Role of surgery for colorectal cancer in the elderly

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Abstract

The prevalence of subjects with colorectal cancer is expected to grow in the next future decades and surgery represents the most successful treatment modality for these patients. Anyway, currently elderly subjects undergo less elective surgical procedures than younger patients mainly due to the high rates of postoperative morbidity and mortality. Some authors suggest extensive surgery, including multistage procedures, as carried out in younger patients while others promote less aggressive surgery. In older patients, laparoscopic-assisted colectomy showed a number of advantages compared to conventional open surgery that include lower stress, higher rate of independency after surgery, quicker return to prior activities and a decrease in costs. The recent advances in chemotherapy and the introduction of new surgical procedures such as the endoluminal stenting, suggest the need for a revisitation of surgical practice patterns and the role of palliative surgery, mainly for patients with advanced disease. In this article, we discuss the current role of surgery for elderly patients with colorectal cancer.

Key words: Laparoscopy; Colorectal cancer; Elderly; Comorbidities; Colorectal surgery

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Core tip: Age itself should not be considered as a risk factor for the development of complications in patients undergoing surgery for colorectal cancer. Many studies underlined that age is not a predictor of post operative complications in these patients. Therapeutic or palliative surgery should not be avoided in the elderly based exclusively on age.
INTRODUCTION

Colorectal cancer (CRC) represents the third most commonly diagnosed cancer in developed countries, with almost 694000 deaths estimated to have occurred in 2012[1]. The prevalence of elderly subjects with CRC is expected to grow in the next future decades due to the increase of age in the general population[2]. In fact, CRC is infrequently diagnosed before age of 40, with a highest risk around age of 70.75% of CRC are identified in patients aged 65 years or older[3]. In both Europe and United States approximately 50% of CRC patients are older than 70 years of age and in this age group CRC is the second most common cause of cancer death[4,5]. Thus, age could be considered as a major risk factor for the development of this cancer[6].

Many studies showed that surgical approach represents the most successful treatment modality for patients with CRC. Over the past years it has been observed an improvement in the survival of subjects with this cancer mainly due to a reduction in operative mortality and a raising in the resection rate[7]. However, there is significant evidence that elderly subjects undergo less elective surgical procedures than younger patients[8] mainly due to the high rates of postoperative morbidity and mortality[9].

IMPACT OF AGE ON CRC SURGERY

There is a lack of consensus on the impact of age on postoperative outcome after major colorectal surgery. In fact, comorbidities are higher in elderly subjects thus leading to difficult decisions whether these patients are suitable for extensive bowel resection or not. A review of the literature published in the Lancet in 2000 pointed out that elderly patients are less likely to have curative surgery than younger patients[10].

In 2008, the International Society of Geriatric Oncology (SIOG) created a task force to develop guidelines for the treatment of elderly patients with CRC[11]. The task force confirmed the paucity of clinical trial data in the elderly and pointed out that treatment for elderly CRC patients should be analogous to those of younger patients.

A registry-based study carried out by Damhuis et al[12] on 6457 patients with CRC, evaluated the influence of age and other variables on resection rates and operative risk. All subjects included in the study were enrolled from 1985 through 1992 in hospitals connected to the Rotterdam Cancer Registry. Data analysis showed that 87% of the patients underwent resection but resection rates were lower for patients older than 89 years (67%) and for patients with rectal cancer (83%). Patients younger than 60 years had a postoperative mortality rate of 1% that constantly increased with age. Patients 80 years and older showed an operative risk of 10%. Multivariate analysis was conducted and pointed out that gender, age, cancer subsite and stage could be considered as independent prognostic factors. The authors concluded that chronological age alone should not be an exclusion criteria for performing surgery in elderly patients with CRC. Even in patients aged over 90 years, resections can be performed with acceptable risk.

Another study[13] analysed the electronic records from the Rotterdam Cancer Registry for octogenarians and nonagenarians who underwent resection in the period 1987-2000. The results showed that for CRC, postoperative mortality rates increased from 8% in patients aged 80 to 84 years, to 13% in patients aged 85 to 89 years and to 20% in nonagenarians.

