

REVIEW ARTICLE

Surgical treatment for colorectal cancer in octogenarians and nonagenarians

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Summary

Advances in surgical techniques and perioperative care have improved cancer-related outcomes. However, there are still concerns regarding the safety of octogenarian and nonagenarian patients during surgery. Clinicians may be reluctant to perform a radical resection for colorectal cancer and administer adjuvant or palliative cytotoxic chemotherapy to octogenarian and nonagenarian patients. In the elderly, setting a primary goal based on multidisciplinary team discussions prior to treatment is important. The overall treatment scheme, risks, and potential benefits should be discussed with elderly patients and their families. In this review, we will discuss multidimensional aspects of colorectal cancer surgery for octogenarian and nonagenarian patients with respect to

age-related physiological declines, preoperative assessments, appropriate surgical procedures, and short-term and oncologic outcomes. In this era of an aging society, clinicians should provide objective evidence to octogenarian and nonagenarian patients regarding estimated short-term and oncologic outcomes. However, there is a limited number of studies concerning outcomes following colorectal cancer surgery in octogenarians and nonagenarians. In the future, a prospective study with a larger cohort would be helpful to collect objective data on octogenarian and nonagenarian patients.

Key words: age 80 and over, colonic neoplasms, octogenarians, rectal neoplasms, surgery, treatment outcome

Introduction

Over the past few decades, life expectancy has increased and aging populations are growing remarkably. In the United States, life table cohort data from 2011 showed that in 1900, only 13.5% of the cohort survived to age 80. However, in 2011, 57.5% survived to 80 years of age [1]. In addition, the life expectancies of individuals at 80 years of age were 8.2 years for men and 9.6 years for women [1]. Colorectal cancer is the third and second most commonly diagnosed malignancy in men and women, respectively, worldwide. Its incidence increases steadily with advancing age [2,3]. The incidence of colorectal cancer was ap-

proximately 40 to 50 per 100,000 persons in a general population over 75 years. In contrast, the incidence was approximately 15 to 20 per 100,000 persons in a population aged 60 to 65 years [4].

Surgery is the established treatment modality for either localized or metastatic colorectal cancer. Advances in surgical techniques and perioperative care have improved cancer-related outcomes in the past few decades [5]. However, there are still concerns regarding surgical safety for octogenarian and nonagenarian patients. Until recently, elderly patients, especially octogenarians and nonagenarians, have been excluded from many clinical trials. Surgical outcomes in octogenarian and nonagenarian patients with colorectal

cancer are available only in a limited number of studies [6-9]. In this era of an aging society, colorectal surgeons are increasingly likely to operate on both age groups patients. In clinical practice, surgeons should provide evidence-based information regarding the risks and benefits of surgery to elderly patients and their care providers.

In this review, we will discuss the multidimensional aspects of colorectal cancer surgery for octogenarian and nonagenarian patients in terms of age-related physiological declines, preoperative assessments, appropriate surgical procedures, and short-term and oncologic outcomes.

Age-related physiological decline

At the time of admission, a patient's chronological age can be calculated based on his/her birth date. The age at which a patient should be classified as elderly is a matter of debate. Several investigators have defined elderly patients as patients older than 65 [10], 70 [11], 75 [12], and 80 [13] years of age. Currently, a significant proportion of the population survives more than 80 years. The life expectancy at birth for the US population was 78.7 years in 2011 [1]. Thus, it is important to investigate outcomes in patients older than 80 years who have not received particular attention in previous medical studies.

Chronological aging induces a progressive reduction in the homeostatic reserve, i.e., homeostasis of whole-organ systems. The aging process influences each individual differently. The degree of aging-related change is closely associated with genetic, dietary, environmental, and lifestyle factors. Aging-related physiological decline increases susceptibility to chronic illnesses. Accordingly, elderly patients have a high probability of suffering single or multiple comorbidities, which lead to unfavorable postoperative outcomes [3].

Aging-related changes in the cardiovascular system include phenotypic changes, such as decreased number of myocytes, fibrosis of the sinoatrial conduction pathway, decreased ventricular compliance, and increased diastolic dysfunction [14]. These changes result in an increased risk of heart failure or arrhythmia. Aging increases the risk for developing hypertension, coronary artery disease, and silent myocardial ischemia [15]. Therefore, age- and disease-related cardiovascular changes impair compensatory function of the heart during the perioperative period in elderly patients.

