates are similar to those seen in younger patients. However, Stockholm I and II Trials have shown the distinct negative effects of neoadjuvant radiotherapy in older patients (> 80 years). The incidence of venous thromboembolism, femoral neck and pelvic fractures, intestinal obstruction, and postoperative fistulas was significantly increased after preoperative radiotherapy in this group of patients[90,94].

The aim of rectal cancer surgery in older patients should be not only to avoid local recurrence but also to maintain health and function with a view to optimizing their chances of coping with their treatment. Older patients are keen to avoid a permanent stoma and may accept a higher risk of local recurrence to achieve this. The impact of cancer surgery on quality of life is very important in elderly people. Sphincter function, assessed clinically and if necessary after manometry, is an essential element to consider in the preoperative assessment and the decision-making procedure. The delay of surgery following short-course radiotherapy has also been associated with a decrease in postoperative morbidity.

Rather than age itself, the frailty of patients and preoperative sphincter function determine the operative indication and type of surgery[94,95]. Sphincter preservation in the elderly could give poor functional results with a higher risk of anal incontinence, and the potential effect of a permanent stoma on quality of life should be considered. Age was found as a significant risk factor associated with a decreased likelihood of stoma reversal[95].

Proctectomy in nursing-home residents has been associated with a 1 year postoperative mortality of 51% in patients with a permanent colostomy. Substantial postoperative mortality occurred in the first 6 mo after proctectomy and was significantly higher in elderly populations[96,97].

It has been observed that with neoadjuvant treatment there is a percentage of patients who present a

complete pathological response (pCR), up to 44%[98,99]. There is an increasing interest in a more conservative treatment for these patients. Several authors have proposed a "watch and wait" policy for patients when no residual tumor can be found. In a study published in 2010[100], the authors proposed an analytical decision model comparing the results between empirical radical surgery and observation alone in patients with pCR, and concluded that observation is better than surgery in cases where the ability to detect patients with pCR is higher than 58%, when patients will not have a good quality of life after surgery, or when the risk of recurrence was less than 43% when compared to observation. This study only included patients < 65 years of age, and excluded elderly patients with comorbidity[100].

Following the same working model, Smith *et al*[101] published a study in 2015 evaluating the differences between radical surgery and observation after neo-adjuvant treatment in cases of pCR and divided patients into three groups: Healthy 60-year-old patients, healthy 80-year-old patients, and 80-year-old patients with associated comorbidity. The study concluded that elderly patients, because of their higher surgical risk, obtained the greatest benefit from the "watch and wait" policy and showed an improved survival at 1 year after treatment.

The groups of patients that present a significant tumor regression with neoadjuvant chemoradiation, and especially those with lymph node regression (ypN0), could be candidates for alternative treatments for rectal cancer without needing total mesorectal excision (TME). Transanal endoscopic surgery could be an interesting option in these patients[102,103]. Recent studies have attempted to detect the subgroups of patients with a good response to neoadjuvant treatment where transanal endoscopic surgery could reduce the recurrence rate[104-106]. Habr-Gama *et al*[107] pioneered the decision not to operate on patients with rectal cancer who presented a complete clinical response after chemoradiation. This same group has published a series of "watch and wait" in 70 patients with cT2-4cN1-2 treated with chemoradiation, and of the 47 patients with a complete clinical response, eight (17%) presented an early recurrence and four a late recurrence. All had subsequent radical R0 surgery and were disease-free 56 mo later. This could be an option for patients who are not considered fit for surgery; the difference would be that it does not have to be considered a palliative treatment but a possible standard treatment with a 50% probability of cure in frail elderly patients.

No prospective randomized trials comparing the results of neoadjuvant chemoradiation and local excision include elderly patients, but the results in the general population can be taken into consideration in these patients. A study by Bhangu *et al*[108] analyzed the results of local excision in elderly patients and concluded that local excision achieved the same results as radical surgery in patients with pT1 tumors, the same as in the general population, but decreased survival in pT2. The difference with the general population could be due to the amount of comorbidities present in this group of patients; they would not be candidates for the same type of chemoradiation treatment, and, therefore, the results would not be comparable with those published up to the present time.