A systematic review of 28 independent studies and 34194 patients, carried out by the Colorectal Cancer Collaborative Group, analysed the results for different groups of patients aged 65-74 years, 75-84 years and 85+ years with those for patients aged < 65 years. Compared with younger subjects, elderly patients have an increased frequency of comorbid conditions, are more likely to present with later-stage disease and undergo emergency surgery[14]. Moreover, many studies focused on the role of adjuvant chemotherapy, demonstrating that elderly are less likely to be recommended or to receive adjuvant treatment[15].

COMORBIDITIES AND COMPLICATIONS

Traditionally, contraindications for major surgery in elderly patients include a poor functional status, associated comorbidities and impaired cognition[16]. Anyway, in the last 30 years elderly patients with CRC took advantage of healthcare progress and a retrospective trend analysis showed a reduction of palliative procedures and a decline in operative mortality for these patients[17].

Most elderly patients with CRC have significant comorbidities such as cardiovascular and pulmonary diseases. Such diseases increase the operative risk and the risk of postoperative morbidity and mortality[18,19]. A study by Hermans et al[20] evaluated the impact of comorbidities on the outcome of colonic surgery in elderly patients with colon cancer. Comorbid assessment tools provide helpful information on the impact of comorbidities at the initial diagnosis and prospective outcome of CRC patients due to their prognostic capacity on survival. According to the classification of Charlson et al[21], the evaluated comorbidities included previous malignancies, chronic obstructive pulmonary disease, cardiovascular disease, cerebrovascular disease, hypertension, diabetes, and others (rheumatoid arthritis, hyperthyroidism, hypothyroidism, and scleroderma). Compared to younger
age, elderly subjects presented with more cardiovascular pathology and dementia and with more than one type of the previously described comorbidities. The authors concluded that the type and number of co-morbidities influence post-operative mortality and morbidity. Complications were seen in 24% of younger patients vs 50% of elderly patients. No difference was observed as regards major complications (e.g., anastomotic leakage, fascia dehiscence, or intra-abdominal abscesses). In the elderly group there was a high incidence of delirium, pneumonia, wound infections, and minor complications such as urinary tract infection, and electrolyte alterations. Other factors that may cause poor outcome of surgery in the elderly include delayed presentation and advanced stage of the disease\textsuperscript{[19,20]}

As regards preoperative factors that could influence the choice of treatment, Marventano et al\textsuperscript{[19]} proposed a modified version of the Charlson comorbidity index (CCI) that was specifically developed for colorectal cancer patients. This version of CCI emphasized the importance of specific conditions to better predict the survival of the patients. Particularly, the inclusion of 6-mo weight loss \(\geq 20\%\), smoking > 20 cigarettes/d, underweight condition, and cardiac arrhythmias to the other comorbid conditions tested in the CCI showed a better predictive value compared with the original CCI and other comorbidity indices (e.g., the Elixhauser method, the National Institute on Aging and National Cancer Institute comorbidity index, and the Adult Comorbidity Evaluation-27). Noteworthy, the Authors found that only moderate or severe renal disease and diagnosis of AIDS were independently associated with higher risk of death\textsuperscript{[19]}.

An analysis of 31574 patients in the surveillance, epidemiology and end results–medicare database for patients diagnosed with colon cancer between 1992 and 2005 was conducted to describe patterns of surgery in patients aged > 80 years and examine outcomes with and without colectomy. The Authors demonstrated that 80% of the “oldest old” patients with colon cancer in the United States are undergoing surgical resection\textsuperscript{[21]}. In this study, 46% of subjects were diagnosed during an urgent or emergent hospital admission, with decreased 1-year overall survival (70% vs 86% for patients diagnosed during an elective admission). Older age, black race, more hospital admission, use of home oxygen, use of wheelchair, frailty and dementia were most predictive of nonoperative management. The 1-year overall survival rate for both operative and nonoperative patients was lower than the colon cancer-specific survival rate (operative patients: 78% vs 89%; nonoperative patients: 58% vs 78%)\textsuperscript{[21]}

A study by Kahn et al\textsuperscript{[22]} showed that older age is not independently associated with complications after surgery for colorectal cancer. The Authors underlined the importance of clinical status and American Society of Anesthesiologists (ASA) class in patients’ selection rather than age.

