

WJG 20th Anniversary Special Issues (5): Colorectal cancer**Personalized surgical management of colorectal cancer in elderly population**

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Abstract

Colorectal cancer (CRC) in the elderly is extremely common but only a few clinicians are familiar with the complexity of issues which present in the geriatric population. In this phase of the life cycle, treatment is frequently suboptimal. Despite the fact that, nowadays, older people tend to be healthier than in previous generations, surgical undertreatment is frequently encountered. On the other hand, surgical overtreatment in the vulnerable or frail patient can lead to unacceptable postoperative outcomes with high mortality or persistent disability. Unfortunately, due to the geriatric patient being traditionally excluded from randomized controlled trials for a variety of factors (heterogeneity, frailty, *etc.*), there is a dearth of evidence-based clinical guidelines for the management of these patients. The objective of this review was to summarize the most relevant clinical studies available in order to assist clinicians in the management of CRC in the elderly. More than in any other patient group, both surgical and non-surgical management strategies should be carefully individualized in the elderly population affected by

CRC. Although cure and sphincter preservation are the primary goals, many other variables need to be taken into account, such as maintenance of cognitive status, independence, life expectancy and quality of life.

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Core tip: More than 50% of colorectal cancer cases are diagnosed in patients over 70 years of age. As the geriatric patient is traditionally excluded from randomized controlled trials for a variety of factors (heterogeneity, comorbidities, polypharmacy, inability to consent, *etc.*) there is a dearth of evidence-based clinical guidelines for the management of these patients. Although cure and sphincter preservation are the primary goals, many other variables need to be taken into account, such as the maintenance of cognitive status, independence, life expectancy, and quality of life. Personalized and patient-centered care should be the goal when caring for elderly patients with colorectal cancer.

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INTRODUCTION

The world population is aging^[1]. This process is especially evident in Western society due to a combination of increased life expectancy and a reduced birth rate^[2]. With

aging, the incidence and prevalence of cancer increases^[3,4]. With a median age of 70 years at diagnosis and an incidence drastically increasing with age, colorectal cancer (CRC) is by far one of the most commonly diagnosed malignancies in the elderly. It has recently been demonstrated that the highest risk of being diagnosed with CRC is between 80 and 89 years of age; thus, in future decades, CRC will constitute a major burden for health care systems^[5]. Surgical resection is still the cornerstone of curative treatment for this disease. Although improvements in perioperative care, surgical techniques and the introduction of multimodal treatment have made surgery feasible for the vast majority of patients, elderly cancer patients still represent a challenge for the surgeon^[6].

The intrinsic reduction in tolerance to stressors, and the frequent presence of one or more disorders in addition to the cancer increase the risk of a poor surgical outcome in elderly patients undergoing cancer-related surgery. It is important to remember that there is great variation in individual health status with increasing age; as a consequence, a multidimensional approach by a multidisciplinary team should be incorporated into daily practice before planning treatment^[7].

For this population group, the goal of each assessment is to customize optimal management according to physiological/biological age instead of crude chronological age in order to avoid overtreatment of the frail and undertreatment of fit senior adults. Considering the frequent complexity of geriatric patients and their underrepresentation in randomized studies^[8], surgical decisions made on an individual basis are increasingly more important. Surgical treatment is a potential promoter of permanent disability in elderly patients, but this is mainly the case for vulnerable and frail individuals^[9]. We therefore reviewed the key elements of personalized surgical management for CRC in the elderly population (Table 1).

PREOPERATIVE CONSIDERATIONS BEFORE CRC SURGERY IN THE ELDERLY

Elderly patients are a heterogeneous population, often presenting with various degrees of coexisting medical and psychosocial issues which need to be weighed before selecting and initiating surgical treatment. Therefore, the importance of a holistic evaluation, a multidisciplinary approach and careful preoperative screening are emphasized as first steps in providing a more tailored approach to ensure the best treatment among different therapeutic strategies. Furthermore, specific considerations regarding the perspectives and expectations of elderly patients regarding CRC surgery are addressed and attention is also focused on prehabilitation, a promising aspect in the onco-geriatric field.

Multidisciplinary approach

One of the greatest challenges of modern medicine is the promotion of close collaboration among the specialists involved in the different aspects of a patient's

management, favoring a patient-oriented approach. This is particularly true within the field of geriatric oncology where the mixture of a disease- and a patient-oriented approach seems to be the most appropriate modality for better treatment of this complex and heterogeneous population. By close interaction, achieved by the creation of multidisciplinary teams, physicians must assess patient malignancy as well as their global health status, including comorbidities, treatment, psychosocial issues, nutritional and functional status.

Close collaboration among specialists has already been attempted in heterogeneous settings; clinical studies have shown the benefits of interdisciplinary team care in both inpatient (*e.g.*, acute care, elective orthopedic surgery)^[10,11] and outpatient management (*e.g.*, fall prevention, functional recovery)^[12,13]. Recent attempts involving a growing interest in collaboration between cancer centers and geriatric departments as regards geriatric oncology have been described^[14]. A multidisciplinary approach, where surgeons work side by side with anesthesiologists, geriatricians, physiotherapists, nutritionists and other ancillary professionals, can provide favorable surgical outcomes (*e.g.*, disability-free life expectancy and overall survival)^[15] through improved selection of candidates for intervention and a more considered exclusion of patients characterized by high risk profiles or a poor prognosis.

Holistic evaluation

In this section, the most important aspects which have a notable impact on the morbidity and mortality rates associated with CRC surgery are discussed in an attempt to obtain an accurate presurgical evaluation. Recently, checklists for the optimal preoperative assessment of the geriatric surgical patient have also been made available in order to pursue an optimal preoperative assessment^[16]. Sarcopenia, with a prevalence ranging from 11% to 50% in the population 80 years of age or older, is often related to the aging process and is recognized to be associated with decreased survival in cancer patients and with an elevated risk of poor outcome in CRC patients undergoing surgical resection^[17,18]. A recent study by Lieffers *et al*^[19] showed that, in CRC patients 65 years of age and older, sarcopenia was independently predictive of postoperative infections (OR = 4.6; 95%CI: 1.5-13.9), convalescent care (OR = 3.1; 95%CI: 1.04-9.4), and significantly associated with a prolonged length of hospital stay (15.7 ± 9.8 d *vs* 11.8 ± 6.4 d for non-sarcopenic patients).