However, transanal endoscopic surgery can also be considered as a palliative treatment in patients with comorbidities who are not fit for radical surgery or who refuse a stoma, after carefully considering all options[109].

BIOLOGICAL FEATURES OF CRC IN THE ELDERLY

CRC is related to age, but there are few available data on the genetic differences and alterations in the carcinogenesis process between younger and older patients.

In many studies, younger patients are more likely to have mucinous, poorly differentiated and signet ring tumors, but there are mixed results in terms of prognosis. Several studies have suggested that younger age was a poor prognostic factor[110-112], but others suggested the opposite when adjusting for confounding variables, such as tumor, treatment, and patient factors[113-118].

The most frequently observed somatic mutations in CRC were found in the *APC*, *TP53*, *KRAS,* and *PIK3CA* genes.

A model has been proposed for the carcinogenic process in sporadic CRC, in which normal colonic mucosa would transform into invasive carcinoma. This model, named chromosomal instability pathway (CIN), implicates somatic mutations in a multi-step process, with alterations in different genes in chronological order [APC, Kirsten rat sarcoma (KRAS), Smad2/4, and tumor protein 53 (TP53)]. In a minority of cases of sporadic CRC, approximately 15%, the pathway responsible for the transformation of the colon epithelium is through an inappropriate mismatch repair system (MMR). The system cannot repair the mismatches, resulting in a length variability of DNA microsatellites, called microsatellite instability (MSI). Another proposed pathway responsible for the carcinogenic process is DNA hypermethylation [CpG island methylator phenotype (CIMP)][119,120].

Patients with the same stage of disease have a different natural history and a different prognosis, as a result of the heterogeneity of the process. Some conditions give a more favorable prognosis (MSI, BRAF not mutated) or a worse prognosis (hypermethylation and not MSI). Currently, the only marker applicable to clinical practice is the *RAS* mutation.

In an analysis of 181 patients with CRC, patients were divided into different groups: Those under 50 years of age, from 51 to 70, and over 70. In the

group of patients over 70 years of age, the MSI and BRAF mutations were correlated, but there was no correlation in the group under 50. Mutations in the *KRAS* and *BRAF* genes were more common with age, but no phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha (PIK3CA) mutations were found. TP53 mutations were more common in older patients. There were no differences in the frequency of phosphatase and tensin (*PTEN*) gene mutations. The conclusions were that older patients had a greater index of genetic mutations, and the incidence of BRAF mutations was higher. CIMP tumors are more common in the older population, who also have a higher rate of KRAS and BRAF mutations. These mutations have treatment implications[120]. TP53 mutation is associated with more advanced stages and vascular and lymphatic involvement[121]. *KRAS* gene mutation is a predictor of resistance to treatment with monoclonal antibody receptor endothelial growth factor (EGFR)[122-124]. BRAF V600E mutation confers worse prognosis[125,126]. A deficiency of the MMR system appears to be a favorable prognostic factor associated with adjuvant treatment in stage Ⅱ CRC[127,128].

CHEMOTHERAPY

The aging process involves an organic functional impairment, with decreased liver and kidney function, decreased bone marrow reserve, increased risk of cardiovascular events, cognitive impairment, other comorbidities, or use of polypharmacy. These conditions favor a greater toxicity with chemotherapy, which results in a diminished quality of life and adherence to treatment. The most commonly used scales to evaluate functional status, such as the Karnofsky performance status or the Eastern Cooperative Oncology Group (ECOG), should be used in the context of a comprehensive geriatric assessment in order to classify the elderly as fit or frail, the latter being more exposed to higher toxicity with chemotherapy, hospitalization, and death.

There is a consensus that frail patients with ECOG PS 3 or 4 or IK less than 60 are not eligible for chemotherapy due to poor benefits and high toxicity; the consensus seems also clear about being more aggressive in fit patients. The challenge is to decide the best treatment for those who are neither fit nor frail[129,130].