Aging-related changes in the pulmonary sys-

tem include weakened respiratory muscles, decreased lung compliance and decreased ability to preserve airway protection through swallowing and the cough reflex [16]. Advancing age increases the risk for chronic obstructive pulmonary disease, and the aforementioned changes contribute to atelectasis, (aspiration) pneumonia, and the use of ventilator care during the postoperative period [17]. Aging-related effects of the renal system include decrease of the renal cortical mass, sclerosis of nephrons, decreased renal blood flow, and a decreased glomerular filtration rate [18]. Renal tubular function declines with age, and the ability to control electrolyte and acid-base balances becomes impaired [19]. Even if serum creatinine is normal, clinicians should be aware of underlying decreased renal function in octogenarian and nonagenarian patients.

There are several aging effects on the hepatobiliary system. Morphologically, the liver volume and hepatocyte number decrease. Hepatic blood flow also decreases. However, hepatic function is rather well preserved due to the large compensatory ability of the liver [20].

The stem cell pool in bone marrow decreases with aging, and the production of naïve T cells in the thymus and B cells in the bone marrow is diminished [21]. The life cycle of red blood cells and blood volume are rather well maintained with age.

In elderly patients, impaired immune function contributes to the occurrence of infection during the postoperative period. However, an increased susceptibility to postoperative infections can be attributed to multiple factors, such as surgical stress and other comorbidities, rather than to immune function alone.

Aging-related changes in the central nervous system include decreased brain volume, both in the white and gray matter [22]. Cerebral blood flow decreases with aging. Therefore, aging increases the risk for cognitive impairment [23]. Postoperative delirium is common in the elderly, and cognitive function influences postoperative recovery and rehabilitation.

Preoperative assessment

An appropriate preoperative evaluation of octogenarian and nonagenarian patients includes assessments of medical, surgical, and medication histories, as well as of functional, nutritional, and cognitive status and frailty. It is important to identify the presence of co-existing medical conditions

and the extent of the compensatory capacity of organ systems. Advancing age is associated with an increased risk for comorbid diseases. Operative risk is influenced by both chronological age and comorbidities. Detailed medical and surgical histories should be taken prior to surgery. Clinicians should be aware of a patient's medication history, such as prescription and over-the-counter medications [24], and weigh the benefits and risks of discontinuing aspirin and other antiplatelet agents for underlying cardiovascular disease [25].

There are several methods for preoperatively evaluating functional status, such as the American Society of Anesthesiologists (ASA) score, Karnofsky score, Eastern Cooperative Oncology Group (ECOG) score, activities of daily living (ADL), and metabolic equivalent of task (MET). The ASA classification is a six-category physical status classification system for the assessment of preoperative functional status by surgeons and anesthesiologists. Patients with an ASA score of 1 (healthy) to 3 (severe systemic disease) are candidates for elective surgery in clinical practice. In the medical oncology field, the Karnofsky score or ECOG score are frequently used to determine a patient's performance status when planning chemotherapy [3]. ADLs refer to an elderly patient's daily living activities, such as bathing, feeding, toileting, dressing, and grooming. ADLs can be subclassified as a basic ADL, intermediate ADL (e.g., driving and shopping), and advanced ADL (e.g., leisure and occupational activities) [26]. The MET refers to the ratio of the metabolic rate associated with a certain physical activity to the resting metabolic rate. Higher METs indicate better exercise tolerance [27].

A preoperative evaluation of nutritional status is also important in octogenarian and nonagenarian patients [28,29]. Poor nutrition in elderly patients with colorectal cancer can be explained by the anorexia of aging and cancer cachexia [30]. The anorexia of aging refers to an age-related physiological decline in appetite and dietary intake [31]. Cancer cachexia, which is more common in patients with advanced cancer, refers to a complex metabolic syndrome characterized by loss of appetite and body weight. The resulting catabolic state is associated with the age-related loss of muscle mass and body fat [32-34]. Popular clinical screening tools are a subjective global assessment, the universal malnutrition screening tool, a mini nutritional assessment, and the malnutrition risk scale. The biochemical data reflecting nutritional status have not been clearly elucidated. However,

a low serum albumin level has been shown to correlate with increased complications and mortality rates in the elderly [35].

Advancing age is also associated with cognitive impairment. Cognitive deficit is associated with the occurrence of postoperative delirium and delayed recovery, such as ambulation and dietary intake. It is important to perform standardized assessments to identify the presence of dementia, delirium, and depression in the elderly. Commonly used tests include the mini-mental state examination, abbreviated mental test score, and general practitioner assessment of cognition [36].