Impaired nutritional status is a common finding among elderly patients, especially among those admitted to hospital^[20]. It is estimated that 40% of elderly hospitalized patients with cancer are at risk of malnutrition, which has been found to be associated with prolonged hospital stays, and increased morbidity and mortality in patients undergoing elective gastrointestinal surgery. Sun-gurtekin *et al*^[21] preoperatively assessed the nutritional status in 100 patients undergoing major abdominal surgery using different assessment tools and found that malnourished patients were at a higher risk of complications, with

Table 1 Key elements of personalized surgical management for colorectal cancer in the elderly population

Preoperative considerations before CRC surgery in the elderly
Multidisciplinary approach
Holistic evaluation
Preoperative risk screening tools in surgery
Prehabilitation
Perspectives and expectations regarding CRC surgery
Personalized surgical management of colon cancer in the elderly
Stage I-III colon cancer
Stage IV colon cancer
Malignant bowel obstruction in the elderly
Laparoscopic approach for colon cancer in the elderly
Personalized surgical management of rectal cancer in the elderly
Specific considerations regarding morbidity and mortality
Functional results
Laparotomy <i>vs</i> laparoscopy for TME
The Habr-Gama effect
Postoperative recovery after CRC surgery in the elderly
Laparoscopic approach and independence
Rapid rehabilitation program
Considerations regarding QoL

CRC: Colorectal cancer; TME: Total mesorectal excision; QoL: Quality of life.

the ORs for the association between malnutrition and complications varying from 1.92 to 9.85 depending on the assessment tool used. Furthermore, higher death rates were found in the malnourished group. Similar findings were observed among gastrointestinal cancer patients^[22]. Regarding CRC patients, Mohri *et al*^[23] found that malnutrition was an independent predictor of poor survival (OR = 2.04; 95%CI: 1.39-3.09) and was significantly correlated with the incidence of postoperative complications, especially serious ones, in a cohort of 365 patients (171 patients > 65 years old).

With a median of 4 comorbidities present at the time of CRC diagnosis, multimorbidity, defined as the occurrence of multiple diseases in the same individual, often affects older patients with CRC. Available evidence clearly indicates that comorbidities are one of the major predictors of surgical morbidity, mortality and survival. Regarding survival, a retrospective study of a cohort of 29733 patients 67 years of age or older with a primary diagnosis of stage I-III CRC showed that comorbidities exert a substantial influence on survival as the predicted 5-year survival in patients with stage I CRC and comorbidities was approximately 50% *vs* 78% for patients with stage I cancer without comorbidities^[24]. Zingmond *et al*^[25] found that, of 56621 CRC patients undergoing tumor resection, those with a higher Charlson comorbidity index (CCI) were significantly associated with postoperative complications. Similarly, Tan *et al*^[26] showed that the CCI was an independent predictor of morbidity in a population of 121 octogenarians undergoing CRC surgery. Similarly, Ouellette *et al*^[27] demonstrated that CCI was associated with a longer length of stay, perioperative mortality, and overall mortality in 239 CRC patients.

Disability is a crucial predictor of a poor postoperative outcome. A recent study identified any functional

dependence to be the strongest predictor of 6-mo mortality in 110 elderly subjects (mean age, 74 ± 6 years) undergoing major surgery requiring postoperative intensive care unit admission^[28]. Cancer patients defined as being functionally dependent according to the validated instrumental activity of daily living were found to have a 2- to 3-fold increased risk of postoperative morbidity compared with those defined as independent^[29,30]. Although for the most part, attention has to be drawn towards the assessment of comorbidities, nutritional impairment and disability, physicians should not forget to focus on elderly psychosocial issues as their presence has been associated with an increased risk of mortality and poor surgical outcome^[31]. Hu *et al*^[32] have recently examined the role of dementia on surgical outcome in 207693 patients 60 years of age or older who underwent inpatient major surgery. The authors showed that patients with dementia had a significantly higher overall postoperative complication rate compared with controls (adjusted OR = 1.79; 95%CI: 1.72-1.86). Finally, despite the fact that the role of depression on surgical outcome in cancer patients undergoing tumor-related surgery needs additional future clarification, presurgical depression has been found to be an important independent contributor to medical morbidity in patients undergoing cardiac surgery^[33].

Preoperative risk screening tools in surgery

The ideal objective of the preoperative assessment of elderly cancer patients should be the correct definition of those who are characterized by frailty, a multifactorial and continuous decline of multiple physiologic systems which still represents a challenge to the surgical community. Studies focusing on older patients undergoing elective cardiac and non-cardiac surgery estimate the prevalence rates of frailty to vary from 41.8% to 50.3%^[9]. Over time, several comprehensive assessment scales have been developed to pursue this goal and to enable risk stratification in cohorts of elderly people. Comprehensive geriatric assessment (CGA), a multidisciplinary diagnostic process which evaluates multiple aspects of the elderly has been broadly used for this purpose within the geriatric oncology setting. There is evidence that abnormalities in preoperative geriatric assessment are strongly related to the occurrence of adverse postoperative outcomes including institutionalization, prolonged length of hospitalization, morbidity and mortality^[30,31,34,35].

Furthermore, a review focusing on frailty in the elderly surgical patient states that frailty is predictive of mortality, postoperative complications and institutional discharge in elderly patients undergoing both cardiac and non-cardiac surgery^[36]. Regarding CRC surgery, a recent study has found that CGA was able to predict surgical morbidity in a cohort of 178 elderly CRC patients where the CGA-defined group of frail individuals was found to be significantly associated with severe complications (OR = 3.13; 95%CI: 1.65-5.92)^[37]. Patients were defined as frail when fulfilling one or more of the following criteria: personal activity of daily living score less than 19, any

grade 4 comorbidity according to the cumulative illness rating scale (or more than 2 grade 3 comorbidities), more than 7 daily medications, a Mini Nutritional Assessment score of less than 17, a poor score on the mini mental state examination (< 24) and on the geriatric depression scale (> 13).