Adjuvant treatment

The benefit of adjuvant chemotherapy for stage Ⅲ (node positive) CRC is well established, representing approximately a 30% reduction in the risk of recurrence and a 22%-32% reduction in the risk of death compared with observation alone. Elderly patients are referred to the oncologist less frequently than younger patients, especially those with comorbidities, and when referred they are less likely to be treated with chemotherapy. An update of SEER - Medicare analysis data and three population-based data sets conducted by Sanoff *et al*[131] showed that only 44% of the 5941 patients evaluated received adjuvant chemotherapy within 3 mo of surgical resection for stage Ⅲ CRC.

Since 2001, intravenous 5-fluorouracil modulated with leucovorin (FU/LV) in the adjuvant setting has shown better outcomes than observation, even in elderly patients. A pooled analysis of 3351 patients from seven randomized phase Ⅲ adjuvant chemotherapy trials comparing chemotherapy *vs* surgery alone for stage Ⅱ or Ⅲ colon cancer showed a 29% reduction in the risk of death at 5 years[132]. The benefit was independent of age, and no differences in toxicity were seen with respect to younger patients. Only one study showed a greater proportion of grade 3 or 4 neutropenia (8% *vs* 4%) without increased neurological toxicity, diarrhea, infection, nausea, or vomiting.

Capecitabine (an oral fluoropyrimidine) also proved to be as effective as FU/LV in adjuvant treatment in a subgroup analysis of patients equal to or greater than 70 years of age, with no differences in toxicity by age, although it was more toxic than FU/LV[133,134].

These results are supported by other studies with patients of 80 years of age or more, where there was a higher incidence of grade 3 or 4 toxicity, especially diarrhea (31% *vs* 13%) and hand-foot syndrome[135]. With the MOSAIC trial, oxaliplatin was established as a new adjuvant standard in combination with 5FU/LV plus infusional 5FU short-term and leucovorin (FOLFOX) as compared with 5FU and leucovorin alone in resected stage Ⅲ colon cancer, with a 20% reduction in the risk of recurrence and a 16% reduction in risk of death at 6 years. But the analysis of 315 patients over 70-75 years of age revealed that although there was a survival benefit with fluoropyrimidines, there was no benefit in disease-free survival (DFS), overall survival (OS), or time to recurrence (TTR) by adding oxaliplatin [OS hazard ratio (HR) 1.10, 95%CI: 0.73-1.65] or in patients with stage Ⅱ tumours[136].

The National Surgical Adjuvant Breast and Bowel Project (NSABP) C-07 trial analyzed 2409 patients in stage Ⅱ or Ⅲ treated with weekly bolus of FU and leucovorin with or without oxaliplatin. The results showed that the addition of oxaliplatin to 5FU/LV gave no survival benefit in patients equal to or greater than 70 years of age in stage Ⅱ or Ⅲ colon cancer (n = 396), but a higher grade 4 toxicity (20% *vs* 13%) was found. The benefit in OS was only observed in patients under 70 years of age[137]. In contrast, the N016968 trial, which randomized capecitabine *vs* bolus 5FU and oxaliplatin in stage Ⅲ exclusively, showed an increase in DFS in both populations under or over 65 years of age with an HR 0.8[138].

The Adjuvant CC End Points (ACCENT) database (including seven randomized trials such as MOSAIC, NSABP C-07, and N016968) included 14528 patients in stage Ⅱ or Ⅲ treated with a 5FU combination with oxaliplatin or irinotecan *vs* 5FU alone. The results of the 2575 patients greater than or equal to 70 years of age did not show a benefit in DFS or OS by

adding oxaliplatin to adjuvant treatment (DFS: HR = 0.94; 95%CI: 0.78-1.13; OS: HR = 1.04; 95%CI: 0.85-1.27). They did not consider death from other causes or change in efficacy due to reductions or delays of doses[139]. In contrast to these data, the analysis of Sanoff *et al*[131] with 4060 patients in stage Ⅲ CRC including five cohorts, the largest cohort of the SEER-Medicare database, saw a marginal benefit with no statistically significant difference when adding oxaliplatin. Also, there were more adverse events with oxaliplatin compared with fluoropyrimidine. Among patients older than 75 years of age, more neutropenia (OR = 17.3, 95%CI: 9.8-30.42) and nausea or vomiting were found (OR = 2.14, 95%CI: 1.73-2.65) without differences in diarrhea or hydration[140]. In summary, it seems that the benefit and toxicity of 5FU/LV in the adjuvant setting is similar between young and elderly patients.