Frailty in the elderly refers to clinical geriatric syndrome characterized by involuntary weight loss, self-reported exhaustion, weakness (grip strength), slow walking speed, and low physical activity [37]. The presence of frailty has been shown to correlate with unfavorable surgical outcomes, such as increased complication rates and delayed hospital discharge [38]. A comprehensive geriatric assessment is a multidimensional assessment for elderly cancer patients that aims to identify disabilities and geriatric conditions associated with frailty. In a recent study, the frailty score based on a comprehensive geriatric assessment was a predictor of postoperative outcomes in elderly patients undergoing gastrointestinal surgery [39].

Treatment strategy

In the elderly, setting a primary goal based on multidisciplinary team discussions is important. Clinicians may be reluctant to perform a radical resection for colorectal cancer and administer adjuvant or palliative cytotoxic chemotherapy in octogenarian and nonagenarian patients. The overall treatment scheme, risks, and potential benefits should be discussed with elderly patients and their families. If anticipated, unfavorable functional consequences, such as a permanent stoma or fecal incontinence, should be explained, and a patient's preference should be simultaneously considered. Before we can consider a surgical approach, it is essential to distinguish between the chronological and physiological age of patients. Currently, we are unable to accurately calculate physiological age; however, multidimensional assessments with regard to comorbidity, functional, nutritional, and cognitive status and frailty may guide the selection of more appropriate treatments.

There is no consensus regarding the appro-

appropriate extent of surgery in elderly patients with colorectal cancer. In selected cases, suboptimal treatment is performed based on a patient's willingness or poor functional status. Total mesorectal excision is an established surgical treatment for rectal cancer [40]. However, preoperative chemoradiation therapy followed by local transanal excision can be an option for patients who want to avoid poor bowel function after a radical proctectomy [41]. Omission of a long course of preoperative chemoradiation therapy and a radical resection-only approach is another treatment option for locally advanced rectal cancer. For colon cancer, a complete mesocolic excision in conjunction with a central vascular ligation or D3 lymphadenectomy in Asian countries has been shown to be more effective in terms of oncologic outcomes. However, there are still concerns regarding prolonged operative times and higher complication rates after complete mesocolic excision or D3 lymphadenectomy [42]. Generally, a

D3 dissection is indicated for clinical stage II/III colon cancer [43,44]. However, surgeons should consider the tolerability of a D3 dissection in octogenarian and nonagenarian patients [45]. When considering the higher morbidity and mortality associated with a more extensive surgery, a complete mesocolic excision or D3 lymphadenectomy may be more suitable for younger patients and physiologically fit elderly patients. Combined resections, such as hepatectomy for liver metastasis or pneumonectomy for lung metastasis, carry high risks for perioperative morbidity. However, favorable oncologic outcomes can be expected in patients undergoing R0 resection for metastasis [5]. Selection of the appropriate chemotherapy regimen in an adjuvant or palliative setting is also important. The time to commencement of chemotherapy after surgery is usually delayed compared with that in younger patients. The rate of adjuvant chemotherapy is lower in elderly patients due to various reasons, such as poor performance status,

Table 1. Literature review of colorectal operations in patients aged 80 or more years

First author	Patients, n	Surgical disease	Benign/emergency	ASA \geq 3 (%)	OT (min)	Conv (%)	Diet (day)	LOS (day)	Cx (%)	AL (%)	Mortality (%)	Comments
Wise [51]	0:56	CR	+/+	71	-	-	-	19	52	5	7	ICU (2.84 days)
Stewart [50]	0:35 L:42	CR	+/-	0:49 L:48	-	12	-	0:17 L:9*	0:57 L:17*	0:3 L:0	0:11 L:7	ICU 0:14 L:7*
Ses-hadri [49]	L:62	CR	+/-	-	-	11	-	10	31	-	5	intra-operative Cx 6%
Abbas [52]	0:180	Major abdominal	+/+	63	-	-	-	12	33.3	-	19.4	Survival data
Hamel [53]	26648	Noncardiac	+/+	85.7	-	-	-	-	26.1	-	11.9(189/1595)	colectomy
Turrentine [55]	7696	General, thoracic, vascular	+/+	-	-	-	-	-	49 in octogenarians 61 in nonagenarians	-	6.0 in octogenarians 11.4 in nonagenarians	
Lian [48]	0:97 L:97	CR	+/-	0:82.4 L:82.5	0:111 L:131*	14.4	0:5 L:4b,*	0:7 L:6*	0:43.3 L:37.1	0:3.1 L:4.1	0:5.2 L:5.2	Discharge status
White [56]	0:54 L:60	R	+/-	2.5 ^a	-	13	-	0:13 L:17	0:33 L:46	-	0:0 L:0	Rectum only
Modini [54]	93:122 ^a	CR	+/+	98.9:88.5	-	-	-	-	14:19.8	3.1:5.5	30.1:5.7*	Emergency only