**THERAPEUTIC OPTIONS FOR CRC IN THE ELDERLY**

Different approaches to treat elderly subjects with CRC have been proposed over the past years. Some authors endorse extensive surgery, including multistage procedures, as carried out in younger patients\textsuperscript{[23,24]}, while others promote less aggressive surgery\textsuperscript{[25,26]}

Most subjects with stage I or II CRC are treated by surgery, even if some patients with stage II could benefit from adjuvant therapy\textsuperscript{[27,28]}. Surgery followed by adjuvant chemotherapy is the standard treatment for stage III CRC. Subjects with metastases could benefit from chemotherapy alone or combined with targeted therapy. At this stage, surgery is indicated in selected patients. The treatment for stage IV CRC includes surgery and preoperative or postoperative, radiotherapy and/or chemotherapy.

Different factors could influence surgical outcomes in stage IV CRC, including the presence of liver metastases\textsuperscript{[29,30]} and cardiovascular disease\textsuperscript{[31]}, the degree of peritoneal involvement and primary cancer resection\textsuperscript{[32]}, the tumor differentiation, and age older than 75\textsuperscript{[33]}

There is still uncertainty about the effective benefit of surgery directed toward removal of the primary tumor for the management of asymptomatic patients with stage IV CRC and unresectable metastases. Palliative surgery is indicated for most patients with bowel obstruction or uncontrollable bleeding\textsuperscript{[34]}

Guidelines from the National Comprehensive Cancer Network recommend surgical treatment in stage IV CRC only in symptomatic patients at risk of obstruction, or with metastases suitable for potentially curative resection\textsuperscript{[35]}

A study by Temple et al\textsuperscript{[36]} evaluated surgical practice patterns for patients over 65 years of age with stage IV CRC in a United States population-based cohort. They observed that 72% of patients received primary-cancer-directed surgery (CDS) with a 30-d postoperative mortality of 10%. CDS was less performed on patients with left-sided or rectal lesions, subjects older than 75 years, blacks, and those of lower socioeconomic status; but even among those older than age 75, the CDS rate was 69%. Chemotherapy was administered to 47% of patients that underwent CDS vs 31% of patients who did not. The resection of metastases was performed only on 3.9% of patients at any point from diagnosis to death\textsuperscript{[34]}

There is evidence that subjects with stage IV CRC could tolerate chemotherapy without requiring surgery to remove the primary tumor. In fact, a study by Tebbutt et al\textsuperscript{[36]} showed that there were no differences in gastrointestinal complications (e.g., fistulas, peritonitis, obstruction) in patients who did not undergo CDS compared to those who had CDS\textsuperscript{[36]}. The recent advances in chemotherapy and the introduction of new surgical procedures (e.g., endoluminal stenting) suggest the need for a revisitation of surgical practice patterns and the role of palliative surgery for IV stage CRC patients.
Many studies underlined the importance of laparoscopic assisted colectomy (LAC) for the treatment of CRC. However the majority of them were conducted on patients younger than 65 years. In general, LAC showed a number of advantages compared to conventional open surgery that include lower stress, higher rate of independency after surgery, quicker return to prior activities and a decrease in costs\(^{37,38}\).

There are many issues related to the limited number of LAC carried out on elderly subjects requiring colectomy: First of all, the high number of comorbidities; second, the longer operative times; and third, the paucity of scientific literature assessing risks and benefits of this procedure in the elderly. A review of the literature carried out by Mutch\(^{37}\) identified 18 studies on LAC in the elderly. There is significant evidence that LAC could be performed in the elderly population safely and without significant increase in morbidity and mortality\(^{29}\).

A study by Vara-Thorbeck et al\(^{39}\) represents the first report of LAC in older patients. The study was conducted on 18 patients that underwent LAC for CRC. Eleven subjects were older than 70 years. None of the cases were converted to open laparotomy, and the mortality was null. The results showed that LAC could be performed safely on both older and younger patients while maintaining the same principles of surgical technique as open colectomy. A number of more recent studies confirmed that laparoscopy-assisted colectomy in the elderly can be performed with no difference in morbidity or length of hospital stay compared with open surgery\(^{40-44}\). Vignali et al\(^{45}\), compared the outcomes of open colectomy vs LAC in a population of octogenarians. They observed that the patients undergoing LAC had a shorter hospital stay (LAC 9.8 d vs open 12.9 d), reduced morbidity (LAC 21% vs open 31%), and higher rate of independence at discharge (LAC 98% vs open 82%), thus confirming that the benefits of LAC are maintained with advancing age.