Although adjuvant treatment is offered to patients in stage Ⅱ CRC with risk factors (T4, perforation, lymphovascular or perineural invasion, poorly differentiated histology), the benefit of adjuvant chemotherapy for stage Ⅱ is more controversial, and there are no data to ensure which patients are most likely to benefit from adjuvant treatment.

In an attempt to identify the subgroup of patients with stage Ⅱ CRC who may benefit from adjuvant therapy, there have been efforts to find prognostic biomarkers. The deficiency of the MMR system or MSI seems a promising marker. Several studies have found an association between high microsatellite instability (MSI-H) and better prognosis but resistance to treatment with fluorouracil[141].

It seems reasonable to analyze the MMR deficiency in patients with T3 stage Ⅱ to select those who could benefit from treatment with 5FU. Its application has not been validated in clinical practice, and, therefore, clinical decisions to administer chemotherapy should not be based on this analysis. It is not a common occurrence in the metastatic context and does not seem to play a role in the prognostic stratification.

Data from the SEER-Medicare database indicate that adjuvant treatment does not increase the OS in patients over 65 years of age with stage Ⅱ CRC with or without risk factors[142]. In stage Ⅱ patients with risk factors, the chemotherapy options are FU/LV or capecitabine if the patient is capable of adhering to the medication, although no differences were found in the Quasar study. This study showed a marginal benefit in OS of 3.6% in patients greater than or equal to 70 years of age with stage Ⅱ CRC[143]. The lack of benefit in stage Ⅱ does not justify the use of oxaliplatin. The benefit of adding oxaliplatin in patients > 70 years of age in stage Ⅲ CRC is doubtful and is not supported by data from the results of clinical trials, such as MOSAIC and NSABP, even though the elderly population included was very small. It is difficult to establish whether 70 years old is a reasonable cut-off age to safely extrapolate these results or if the decision should depend on the physical and functional status of the patient, not only on the chronological age. In fit elderly patients with stage Ⅲ CRC with a life expectancy of at least 5 years, the benefit of adding oxaliplatin must be discussed. The modified FOLFOX 6 scheme (due to less hematologic toxicity, without bolus if necessary), or XELOX with capecitabine at 1000 mg/m^2, should be considered. If the patient has no serious comorbidity, the full dose should be given. In patients neither fit nor frail with some comorbidity, dose reduction should be considered.

Frail patients with Eastern Cooperative Oncology Group Performance Status 3 or 4 are not candidates for chemotherapy treatment. Therapy with targeted agents is not indicated in adjuvant treatment because of lack of benefit[144].

Treatment in metastatic patients

The goal of palliative chemotherapy in the elderly should be the same as in young patients but with special attention to treatment toxicity. It has been demonstrated in several studies and a meta-analysis that chemotherapy improves the overall survival and time to progression compared to observation. An analysis by Folprecht *et al*[145] of 22 trials showed benefits in OS, progression free survival (PFS), and TTR similar to younger patients (in 629 patients over 70 years of age).

Exposure to the drugs currently available is able to increase the OS, time to response , and the rate of metastatic resection with an average of approximately 24 mo of OS. Even with this data and probably due to toxicity concerns, elderly patients are less likely to be treated with these agents. A population-based study by Ho *et al*[146] reported that less than 50% of elderly patients with mCRC received palliative systemic chemotherapy.

Fluoropyrimidines are the mainstay of treatment and can also benefit elderly patients. Depending on the administration schedule, the toxicity profile is different; diarrhea and leukopenia are more frequent when administered in bolus (24% *vs* 14% and 24% *vs* 10% respectively)[147]. Treatment with capecitabine, because it is administered orally, is perceived to be innocuous, but although it is well tolerated in fit elderly patients, it is still more toxic than 5FU in combination therapy[148-154]. The MRC Focus 2 trial of elderly and frail patients confirmed the higher rate of gastrointestinal toxicity, such as diarrhea, vomiting, and anorexia, with no differences in efficacy[155].