ASA: American Society of Anesthesiologists score, OT: operative time, Conv: conversion to open surgery, Diet: time to resumption of a normal diet, LOS: length of stay, Cx: postoperative complication, AL: anastomotic leakage, L: laparoscopy, O: open surgery, C: colon, R: rectum, CRC: colorectal cancer, CC: colon cancer, * $<$ 0.05, ^a \geq 80 vs $>$ 65

Table 2. Literature review of colorectal cancer operations in patients aged 80 or more years

First author	Patients, n	Surgical disease	Benign/emergency	ASA \geq 3 (%)	OT (min)	Conv (%)	Bowel function (day)	LOS (day)	Cx (%)	AL (%)	Mortality (%)	Comments
Vignali [9]	O:61 L:61	CRC	-/-	O:2.6 ^a L:2.5 ^a	O:171 L:220*	6.1	O:5.9 L:4.8*	O:12.9 L:9.8*	O:31.1 L:21.5	O:5 L:7	O:3.3 L:1.6	Independence status*
Gurevitch [8]	40:84 ^b	Rt CC	-/+	23.7*	-	-	-	7.5:7.6	27.5:17.9	-	10.3.5*	\geq 80 vs <80
Kunitake [6]	26108	CRC	-/+	-	-	-	-	10.6-12.4 (C) 11.4-12.6 (R)	-	-	5.8 (C) 5.9 (R)	One-year mortality
Chaudhary [7]	L:173	CRC	-/-	42	-	7.5	-	5	12	1.2	1.7	Multi-center

Rt CC: right colon cancer. For other abbreviations see footnote of Table 1

* $<$ 0.05, ^a Mean, ^b \geq 80 vs $<$ 80

presence of underlying disease, advanced TNM stage, and occurrence of surgical complications [46]. Oxaliplatin- or irinotecan-based regimens are rather intolerable to the elderly. Therefore, either intravenous or oral fluoropyrimidine is commonly used for elderly patients [47].

Outcomes

In this era of an aging society, clinicians should provide objective evidence to octogenarian and nonagenarian patients regarding estimated short-term and oncologic outcomes. However, there is a limited number of studies concerning outcomes following colorectal cancer surgery in octogenarians and nonagenarians (Tables 1 and 2). Several studies include a variety of benign colorectal diseases in addition to colorectal cancer [48-56]. Cancer surgery is different from surgery for benign colorectal diseases [40,42,57]. Unlike elective surgery, emergency surgery carries a higher risk for perioperative morbidity and mortality [58]. Increased chronological age is a predictor of poor outcomes in colorectal cancer. Higher rates of postoperative complications and reduced survival in octogenarian and nonagenarian patients with colorectal cancer can be attributed to tumor biology, impaired physiological function, and treatment disparities associated with delayed diagnosis, limited extent of surgery, and decreased use of adjuvant chemotherapy or preoperative chemoradiation therapy [59].

The published literature shows heterogeneous study characteristics in patients over 80 years of age, and all studies were retrospective [6-9,48-56]. With respect to disease characteristics, benign colorectal diseases with/without colorectal cancer [48-51,54,56], colorectal cancer only [6,7,9] or right colon cancer [8] were the main subjects of these

studies. One study focused on patients undergoing an emergency operation [54]. Single-center studies were more common [8,9,48-52,54,56] than multicenter studies [6,7,53,55]. With respect to study design, single-arm studies [49,51-53], comparisons of surgical approaches (e.g., laparoscopy versus open surgery) [9,48,50,56] and comparisons of outcomes based on age groups [6-8,54,55] have been performed. Most studies have reported short-term outcomes in terms of postoperative complications and in-hospital mortality. A few studies have reported survival outcomes [6,52]. In Table 2, studies on colorectal cancer operations in patients aged 80 or more years are summarized. Vignali et al. [9] performed a case-matched analysis in octogenarian patients undergoing open and laparoscopic surgery for colorectal cancer. Gurevitch et al. [8] compared outcomes between patients aged 80 years or more and less than 80 years who underwent a right colectomy for colon cancer. Kunitake et al. [6] analyzed the California Cancer Registry data of octogenarian patients undergoing a colorectal cancer operation. Chaudhary et al. [7] performed a multicenter study. Short-term outcomes were evaluated in patients over 80 years who underwent a laparoscopic resection for colorectal cancer.