However, two issues need to be carefully pointed out when focusing on frailty. First, despite years of research, the quantification of frailty remains a controversial and complex topic^[38] and second, the use of preoperative geriatric assessment hardly seems applicable in daily practice as it is time consuming. Thus, rapid tools have been developed with the aim of quickly identifying frail patients^[30,39,41]. Among the above-mentioned tools, the timed up and go (TUG) test, a test used to assess a person's gait speed and mobility, seems to be the most promising^[42]. Poor performance on this test correlates with the presence of other aspects of frailty; thus, its use as a rapid and simple means of stratifying preoperative risk in the elderly seems reasonable. Since its introduction, several studies have pointed out a clear correlation between a prolonged TUG and poor functional status, cognitive impairment and fall risk^[43]. Furthermore, a slower TUG test has recently been demonstrated to predict postoperative complications, 30-d readmission, institutionalization and 1-year mortality in a cohort of 272 elderly patients undergoing elective surgery^[28]. Clarifying the role of TUG and other forms of rapid presurgical assessment in the specific field of geriatric oncology is imperative. The international prospective project preoperative risk estimation for onco-geriatric patients (PREOP study) has recently been launched with the aim of providing new evidence regarding the predictive value of these new tools and comparing them with more complex forms of geriatric assessment^[44].

Prehabilitation

Despite modern and sophisticated efforts for decreasing postoperative morbidity and mortality, and facilitating full recovery after CRC surgery, there is evidence that, 6-9 wk after major abdominal surgery, many patients are not back to their active lives^[45,46]. Prehabilitation is a modern strategy, gathering together all the initiatives carried out from the time of diagnosis to the time treatment starts in order to improve functional capacity and functional recovery. Cancer prehabilitation is a novel topic compared with the amount of knowledge of post-treatment rehabilitation programs and outcomes for both cancer and non-cancer patients^[47].

Interestingly, the first study on prehabilitation was published in 1946, describing nutritional and physical training, and even recreational intervention in order to turn the unfit military into robust soldiers ready for the battlefield^[48]. In recent years, cancer patient prehabilitation has become more and more intriguing for surgical oncologists as a result of the great benefits shown in the fields of orthopedic and cardiac surgery, even for the elderly^[49,56]. Medical prehabilitation clearly includes the

management and optimization of preoperative conditions, such as diabetes, cardiovascular function and the promotion of smoking cessation. Moreover, the goal of this strategy should not only focus on muscle strength reinforcement but also on the nutritional and emotional/psychological management of patients undergoing major surgery for cancer. The work that Carli *et al.*^[57] have accomplished in recent years has been of great value in the daily life of clinicians and patients. They actually showed that functional capacity regarding CRC surgery was improved by prehabilitation, whether by adherence to a strenuous preoperative activity schedule (bike and muscle strengthening exercises) or by a 30-min walking and breathing exercise regimen 3 times a week^[57].

On the other hand, many questions are still open as to how older adults undergoing cancer surgery may or may not benefit from perioperative regimens^[58]. The Enhanced Recovery After Surgery (ERAS) guidelines for patients undergoing colorectal surgery have recently clearly defined any potential benefits from a pretreatment regimen as inconsistent^[59]. The ERAS panel basically pointed out the lack of large randomized trials in the CRC field, the low adherence of patients to the prehabilitation regimen and the need for a prolonged time period from diagnosis to surgery (at least 4-6 wk) in order to observe tangible improvement in postoperative outcomes. The majority of confusion regarding the potential usefulness of this intervention comes from incorrect expectations regarding prehabilitation outcomes. What is clear is that prehabilitation is not a substitute for good surgical and tailored postoperative treatment, above all in the elderly. As a consequence, it does not reduce the morbidity and mortality rate. Prehabilitation improves functional recovery and perhaps patient independence and active life expectancy time.

Li *et al.*^[60] recently showed how a trimodal prehabilitation program dramatically changed postoperative functional walking capacity, self-reported physical activity and health-related quality of life (QoL). The randomized trial was designed for CRC patients awaiting surgical treatment and included 30 min of walking and breathing exercises 3 times a week, a nutritional supplement of up to 1.2 g/kg body weight and anxiety reduction techniques. The mean age of the 42 patients enrolled and the 45 patients in the control group was 67.4 ± 11 years; a prehabilitation protocol was carried out for a mean time of 33 d (range, 21-46 d). Interestingly, the patients in the intervention group increased the distance covered at the 6-min walking test during prehabilitation, surpassing the preoperative results of the control group. Four and 8 wk after surgery while control patients' physical ability declined and did not reach their pretreatment level, rehabilitate patients regained the ability to walk farther than their preoperative baseline. The same trajectory was shown for self-reported physical activity while anxiety and depression were shown to be way below the patient baseline 4 wk postoperatively. Even more interestingly, fewer postoperative complications were recorded in pa-

tients who improved their walking ability during prehabilitation while people whose functional capacity declined during the pretreatment time had poorer outcomes. This might help in considering the response to the prehabilitation regimen to be an additional screening tool for elderly patients undergoing surgery for cancer.

Several issues regarding the feasibility and effectiveness of this approach have still not been completely resolved. The lack of time which often forces surgeons to bring elderly patients with CRC to the operating room sooner rather than later because of impending obstruction or perforation might reduce the practicability for a very large number of patients. At the same time, lack of adherence to prehabilitation regimens is indeed higher in the elderly, above all in cases of inconsistent family or financial support. On the other hand, the results obtained before CRC surgery are so promising for restoring active life and independence in this frail group of patients that it may be worth a try, above all, for those patients who are able to wait 4-6 wk before surgery (*e.g.*, neoadjuvant therapy). Good clinical data and larger trials focused on elderly patients are needed to eventually shed light on this fascinating field.

Perspectives and expectations regarding CRC surgery

Patient perspective is essential in establishing a proper understanding of the QoL goals and achieving good postoperative outcomes for senior adults with CRC. Despite the prevalence of CRC in the elderly population and the increasing requirement for QoL measurement, not many studies have been published which focus on patient experience regarding their cancer treatment^[61]. In recent years, some qualitative information has been gained from studies designed for younger patients where “uncertainty”, “fears for cancer recurrence”, “pain”, “fatigue”, “managing on a day to day basis” and “feeling alone” were described as the highest concerns of CRC patients^[62-64]. Mental and physical health seemed to be interrelated in both young and senior adults with cancer as reported by Weaver *et al*^[65], affecting their perspective regarding their disease and the expectations as to the cure they were undergoing.

In an interesting review, Banks *et al*^[66] were able to analyze self-reported questionnaire-based data from 89574 Australian men and women with cancer sampled from the Medicare database. In their study, they were able to conclude that, although approximately 8% of people suffer from severe psychological distress, “the risk of psychological distress in individuals with cancer relates much more strongly to their level of disability than it does to the cancer diagnosis itself”. Disability and lack of independence in the activities of daily living seem to impact cancer patients more than the cancer prognosis *per se*. Unfortunately, the cohort of patients analyzed also included non-CRC patients 45 years of age and older but, despite this, it seemed quite feasible to translate the results to our study population.