The question is whether a more aggressive regimen is better. There are conflicting data: three phase Ⅲ studies did not observe a survival benefit with combination chemotherapy *vs* 5 FU/LV alone[155-157]. The MRC FOCUS 2 trial included 459 patients who were deemed not fit or too frail for full doses. They were randomized to 5 FU/LV with or without oxaliplatin, or capecitabine with or without oxaliplatin. Approximately 43% were older than 75 years of age, 13% older than 80%, and 29% with a Performance Status of 2. The addition of oxaliplatin improved response rate but not

DFS or OS, and the rate of grade 3 or 4 toxicity was not increased in the oxaliplatin arm, perhaps due to a lower administered dose. Capecitabine and 5FU were equivalent in terms of benefit on PFS (HR = 0.99, 95%CI: 0.82-1.2, *P* = 0.93) or OS (HR = 0.96, 95%CI: 0.79-1.17, *P* = 0.71); however, higher toxicity was observed with capecitabine and, as a consequence, also a lower quality of life.

The combination of irinotecan and 5FU provides the same benefits in the elderly as it does in younger patients, as seen in phase Ⅱ and Ⅲ trials, albeit at the expense of an increased gastrointestinal and hematologic toxicity[158,159]. The tri-weekly administration of irinotecan requires dose reduction in patients over 70 years of age because of an increase in the rates of neutropenia and diarrhea[160].

A phase Ⅲ French study FFCD 2001-02 randomized 282 patients older than 75 with mCRC treated by a first line of palliative chemotherapy with 5FU with or without irinotecan. A geriatric assessment was obtained in 123 (44%). Greater toxicity grades 3-4 (61% *vs* 39%) were observed in the combination arm, and these patients required more hospitalizations or dose reduction. There is no OS data available to justify the increase in toxicity. The study was not designed with sufficient statistical power, so more studies are still needed. IADL dependence and cognitive impairment were established as predictors of greater toxicity[154]. The combination of oxaliplatin and capecitabine (denominated Xelox) is well tolerated, although more toxic as seen in the MRC FOCUS 2 trial[152]. The combination of capecitabine with irinotecan (XELIRI) is more toxic with a high rate of dehydration and asthenia, and it is infrequently used in elderly patients[154-158].

The benefit of the new molecular targets has also been reported in the elderly population[159]. Specifically, bevacizumab (the vascular endothelial growth factor VEGF) increases both PFS and OS, as was observed in a retrospective subgroup analysis and pooled analysis of randomized trials, along with observational cohort studies. A pooled analysis of two randomized trials by Kabbinavar *et al*[160] with 439 patients older than 65 and 276 > 70 years of age, showed an improvement with bevacizumab in PFS of 9.2 mo *vs* 6.2 mo; HR = 0.52: *P* < 0.0001, and OS of 19.3 mo *vs* 14.3 mo, which is statistically significant (HR = 0.7). Another analysis by Cassidy *et al*[161], which included two more phase Ⅲ trials with 712 patients equal to or > 70 years of age and 1142 > 65, confirmed the benefit in OS and PFS with bevacizumab, even though an increased incidence of thrombotic events in patients over 65 years of age was seen (5.7% *vs* 2.5% patients > 65 years, and 6.7% *vs* 3.2% in those > 70 years of age).

The BRITE observational study, which included 896 patients > 65 years of age, also showed better PFS, despite a greater toxicity profile with regard to the incidence of thromboembolic events, that increased with age[162].

The AVEX study, designed to assess the efficacy and tolerability of capecitabine plus bevacizumab *vs* capecitabine alone, included 280 frail patients equal to or greater than 70 years of age. The results showed an increase in PFS (9.1 mo *vs* 5.1 mo) and relative risk (RR) (19.3% *vs* 10%) with no statistically significant difference in OS (21 ms *vs* 17 ms) but more toxic events in the bevacizumab arm (40% *vs* 22%) at the expense of hypertension, hand-foot syndrome, bleeding, and thromboembolic events[163].