A study by Bardram et al\(^{46}\) analyzed the outcomes of laparoscopy combined with a perioperative multimodal rehabilitation protocol in 50 patients of median age 81 years. After LAC, patients were treated with epidural local anesthesia for 2 d, early mobilization and oral nutrition, with a significant improvement in recovery.

O’Connell et al\(^{47}\) pointed out that in frail elderly with limited life expectancy, the benefits of cancer surgery are frequently unclear, and surgical resection of tumors is less performed as the patient ages.

A study by Finlayson et al\(^{48}\) aimed to determine functional status and mortality rates after colon cancer surgery in older nursing home residents. They conclude that even when not curative, surgery for CRC may be an effective palliative procedure. Less invasive treatments, such as endoscopic treatment or embolization of bleeding tumors or the use of endoluminal stents for large bowel obstruction, may represent an alternative to surgery for individuals with limited life expectancy.

The international SIOG expert recommendations, according to the available evidence on CRC in the elderly, suggested that emergency surgery should be avoided when possible; the use of colorectal stents should be taken into account to improve patient nutrition thus facilitating elective surgery 1-2 wk after the patient has presented as an emergency; the pathway of choice should be elective surgery with a prospective analysis of the perioperative variables and careful treatment; possible curative resection of liver metastases should be performed in healthy elderly subjects receiving a careful preoperative assessment and a high quality postoperative care\(^{10}\).

As regards rectal cancer, analysis of 991 treatments, in the 838 elderly rectal cancer patients from the Cote d’Or and Calvados tumor registries study\(^{49}\), showed 54% of patients to undergo curative resection, 7% to undergo palliative resection, 12% to undergo by-pass laparotomy, 27% to undergo no surgery, 17% to receive radiotherapy and 2% to receive chemotherapy. These data highlighted a low use of radiotherapy either combined with surgery or alone, while chemotherapy was almost never administered. Both surgery and radiotherapy are important for controlling local recurrence and therefore local failure rates. Recently the use of the surgical technique total mesorectal excision\(^{50}\) has contributed to a reduction in pelvic recurrences. A study by Kim et al\(^{51}\) assessed the long-term oncological and functional outcomes of intersphincteric resection for T2 and T3 low rectal cancer. The authors observed a 5-year overall survival rates of 95.8% for T2 and of 94.7% for T3. The 5-year recurrence-free survival rates were 87.5% for T2 and 86.8% for T3 (Table 1). Radiotherapy has been shown to impact significantly on survival in resectable tumors\(^{52}\) and is critical for the management of patients with all stages of rectal tumors.