Among the possible stressors, having a stoma has

been historically considered as a factor which increases psychological distress in patients with CRC. This fact has also been reconsidered in the past few years. A large meta-analysis on the impact of a stoma forming procedure [abdominal perineal resection (APR) vs low anterior resection (LAR)] on 1443 patients with CRC failed to show a reduction in the QoL of patients with fecal diversion. The mean age in the two groups was 66.3 ± 6 and 65.6 ± 6 years for APR and LAR, respectively^[67]. This important finding was again confirmed by a smaller but more recent study from the Netherlands where no difference was seen in terms of health-related QoL, emotional function and understanding of the illness among elderly rectal cancer patients with or without a stoma^[68]. This may indicate that having a stoma and the risk of incontinence are considered equally troublesome for patients. Regardless of the large amount of literature on the preoperative assessment of onco-geriatric patients, not many studies have been carried out which focus on elderly patients’ needs and expectations before and after CRC surgery.

Patient-centered outcome studies should be implemented in the onco-geriatric field in order to face modern health care system challenges^[69]. Data seem to suggest that disability and lack of independence are considered more important than the cancer diagnosis *per se*. The risk of postoperative disability, and not just the risk of having a fecal diversion, need to be fully discussed with patients and family with the goal of promoting faster functional recovery and regaining independence.

PERSONALIZED SURGICAL MANAGEMENT OF COLON CANCER IN THE ELDERLY

Stage I -III colon cancer

Surgery represents the treatment of choice for stage I to stage III colon cancer^[70]. Given that many advances have been achieved in surgical techniques, anesthesia and perioperative supportive care, it is now accepted that age *per se* is not a contraindication for surgery in senior colon cancer patients^[71], even if it is still hard to overcome the general thinking that a less aggressive and radical approach should be provided for this population^[72,73]. A recent study by Dekker *et al*^[74] described a population-based analysis of 9397 stage I -III CRC patients operated on in the Netherlands from 1991 to 2005. They showed that decreased survival in the elderly is mainly due to differences in early mortality. Elderly CRC patients who survived the first year had the same cancer-related survival as younger patients; therefore, treatment of elderly CRC patients should focus on perioperative care and the first postoperative year.

It is well known that elderly patients have an increased number of comorbidities which leads to a higher rate of morbidity and mortality^[75]. A systematic review including 34194 patients conducted by the Colorectal Cancer Collaborative Group^[76] compared the outcomes of patients

65-74 years of age, 75-84 years of age and those 85 years of age and over with those 65 years of age or younger. The study showed that elderly patients had an increased rate of comorbidities, they were more prone to undergo emergency surgery and they were less likely to undergo curative treatment. Surprisingly, the same review demonstrated that, even if overall survival was reduced, cancer-specific survival was not. The two studies definitely showed that, when carefully selected, even very elderly patients benefit from surgery since a large proportion survive for 2 or more years after surgery^[77]. A study conducted by the Colon/Rectum Cancer Working Group recruited a total of 19080 CRC patients (2932 over 80 years of age) to analyze the impact of the risk factor “age” on early postoperative results. The rate of surgically-specific postoperative complications was identical among younger and elderly patients. Also in this case, elevated morbidity and mortality rates were found to be associated with increasing age due to more cardiovascular and pulmonary adverse events^[77]. Kunitake *et al.*^[78] described outcomes of 83987 elderly colon cancer patients identified in the California Cancer Registry. Octogenarians and nonagenarians had worse outcomes in terms of morbidity, mortality and readmission rates compared with younger patients. An increased number of comorbidities and emergency procedures were found to be consistent risk factors for adverse outcomes while, interestingly, adjuvant chemotherapy and surgery in high volume hospitals were associated with lower odds of in-hospital and 1-year mortality.

Furthermore, a pooled analysis conducted by Sargent *et al.*^[79] provided good evidence to support the fact that 5-fluorouracil adjuvant therapy is well tolerated by elderly patients with benefits comparable to younger patients in terms of overall survival. On the other hand, no benefits from the addition of newer agents (*e.g.*, irinotecan and oxaliplatin) have been shown in large multicenter trials^[80]. Since a correlation with poorer outcomes^[81] is well known, emergency procedures should be avoided whenever possible, always considering bridge solutions to improve performance status.

Stage IV colon cancer

Twenty to 34% of patients with CRC present with synchronous liver metastases, and a higher rate will develop after primary diagnosis. The role of surgery in advanced CRC is limited. Guidelines from the National Comprehensive Cancer Network recommend that patients with stage IV CRC should undergo surgery only if they are symptomatic (*e.g.*, bleeding, obstruction, perforation) or have a potentially resectable metastatic localization. Despite progress in the quality of chemotherapeutic agents, liver resection still remains the only chance for long-term survival in patients with CRC liver metastases.

In recent years, several studies have evaluated the feasibility of liver resection for colorectal metastases. De Liguori Carino *et al.*^[82] analyzed data from 181 liver resections performed on 178 consecutive senior adult patients. The overall survival rate at 5 years was 31.5%. Similar

results were reported by Nagano *et al.*^[83] who reported 34.1% 5-year survival in 202 elderly patients undergoing surgery for CRC liver metastatic disease. An interesting study evaluated the outcome of liver surgery for colorectal metastases in patients over 70 years of age in a large international multicenter cohort^[84]. The elderly were compared to a younger population, and a higher rate of 60-d postoperative mortality and morbidity was found but, surprisingly, the 3-year survival rate was similar in the two groups (57.1% *vs* 60.2% for elderly and younger patients, respectively). Liver resection for CRC metastases in elderly patients can achieve a reasonable survival rate. There should be no upper age limit, but the surgical approach should be planned taking into consideration disease stage, patient life expectancy, performance status and the presence of comorbidities. Benefits related to neo-adjuvant treatment for initially unresectable metastatic disease are still not clear in the younger population; additional data are needed to evaluate possible implications for elderly cancer patients.