In elderly patients, the combination of capecitabine and bevacizumab is effective, but the risk *vs* benefit must be discussed, especially in patients with vascular disease, myocardial infarction, thrombotic events, or severe uncontrolled hypertension in the 6-12 mo prior to the start of treatment.

Aflibercept, another angiogenesis-targeting agent, has demonstrated efficacy in treating mCRC in a recent randomized Phase Ⅲ trial (VELOUR). As a result, it has been approved in combination with FOLFIRI in the second line treatment for metastatic mCRC, supported by an improvement in OS of 13.5 mo *vs* 12.1 mo. The efficacy was similar in the elderly population studied. However, there is no more data available in this population[164]. The most frequently reported adverse events with aflibercept compared with the placebo arm were hemorrhage (2.9% *vs* 1.7%), arterial and venous thromboembolic events (9.7% *vs* 6.8%), grade 3 hypertension (19.1% *vs* 1.5%), and grade 3 or 4 proteinuria (7.9% *vs* 1.2%). Other adverse effects associated with chemotherapy were higher in the aflibercept arm: diarrhea, asthenia, stomatitis, infections (12.3% *vs* 6.9%), palmar-plantar erythrodysesthesia (2.8% *vs* 0.5%), neutropenia (36.7% *vs* 29.5%), and thrombocytopenia (3.3% *vs* 1.7%).

The data on the anti-EGFRs cetuximab and panitumumab in the elderly population are limited. They have been investigated in several trials either in combination or monotherapy in mCRC, with a manageable toxicity profile. Patients with mutations in codon 12 or 13 of the *KRAS* gene should not be treated with anti-EGFR antibody due to lack of benefit. The main adverse effect of these drugs is skin toxicity. The correlation between development and severity of rash with treatment response is unclear. An analysis of EGFR polymorphisms observed that carriers of D994D polymorphism have lower dermatological toxicity than other genotypes, with no difference in PFS or OS and age[165-169]. Mutations in RAS, BRAF, and PIK3CA have also been shown to be associated with resistance to anti-EGFR[170].

Several prospective and retrospective studies have shown no differences in toxicity compared to younger patients and the same clinical benefit. Therefore, these agents should be considered in fit elderly patients[163-169].

The latest drug approved for the treatment of mCRC, the multikinase inhibitor regorafenib, adds a modest increase in PFS without increasing OS. Median overall survival was 6.4 mo with regorafenib *vs* 5.0 mo with placebo (HR = 0.77; 95%CI: 0.64-0.94; one-sided *P* = 0.0052). Adverse events due to treatment

occurred in 465 (93%) patients with regorafenib and in 154 (61%) of those assigned to placebo. The most common adverse events of grade 3 or higher related to regorafenib were hand-foot skin reaction (17%), fatigue (10%), diarrhea (7%), hypertension (7%), and rash or desquamation (6%). There were no differences in toxicity between patients older or younger than 65 years of age in the subgroup analyzed, but there are no available data on efficacy or toxicity in the elderly or frail population[168]. Ramucirumab is a human IgG-1 monoclonal antibody that targets the extracellular domain of VEGF receptor 2. Ramucirumab in combination with FOLFIRI has recently been approved as a second line treatment, after progression with bevacizumab, oxaliplatin, and a fluoropyrimidine. Median overall survival was 13.3 mo for patients in the ramucirumab group *vs* 11.7 mo for the placebo with FOLFIRI group (HR = 0.844, P = 0.0219). The most frequently observed adverse effects grade 3 or worse were neutropenia (38% *vs* 23%), hypertension (11% *vs* 3%), diarrhea (11% *vs* 10%), and fatigue (12% *vs* 8%). The median patient age was 62, and, therefore, there is still not enough data in the elderly or frail population. One of the latest drugs, pending Food and Drug Administration approval, for the treatment of CRC is TAS-102. TAS-102 is an antitumor agent composed of a combination of trifluorothymidine (FTD), a nucleoside that incorporates into DNA and inhibits a variety of genetic functions required for the proliferation of cancer cells, and tipiracil hydrochloride, an inhibitor of thymidine phosphorylase (which degrades FTD) that maintains an effective blood concentration of FTD. Tipiracil protects trifluridine from being broken down when taken orally.