**CONCLUSION**

In general, there are age-related disparities in colon cancer treatment, with older patients being less likely to receive recommended therapy. According to the SIOG guidelines, elderly subjects should receive screening and earlier diagnosis; the management of CRC should be more aggressive and closer to that received by younger patients; the treatment should be the most intensive and appropriate according to the biological age and the presence of comorbidities\(^{10}\). Many studies pointed out that age is not a predictor of post operative complications in patients with CRC\(^{53-56}\). Age itself should not be considered as a risk factor for the development of complications in patients undergoing surgery for CRC. Thus, therapeautic or palliative surgery based solely on age should not be avoided in these patients. In the future, the surgical assessment of CRC in the elderly should take into account a multidisciplinary process before choosing the best possible therapy for each patient. There will be the need for services specialized in the care of at-risk older patients, rehabilitation and palliative care consultation. An appropriate management should also include the functional status, the grade of frailty, the life expectancy and also patient’s requests.
| Ref.                     | Year | No. of patients | Postoperative mortality | Resection rates | Comorbidities | Survival rate | Independent prognostic factors |
|-------------------------|------|-----------------|-------------------------|-----------------|---------------|--------------|-------------------------------|
| Damhuis et al[9]        | 1996 | 6457            | 1% for patients < 60 yr and steadily increased with age. The operative risk was 10% for patients > 80 yr | 87% of the patients underwent resection. 67% for patients > 89 yr and 83% for patients with rectal cancer | -             | -             | Gender, age, subsite and stage |
| Damhuis et al[11]       | 2005 | 2765            | Increased from 8% for the age group 80-84 to 13% for those 85-89 to 20% in nonagenarian | -               | -             | -             | -                             |
| Hermans et al[17]       | 2010 | 207             | In-hospital mortality was 16% in the elderly and 5% in the younger group (P < 0.01) | No differences between < 75 yr and > 75 yr; ileocolic resection (2% vs 4%); ileocolic resection (2% vs 4%); transverse resection (1% vs 3%); hemicolectomy left (15% vs 8%); sigmoid resection (26% vs 22%); anterior resection (10% vs 9%); subtotal colectomy (5% vs 1%); double resection (1% vs 4%) | More co-morbidities > 75 yr, especially cardiovascular pathology (P < 0.01) and dementia (P < 0.01). more than one type of comorbidity according to the Charlson classification (P < 0.05) | 5-yr survival rate in < 75 yr was 62% compared with 36% in the elderly (P < 0.05) | -                             |
| Neuman et al[18]        | 2013 | 31574           | 30-d mortality rate of 10% after urgent/emergent admission | -               | Hypertension, peripheral vascular disease, and chronic pulmonary disease were found to be associated with improved overall and cancer-specific survival | -             | Older age, black race, more hospital admissions, use of home oxygen, use of a wheelchair, being frail, and having dementia |
| Irvin[21]               | 1988 | 306             | The surgical mortality rates for patients > 70 yr were 6% overall, 4% after elective operations, and 16% after emergency surgery; the corresponding mortality rates for patients < 70 yr were 3%, 1%, and 20% | -               | -             | -             | -                             |
| Temple et al[34]        | 2004 | 9011            | The 30-d postoperative mortality was 10%. The 30-d surgical mortality was significantly greater in the no primary cancer-directed surgery (CDS) group among patients who underwent a surgical procedure, when compared with the primary CDS group (26% vs 9%, P = 0.001) | The rates of CDS declined with age: 76% of 65 to 69-yr-old patients received primary CDS, whereas the rate declined to 62% of patients age ≥ 85 yr | -             | -             | -                             |
| Vallribera et al[42]    | 2014 | 277: Laparoscopic group; 268: Open group | Open surgery group showed a higher mortality (6.7% vs 3.2%, P = 0.034). Mortality was significantly inferior in laparoscopy group in younger patients (< 75 yr, 0% vs 3%, P = 0.038) | Open surgery group showed a higher overall morbidity rate (37.3% vs 21.6%, P = 0.001), medical complications (16.4% vs 10.5%, P = 0.033), surgical complications (23.5% vs 15.5%, P = 0.034), the | -             | -             | -                             |
| Study | Year | Patients | Method | Overall Mortality Rate | Overall Morbidity Rate Difference Between Open and Laparoscopy Approach | Other Findings |
|-------|------|----------|--------|------------------------|-------------------------------------------------|---------------|
| Vignali et al | 2005 | 70: Laparoscopic colectomy; 61: Open colectomy | - | Overall mortality rate was 24%. The morbidity rate was 21.5% in the laparoscopy group and 31.1% in the open group (P = 0.30) | - | - |
| Bouvier et al | 2005 | 157 with colon cancer; 838 with rectal cancer | - | During the study period from 8.7% to 95.5% for colon and from 16.3% to 5.6% for rectum | Overall mortality rate was 24% and morbidity rate was 21.5% in the laparoscopy group and 31.1% in the open group (P = 0.30) | - |
| Heald et al | 1998 | 519 with rectal cancer | - | The operative mortality (30-d) was 3.3% | - | 5-yr overall survival rates were 45.2% for colon cancer and 46.2% for rectal cancer. Overall 5-yr survival rates were 40.9% and 37.3% respectively |
| Kim et al | 2016 | 62 with very low rectal cancer | - | No postoperative mortality in both groups | - | No differences in 30-d morbidity except in postoperative bleeding |
| Schiffmann et al | 2008 | 517 | - | 30-d mortality was higher in the older age group (> 75 yr) | - | The overall five-year survival was 68.7% and 57.3% in the younger and older groups, respectively, whereas colorectal cancer-specific five-year survival was not significantly different (74.0% vs 74.7%) |
| Devon et al | 2009 | 898 | - | The in-hospital mortality rate was 1% in the younger group (< 75 yr) compared with 4.2% in the older (> 75 yr) (P = 0.002) | - | Five-year survival rates for older and younger patients were 33% and 45%, respectively (P < 0.05) |
| Paksoy et al | 1999 | 822 | - | The postoperative (30-d) mortality was 3% in the younger group (< 65 yr) (20/565) and 7% in the older group (17/257) (difference not significant) | - | - |
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