Chronological age and patient functional status are important factors in the occurrence of postoperative complications in octogenarian and nonagenarian patients. Turrentine et al. [55] examined 7,696 patients undergoing major general, general thoracic, and vascular surgical procedures using the American College of Surgeons National Surgical Quality Improvement Program database and observed that the morbidity rate was 49% in octogenarians and 61% in nonagenarians. In addition to chronological age, performance status is an important predictor of outcomes. A poor

performance status in terms of an ASA score of 3 or greater, ECOG score of 2 or greater, and a Karnofsky score less than 60 is associated with poor short-term and oncologic outcomes [60]. The proportions of patients with an ASA score of 3 or higher were 23% [8] and 42% [7] in octogenarians and nonagenarians, respectively, who were undergoing colorectal cancer surgery. A higher ASA score has been reported to be a risk factor for postoperative morbidity and mortality [53]. The mean operative time was 171 min in an open surgery group and 220 min in a laparoscopy group ($p=0.01$) [9]. Conversion to open surgery occurred in 6.1% of octogenarians [9] and 7.5% of nonagenarians [7]. The mean time to bowel function return was 5.9 days in the open surgery group and 4.8 days in the laparoscopy group [9]. The mean hospital stay was 5 to 12.9 days [6-9]. The postoperative complication rate was 12 to 31.1% [7-9]. The anastomotic leakage rate was 1.2 to 7% in the laparoscopy group [7,9] and 7% in the open surgery group [9]. The perioperative mortality rate was 1.6 to 5.9% [6-9]. High-risk cancer resections are also related to increased operative mortality in the elderly. A study in patients undergoing major cancer operations for lung, esophageal, and pancreatic malignancies showed that octogenarians had increased mortality rates compared with younger patients [61]. The impact of a combined surgery, such as metastasectomy, on postoperative morbidities and mortalities has not been studied in octogenarians [6-13,48-51]. A low serum albumin level indicates poor nutritional status and has been shown to correlate with the occurrence of morbidity. Thus, elderly patients with a low albumin level should be regarded as high-risk patients preoperatively [35].

Oncologic outcomes have rarely been reported in octogenarian and nonagenarian patients [6,52]. Abbas et al. [52] studied long-term survival rates following major abdominal surgery in patients 80 years and older. The median survival was 32 months in patients 80 to 84 years and 12 months in patients 85 years or older ($p=0.011$). The median survival was 11 months in patients with malignant disease and 25 months in patients with benign disease ($p=0.37$). Kunitake et al. [6] observed that patients 80 years or older had an in-hospital mortality rate of 6% and a one-year mortality rate of 29%. Medical complications, comorbidities and advanced cancer stage were risk factors for increased in-hospital and one-year mortality. The presence of postoperative complications delays patient recovery and worsens onco-

logic outcomes [62]. The mechanism underlying the association between postoperative complications and unfavorable survival is poorly understood. However, a lack of adjuvant treatment and decreased physical status, such as heart failure due to complications, have been suggested as possible reasons [63]. Thus, clinicians should be aware that avoiding postoperative complications may improve oncologic outcomes.

Conclusions

The occurrence of postoperative complications is associated with a variety of factors, such as chronological age, comorbidities, physiological functional status, nutritional status, invasiveness of surgery, and cancer stage. Thus, age should not be used as the absolute criterion to preclude the administration of appropriate treatment. To decrease one-year mortality, avoidance of postoperative complications and careful patient selection are also important. Understanding age-related physiological decline, performing an appropriate preoperative assessment, carefully selecting treatment modalities, and providing meticulous postoperative care can improve outcomes following colorectal cancer surgery in octogenarians and nonagenarians.

In elderly patients, the higher likelihood of postoperative morbidity may discourage the selection of surgery for colorectal cancer. Currently, evidence of the outcomes of medically managed patients who have resectable colorectal cancer is not readily available. The impact of the treatment decision – either surgery or medical treatment – on the quality of life and oncologic outcome remains to be investigated.

Unfortunately, standard management guidelines for colorectal cancer in octogenarians and nonagenarians are not currently available. Multidisciplinary team discussion should be performed based on objective geriatric assessment, and to improve the quality of cancer care, consensus guidelines should be developed as soon as possible. With these efforts, tailored cancer treatment can be performed in clinical practice, and clinicians and patients can expect increased oncologic benefits. In the future, a prospective study with a larger cohort would be helpful to collect objective data in octogenarian and nonagenarian patients.

Conflict of interests

The authors declare no conflict of interests.

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