In a Phase 3 study, 800 patients with advanced CRC in refractory to oxaliplatin, irinotecan, fluorouracil, bevacizumab, regorafenib, and anti-EGFR (RAS wild type) were randomized to TAS-102 *vs* placebo. An increase of median overall survival was observed, from 5.3 mo with placebo to 7.1 mo with TAS-102 (HR of death 0.68, P < 0.001). The main grade 3 or higher toxicity was neutropenia (38%) and patients in the TAS-102 group were also more likely than those in the placebo group to have nausea of grade 3 or higher (2% *vs* 1%), vomiting (2% *vs* < 1%), and diarrhea (3% *vs* < 1%). The median patient age was 63. The benefit was seen in patients younger than and older than 65, but data are lacking in elderly or frail patients[171].

In summary, an elderly fit patient may be treated with FOLFIRI and FOLFOX (or XELOX) with or without antibodies, given the high response rate, especially if the treatment is given with neoadjuvant intention prior to surgery for metastases (M1), with certain precautions due to different toxicity profiles. Age by itself should not be a contraindication for M1 surgery. There are more data available for hepatic resections than pulmonary resections[172-176]. Surgical series that include all patients have a median OS of 40% at 5 years after liver resection, with a general perioperative mortality lower than 5%. Fit elderly patients with little comorbidity should be offered chemotherapy with the newer agents that increase the response rate and therefore resectability before surgery.

Two retrospective series of neoadjuvant chemotherapy prior to surgery based on oxaliplatin showed higher response rates as expected. Those who were operated had better recurrence-free survival[176,177].

For those patients unfit or with low IK or PS 2, the treatment may be of benefit if deterioration is related to the oncologic disease, although the benefit is lower and the toxicity higher. The risks or benefit should be evaluated and discussed individually in these patients. Fluoropyrimidine monotherapy or supportive care is probably the best choice in frail patients.

PALLIATIVE CARE

The "frail elderly" may be good candidates for palliative treatment, which can provide a better quality of remaining life. When to begin palliative care is a troublesome question for patients, but when frailty is severe, delivery of palliative care focused on relief of discomfort and enhancement of quality of life is highly appropriate. In addition to symptom management, preservation of functional independence is a major goal of treatment in the elderly. The application of multidisciplinary, team-based palliative approaches is beneficial for treating these patients because of the complexity of their coexisting social, psychological, and medical needs. Although death occurs far more commonly in older people than in any other age group, the evidence base for palliative care in older adults is scarce[178].

CONCLUSION

Older patients with colon or rectal cancer are less likely to receive guideline-recommended therapies. Decisions about cancer treatment in the elderly may be influenced by a number of factors, including pre-existing health problems (comorbidities) and other conditions that might cause the potential risks of surgery, chemotherapy, and radiotherapy to outweigh the benefits of treatment. Risk stratification based on comorbidities and biochemical and physiological markers could help to decide whether to perform surgery, what type of surgery, and the timing of surgery. Physiological rather than chronological age should determine the management of cancer in each individual[5].

Optimal treatment of the older adult patient who has cancer starts with a careful delineation of goals through conversation. Most elderly patients with cancer will have priorities besides simply prolonging their lives. Surveys have found that their top concerns include avoiding suffering, strengthening relationships with family and friends, being mentally aware, not being a burden on others, and achieving a sense that their life is complete[179]. The treatment plan should be comprehensive: cancer-specific treatment, symptom-

specific treatment, supportive treatment modalities, and end-of-life care[180].

The careful assessment of the patient, taking into consideration their functional status, level of frailty, life-expectancy, and wishes, should become an essential and central issue in their management, and choosing the appropriate therapy for each patient within a multidisciplinary process should be the future in the treatment of elderly patients with CRC.

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