Malignant bowel obstruction in the elderly

Bowel obstruction is a frequent presentation of advanced disease, especially in the elderly population^[85]. Right colon cancer only rarely presents with obstructing symptoms and, in those cases, surgical treatment is almost always needed. In contrast, left colon cancer is more frequently responsible for bowel obstruction at presentation and its management has been the subject of debate. Several studies have been undertaken to evaluate non-surgical strategies in malignant left-sided large bowel obstruction. Self-expanding metal stents (SEMS) have been proposed since 1991 as a bridge solution to relieve acute symptoms, improve clinical conditions and allow patients to receive elective surgical procedures and to possibly avoid a stoma. Conflicting data are available on the topic. On one hand, some retrospective analyses have suggested that the use of SEMS in the elderly population is an effective and safe therapeutic option compared with primary emergency surgery^[86] for both elderly and younger patients^[87]. On the other hand, two randomized trials tried to establish whether colonic stenting improved patient outcomes compared with emergency surgery, but neither managed to define a decisive clinical advantage^[88,89]. The randomized controlled trial conducted by Cheung *et al.*^[90] compared a multimodal approach (SEMS positioning followed by early laparoscopic resection) to emergency procedures. The authors concluded that the “endolaparoscopic” approach makes a single stage operation more feasible as it is associated with reduced necessity of a stoma.

Another prospective, randomized controlled trial concluded that SEMS as a bridge to elective surgery (performed after 5-7 d) is associated with lower morbidity, a shorter hospital stay, and equally good long-term survival^[91]. Despite this evidence, a recent Cochrane review concluded that the use of colonic stents in malignant CRC obstruction seems to have no advantage in terms of

early mortality and morbidity rates compared with emergency surgery^[92]. Additional randomized trials focusing on large sample sizes are needed to achieve clearer evidence regarding the role of SEMS in the elderly population.

Laparoscopic approach for colon cancer in the elderly

In order to face the frequent poor performance status and the elevated number of comorbidities characterizing the elderly CRC population, surgeons have investigated a wide range of possible solutions for improving outcomes. In the last 15 years, several peer-reviewed studies have been published evaluating the feasibility, safety and advantages of the laparoscopic approach for colonic cancer in elderly patients. The vast majority have illustrated that, in the elderly population, minimally invasive surgery reduces overall mortality and morbidity when compared to a laparotomy, and correlates with a shorter hospital stay and faster functional recovery. Furthermore, it has been clearly demonstrated that postoperative outcomes in the elderly did not significantly differ from those of younger CRC patients.

Many studies focusing on postoperative mortality have been published pointing out favorable short-term results, but the majority of them are characterized by a vast heterogeneity in terms of colorectal pathologies including inflammatory bowel diseases, diverticular disease and functional diseases^[93,94]. Some of them emphasized similar or even lower short- and long-term mortality rates among patients undergoing elective laparoscopic surgery compared with those undergoing a laparotomy^[95,96]. Interestingly, a 10-year retrospective study conducted by Cheung *et al*^[97] analyzed long-term survival with a median follow-up of 24 mo in a population of 101 octogenarians who underwent elective laparoscopic surgery for CRC. The overall 5-year survival rate was 51%, slightly less than other reports referring to the general population, but still a noteworthy result. It should also be noted that, in the same study, more than half of the deaths were caused by non-cancer-related conditions, such as coexisting cardiopulmonary diseases.

It is common knowledge that laparoscopic colectomies performed in the neoplastic elderly population are associated with higher rates of complications^[98]. Data retrieved from a large prospective, observational multicenter study conducted by the Laparoscopic Colorectal Surgery Study Group including 4823 CRC patients (909 treated laparoscopically) showed that intraoperative and postoperative complications were equally distributed among cancer patients over 75 years of age and younger patients^[99]. In particular, no differences were observed regarding anastomotic leaks and the re-operation rate. Cardiac and pulmonary events are the most frequent non-surgical complications and they are often caused by a presurgical coexisting morbidity (*e.g.*, chronic heart failure, atrial fibrillation, chronic obstructive pulmonary disease). A paper presented by Law *et al*^[100] found that cardiopulmonary complications were markedly fewer in patients who underwent laparoscopic surgery. This trend

was even clearer in patients with concurrent preoperative cardiopulmonary pathological conditions.

A remarkable study conducted by Senagore *et al*^[101] illustrated that cardiac and pulmonary postoperative complications were higher in patients 70 years of age or older who underwent open colorectal surgery compared with those who underwent laparoscopic procedures. Moreover, the same study showed that, among those who underwent laparoscopic surgery, the observed morbidity rate was much lower than that predicted by the Physiological and Operative Severity Score for the enumeration of Morbidity and Mortality; the same results were not achieved within the open surgery group, confirming the observed general trend of lower unexpected events with a minimally invasive approach. As previously mentioned, short-term postoperative death in elderly patients is principally caused by non-surgical complications. Thus, reducing this risk will inevitably produce better outcomes. Laparoscopy seems to be markedly effective in achieving this result as the systemic stress induced by the minimally invasive technique appears to be better tolerated^[102]. Data regarding intraoperative blood loss and functional recovery are extremely explanatory in confirming this issue; several studies found less bleeding and faster recovery in elderly patients undergoing laparoscopic resections^[103-106]. Moreover, this minimally invasive approach has been demonstrated to have better results in terms of postoperative pain, allowing physicians to decrease the use of narcotics and opioids, resulting in a decreased risk of postoperative delirium and, consequently, in shorter hospital stays. Nowadays, laparoscopic colonic resections should be mandatory in the elderly neoplastic population due to the massive evidence of advantages related to this approach^[107]. Laparoscopy allows onco-geriatric surgeons to drastically decrease the rate of postoperative complications related to surgery and comorbidities, giving the patients a better chance of fast recovery and long-term survival. There is no longer any need for concern when offering a minimally invasive approach to the elderly population.

PERSONALIZED SURGICAL MANAGEMENT OF RECTAL CANCER IN THE ELDERLY

The management of elderly patients with rectal cancer is frequently influenced by many factors which lead to undertreatment with consequent poorer outcomes as demonstrated in a study performed by Chang *et al*^[108] in a group of 21390 patients identified in the Surveillance, Epidemiology, and End Results database (1991-2002). The authors found a decreased use of multimodal treatment, an increased use of local excision and a decreased use of radical surgery. The study also showed that the rectal cancer-specific survival rates decreased as patient age increased. Many surgical and non-surgical options are available for rectal cancer patients. Careful pretreatment

assessment in order to identify fit, vulnerable and frail patients should be routinely incorporated into daily practice, especially in this subgroup of elderly patients with rectal cancer. The main goal is to avoid undertreatment in the fit and to plan personalized management for vulnerable/frail patients.

Specific considerations regarding morbidity and mortality

Despite the fact that individuals over 75 years of age comprise 8%-10% of the overall population, 35%-45% of patients with rectal cancer fall into this subgroup of patients, with an incidence of approximately 135 new cases per 100000 people in the group from 80 to 85 years of age^[109-111]. Surgery is still the cornerstone for the treatment of these patients. Regardless of the increased risk of postoperative complications, 5-year cancer-specific mortality is comparable to that of younger patients, emphasizing the similarity of the intrinsic prognosis of the disease^[112-114]. Two interesting multicenter studies have confirmed that the increase in postoperative morbidity and mortality (from 0.5% in patients under 50 years of age to 13% in patients over 80 years of age) is not related to age *per se*^[115,116]. As expected, according to the American Society of Anesthesiology (ASA) score, emergency surgery, low rectal cancer and advanced tumor stage were responsible for the higher number of postoperative complications. Unfortunately, elderly people with advanced cancer and in a setting of several comorbidities are more prone to undergo emergency surgery. This amount of evidence reinforces the idea that age is not an indication of a poor prognosis but that biological age (also interpreted as diminished functional capacity) is.

Since low rectal cancer is related to an increased risk of complications, interest has been drawn towards understanding the impact of age on postoperative complications. Two studies by Rutten *et al*^[109,117], analyzing postoperative complications in elderly patients from a Dutch trial, pointed out an unusual finding: anastomotic leak risk was about 10% in people over 75 years of age and 12% in younger patients ($P = 0.63$) but, after 6 mo, more than half of the elderly patients (57.1% *vs* 8.2%) who experienced an anastomotic complication died. Six-month mortality was 22.9% overall *vs* 7.0%, (relative risk: 3.27; 95%CI: 2.05-5.21) among elderly patients who had a postoperative complication (*e.g.*, sepsis, abscess, cardiac and pulmonary complications) compared with younger patients. Once more, this finding demonstrates that postoperative complications are not tolerated very well by elderly patients, therefore, pointing out the importance of accurately monitoring the postoperative course in this patient population.

Functional results

Rectal cancer surgery has two main endpoints: locoregional control and functional results including sphincter, urinary and sexual functions. A clear and realistic description of the possible consequences of the surgical procedure should be explained to patients and caregivers before planning treatment.

Several studies have added data regarding functional results after sphincter-saving surgery in the elderly. Dehni *et al*^[118] examined the long-term functional results of a small group of elderly patients compared with young people in whom LAR and colono-anal J-pouch anastomosis were carried out. The elderly patients reported more constipation and use of laxatives or enemas but the difference with the younger counterparts was not statistically significant. Furthermore, 91% of patients over 75 years of age were satisfied with their functional results. Both Phillips *et al*^[119] and Hida *et al*^[120] found that elderly patients experienced the same or even more satisfaction in their bowel habits and sphincter function compared with younger patients.

More interestingly, Ito *et al*^[121] prospectively explored the risk factors for fecal incontinence (the Wexner score was used) on 96 patients with poor anal function after restorative rectal surgery. Surprisingly, in univariate analysis, age did not correlate with poor sphincter function while only the extent of the sphincter excision and preoperative chemoradiation therapy did. Impressive data are also available regarding the tendency of a diverting ostomy takedown after LAR in the elderly population. The Dutch trial, including 924 patients who underwent LAR, showed that, of the 616 patients on whom an ostomy was performed during surgery, 19% still had a bowel diversion after 7.1 years of follow-up, and that age was a significant risk factor associated with the decreased likelihood of having their stoma reversed^[122]. Advanced age and comorbidities were again significant risk factors for not having a loop ileostomy reversed in a cohort of 964 patients analyzed by David *et al*^[123] where 233 (24.9%) patients still had an ileostomy bag after a 3-year minimum follow-up. All these data should increase the evidence that age is not a contraindication for radical restorative rectal surgery but that the frailty and functional capacity of individual patients should be weighed when major surgery for rectal cancer is planned in this cohort of patients^[124]. When neoadjuvant treatment is considered for rectal cancer, clinicians and patients should be aware that combined treatments are associated with considerable late side effects on bowel and anorectal functions, especially in terms of bowel frequency, urgency and fecal incontinence. Bruheim *et al*^[125] explored long-term morbidity and QoL after radiotherapy (50 Gy) and total mesorectal excision (TME) for rectal cancer in a national cohort of 535 Norwegian patients. The study showed that radiation-treated patients experience considerably worse long-term effects on anorectal function (in terms of bowel frequency and incontinence) compared with non-radiation-treated patients with an impaired QoL.

Laparotomy vs laparoscopy for TME

Laparoscopic rectal surgery is an advanced major procedure and should be performed in dedicated centers by highly trained surgeons in both elderly and younger patients^[126]. No randomized trials have explored the dif-

ferences in short- or long-term outcomes, functional results or QoL specifically in the elderly population, as the mean age of the patients included in those studies has been shown to be not over 69 years of age^[127]. Of the few dedicated studies, Akiyoshi *et al*^[128] cleared the way for additional and more structured, multicenter trials. They prospectively analyzed a single center in which 315 patients were operated on for rectal cancer from 2001 to 2008. A comparison was carried out regarding 44 patients over 75 years of age who underwent laparoscopic TME (Group A), 228 over 75 years of age who underwent the same procedure (Group B) and 43 patients over 75 years of age who had their TME performed in the standard open fashion (Group C). Both the oncological results (distal margins, circumferential margins and number of lymph nodes retrieved), and the postoperative morbidity and mortality did not statistically differ in the three groups despite significant differences in the ASA score. The restoration of bowel function and length of stay were both in favor of the laparoscopic group ($P < 0.0001$ and $P < 0.002$, respectively), reinforcing the benefit of a laparoscopic approach. Furthermore, elderly patients actually seemed to benefit more from the laparoscopic approach in terms of postoperative cardiovascular and pulmonary complications^[128]. No conclusive assumption could be drawn regarding this topic but the available evidence seems to show that laparoscopy, when performed in high volume centers, is feasible and effective for elderly patients with rectal cancer^[124].

Habr-Gama effect

Neoadjuvant chemoradiation treatment (CRT) has been shown to be responsible for significant tumor regression and local recurrence rate reduction^[129,130]. The result of medical treatment has been so remarkable that Dr. Habr-Gama set the bar at a higher level and decided not to operate on patients having a complete clinical response (cCR) after CRT^[131]. The same group of scientists has recently published a paper on watchful waiting in a series of 70 patients with cT2-4, cN1-2 low rectal cancer who underwent extensive CRT (54 Gy + 6 cycles of 5-fluorouracil and leucovorin)^[132]. Of the 47 patients with a complete clinical and radiological response, 8 (17%) experienced an early recurrence after 16-50 wk of follow-up. Late recurrence was instead recorded in 4 out of 39 patients with a cCR after 13-35 mo from CRT. All these patients underwent R0 radical surgery; no recurrence was recorded after 25.5 mo of mean follow-up. Overall, 35 patients (51%) did not require any surgical treatment and they were free from disease after 56 mo of a median follow-up. The mean age of the patients in the study was 60.2 ± 12.9 years old; thus, the study was not specifically addressed to elderly patients.

Despite the lack of focus on rectal cancer, in senior adults, this might be an intriguing solution for patients considered unfit for surgery after a multidimensional/multidisciplinary assessment. The difference from the past is that this will not be considered a palliative solution but standard treatment with perhaps more than a 50%

chance of curing frail elderly patients with rectal cancer. Following the same pathway, the same group designed a different approach for those patients who partially responded to CRT (ypT0-2, N0) and they performed transanal endoscopic microsurgery (TEM) in 27 patients to partially remove the rectal wall (containing the cancer) instead of classic TME radical surgery^[133]. Nine patients had a recurrence after a median follow-up of 15 mo (5 with exclusively systemic relapse and 4 with local relapse). The TEM specimens of 3 patients had shown ypT2 cancer while one patient with local recurrence was previously staged as ypT1. At univariate analysis, initial tumor size and lymphovascular invasion were found to be associated with local recurrence while, in the multivariate analysis, only the lymphovascular invasion remained (OR = 21.9; 95%CI: 1.3-362.9) statistically significant. The conclusion by the authors, subsequently emphasized by other reviewers, was a “word of caution” on both patient selection^[134] (choosing the patients with no cCR is equivalent to choosing those with the highest risk of not surviving) and the treatment itself. Again, the study was clearly not designed for elderly patients (perhaps unfit for major surgery) but it should be considered an interesting start within a promising application regarding frail elderly patient care.

POSTOPERATIVE RECOVERY AFTER CRC SURGERY IN THE ELDERLY

After surgery, the functional recovery of elderly patients is defined as the ability to regain physical mobility, feeding capacity (swallowing, bowel function, performing the necessary movements to bring the food to the patient's mouth) and the attitude of being independent in the activities of daily living. Postoperative memory loss and delirium after general anesthesia and hospitalization have also been widely feared by elderly patients and their caregivers. Several attempts have been made to reduce the risk of postoperative delirium but, unfortunately, no effective strategies have been identified. In a recent study, Hempenius *et al*^[135] designed a dedicated geriatric multidisciplinary approach for patients with solid cancer. Unfortunately, the randomized trial failed to demonstrate any advantage in patients who were treated with a multimodality approach compared with standard care. Several strategies have been promoted in order to achieve early functional capacity after major oncological surgery, beginning with the preoperative period, continuing with less invasive surgical techniques and, subsequently, postoperative strategies.

Laparoscopic approach and independence

The laparoscopic approach for CRC elderly patients has previously been discussed. Two additional papers are mentioned as examples. The first is by Frasson *et al*^[107] who specifically focused on functional recovery after laparoscopic surgery and the specific benefits for the elderly. They analyzed a series of 535 patients with colorectal dis-

ease randomly assigned to laparoscopic ($n = 268$) or open ($n = 267$) resection. The CRC patients represented 78.5% of the entire sample ($n = 420$). Within the two groups, the outcomes of young patients (under 70 years of age) were compared with those obtained in patients over 70 years of age. The authors concluded that laparoscopy should be considered as the first option in elderly patients as it improves the preservation of functional status permitting a higher rate of postoperative independence at discharge and faster postoperative recovery. Notable advantages obtained from a laparoscopic approach compared with open surgery were ultimately more pronounced among the elderly than in younger patients. Stocchi *et al.*^[106] were also able to demonstrate that independent status at admission (assessed in 37 patients undergoing laparoscopic-assisted colectomy and 38 undergoing open colectomy) was more frequently maintained at discharge in those undergoing laparoscopic-assisted colectomy (95% *vs* 76%, respectively, $P = 0.025$).

Rapid rehabilitation program

As is well known, fast-track programs include preoperative patient education, no routine bowel preparation, minimal perioperative starvation, early removal of the nasogastric tube and urinary catheter, tailored anesthesia and postoperative analgesia, early postoperative diet intake and mobilization with minimal fluid infusion. The literature suggests that elderly patients have an advantage in functional recovery if enrolled in a fast-track program. Baek *et al.*^[136] analyzed a group of 337 patients (87 over 70 years of age and 250 under 70 years of age) who underwent laparoscopic colorectal surgery with a perioperative fast-track program. No significant differences were observed in terms of return of flatus, stool passage, progression of diet, complication rate (26% in the elderly patients *vs* 32% in the young patients) and length of hospital stay (12 d for each group). These results were obtained regardless of a significant differences between the two groups when considering age, presence of comorbidities (70% in the elderly *vs* 44.7% in the younger patients) and ASA score. In particular, they observed a lower than expected cardiopulmonary complication rate which they acknowledged was most likely due to the use of a low-pressure pneumoperitoneum (8 mmHg). The only significant differences were observed in readmission rate and emergency room visits (11.7% *vs* 4%, respectively).

Pawa *et al.*^[137] achieved similar results, with a median length of stay of 6 d for a 558 patient group under 80 years of age while a total of 8 d was recorded in a cohort of 130 patients 80 years of age or older ($P = 0.363$). No significant differences in 30-d readmission rate (8.6% of the whole population) were observed in the study. Senagore *et al.*^[101] compared the benefits of an open *vs* a laparoscopic colectomy among elderly (≥ 70 years old) and young patients (< 60 years old) in a fast track program [Controlled Rehabilitation with Early Ambulation and Diet (CREAD) program], and concluded that the

association of CREAD and the laparoscopic technique gives better results in terms of length of stay, hospital costs, readmission rate and reoperation rate for both elderly and young people. Similar results were reported by Keller *et al.*^[138] who prospectively analyzed a group of 302 patients under 70 years of age compared with a group of 153 patients over 70 years of age. Wang *et al.*^[139] randomly divided an elderly patient group undergoing laparoscopic colon resection into a fast-track rehabilitation group ($n = 40$) and a conventional care group ($n = 38$); they concluded that the main advantages were a shorter length of hospital stay and a lower complication rate for patients in the fast-track group. We can conclude that fast track protocols are not only feasible but they also have notable advantages in elderly patients compared with younger patients. Elderly cancer patients greatly benefit from the avoidance of bowel preparation (associated with hydro-electrolyte imbalances) and opioid restriction (associated with ileus, nausea and vomiting). Furthermore, encouraging early ambulation avoids the risk of prolonged bed rest.

Considerations regarding QoL

Personalized treatment for elderly patients with CRC include not only the main goal of obtaining prolonged survival but also the achievement of a satisfactory QoL. Few studies have analyzed the QoL after surgery for CRC in senior adults. Mastracci *et al.*^[140] administered a generic test (Short Form-36) and two specific questionnaires to measure the QoL after medical and surgical treatment for CRC (EORTC QLQ-CR38 and EORTC QLQ-C30) to 29 Canadian patients (mean age, 83.2 ± 2.79 years). The goal was to obtain data regarding their physical function, body pain, social functioning, vitality and general health perception. Only patients who were able to complete the questionnaire were included in the study (possible bias) and a comparison was made with a similar group of randomly chosen 65-70-year-old patients ($n = 29$). There was no statistically significant difference between the groups in mean scores for body image, future perspective, sexual function/enjoyment, gastrointestinal symptoms and weight loss. The domains which differed significantly among the two groups were physical functioning, functional role, micturition, and stoma-related problems. Authors ascribed these differences to natural senescence, with the exception of stoma-related problems.

An interesting prospective multicenter study by Scarpa *et al.*^[141] analyzed the QoL of elderly *vs* younger patients undergoing colorectal surgery. A total of 116 patients were enrolled in this study: 33 patients over 70 years of age had a laparoscopic colectomy whereas 24 had an open colectomy; 44 patients under 70 years of age had a laparoscopic colectomy and 15 of them had an open colectomy. They used three questionnaires regarding generic (EORTC QLQ-C30) and disease-specific QoL (EORTC QLQ-CR29), and treatment satisfaction (EORTC IN-PATSAT32). They showed that elderly patients undergoing a laparoscopic colectomy for can-

cer experienced fewer postoperative local complications than elderly patients undergoing an open colectomy. Nevertheless, in the first postoperative mo, these patients experienced a poorer QoL compared with younger patients undergoing the same surgery ($P = 0.003$), with impairment of all functions and the presence of fatigue, sleep disturbance, appetite loss and shortness of breath. In the laparoscopic elderly patient group, there were no significant differences in satisfaction or QoL, despite a lower postoperative complication rate compared with the elderly open surgery group. Finally, Amemiya *et al*^[142] prospectively analyzed 223 patients over 75 years of age operated on for CRC ($n = 132$) and gastric cancer ($n = 99$). They administered the Short Form-12 and EuroQoL 5-D tests at 1 wk, 1 mo, 3 mo and 6 mo after surgery. The QoL measured at 1 wk and 6 mo showed a significant improvement ($P < 0.005$). Functional recovery and activities of daily living status improved after surgery in the majority of patients; however, a temporary or prolonged decline in recovery was found in those who developed postoperative complications.

CONCLUSION

Aging of world populations is occurring, and especially in Western countries. Becoming old means being less and less independent from a number of perspectives. Among the various causes leading to a decrease in functional capacity, declining health plays a pivotal role. Aging in the populations of Western countries is becoming one of the most significant challenges for our health care systems. Elderly patients have multiple comorbidities, and unpredictable social and family situations; when cancer is diagnosed, this adds to an already complicated situation. Among the elderly, those who are vulnerable or even frail are the ones who really deviate from the standard curves.

Despite aging in Western countries and the clear challenge for healthcare professionals and scientists, few studies have specifically been designed to assess the success of care strategies in this cohort of patients. Elderly people do not fit into randomized control trials and, in many cases, the results obtained from observation studies (as often happens in elderly population) are considered level B/C evidence by the scientific community. This is quite surprising if we consider one of the most frequent causes of cancer-related death in the elderly population: colorectal cancer. Why should we focus our attention on complicated, demanding, unconventional, non-reducible-to-the-standard-practice type of patients who are historically considered less amenable to curative treatment because of their age? The elderly in Western countries who have CRC have a worse prognosis than younger patients; but this is true only during the first 12 mo after surgery while 5-year cancer-related survival does not differ from the rest of the population which is healthier and has access to more sophisticated treatment. We have to focus our attention on that period of time. Our review showed that, as physicians, the only answer we can give is to implement strategies for personalizing the treatment

of the elderly with cancer. Individualized care does not mean being subjective. Many studies have defined rigorous pathways, screening tools and tailored surgical and postoperative strategies in order to obtain this goal. The multidimensional/multidisciplinary approach is the key for rejecting “the gut-feeling type of decision” and for promoting optimal individual patient care. Our review showed how sarcopenia (measured both directly and indirectly with TUG or a 6-min walk test) seems to be the best predictor for postoperative outcomes. Prehabilitation, despite the lack of large randomized clinical trials, has been shown to be a promising start in reducing the most worrisome complication for an elderly individual: the loss of independence. At the same time, less invasive surgery is being implemented in order to reduce pulmonary and cardiologic complications and eventually the length of stay, such as the advanced laparoscopic approach. During the postoperative period, fast track strategies are extremely beneficial for the elderly who have shown positive results with reduced amounts of opioids, early mobilization and oral feeding. Intriguing solutions have also been described for a non- or local-surgical approach to low rectal cancer and, despite the lack of specific trials, it could be an interesting solution to be offered to frail individuals who cannot undergo a standard approach. Therefore, why should we treat these challenging, complicated, demanding, unconventional elderly patients with cancer? This review cannot provide the profound answer that we need to give as physicians and human beings. This study was carried out to reveal the evidence in the current literature in order to help whoever decides to assist these frail patients and devote their professionalism to rediscovering the true essence of Medicine: personalized care for the patient.

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