Review Article

Management of locally advanced rectal cancer in the elderly: a critical review and algorithm

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Contributions: (I) Conception and design: SK Jabbour, L Hathout; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: L Hathout, SK Jabbour; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Colorectal cancer incidence and death rates have been declining over the past 10 years. However, it remains the second leading cause of death in men ages 60–79 and the third leading cause of death in men over 80 and in women over 60 years old. However, there is little data specific to the treatment of the elder patient, since few of these patients are included in trials. With the advent of improved therapies, there are many alternative options available. Still, no definitive consensus or guidelines have been defined for this particular patient population. The goal of this study is to review the literature on the management of rectal cancer in the elderly and to propose treatment algorithms to help the oncology team in treatment decision-making.

Keywords: Rectal cancer; elderly; treatment algorithm

Submitted Jul 26, 2017. Accepted for publication Sep 22, 2017.
doi: 10.21037/jgo.2017.10.10
View this article at: http://dx.doi.org/10.21037/jgo.2017.10.10

Introduction

In 2016, the estimated number of new cases of rectal cancer was 39,220 in the United States. Although the incidence and death rates of colorectal cancer declined by 3% per year from 2003 to 2012, colorectal cancer remains the second leading cause of death in men ages 60–79 and the third leading cause of death in men over 80 years old and in women over 60 years old (1).

Among patients with colorectal cancer, rectal cancer accounts for about 30% of cases. This high mortality rate highlights the need for improved awareness of possible issues in caring for an elderly group of patients (2). Management of rectal cancer is challenging and involves multidisciplinary care. The data to guide treatment of elderly patients with rectal cancer are sparse since the elderly population has been underrepresented in prospective clinical trials involving colorectal cancer (3).

Older patients diagnosed with colorectal cancer are less likely to be referred to medical oncology, to receive standard of care chemotherapy (4) and more likely to undergo dose reductions and early termination of therapy (5). A population-based study in rectal cancer showed that age was the strongest determinant of treatment and that with advancing age there was a decline in the proportion of patients receiving standard of care adjuvant therapy even after adjusting for co-morbidities (6).

The goal of this consensus statement is to review the available literature and establish a treatment algorithm to aid the oncologist in treatment planning and decision-making in

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Table 1 Elements of a comprehensive geriatric assessment questionnaires pertinent for oncology patients (11-19)

Parameter assessed	Elements of the assessment
Age	>85, 80–85 or <85
Functional status	Performance status
Autonomy assessment	ADL (11)
	IADL (12)
Comorbidity	The Cumulative Illness Rating Scale for Geriatrics (CIRS-G) (15)
Socioeconomic conditions	Presence and adequacy of a caregiver
Cognitive function	Folstein's Mini-Mental Status (13)
Mobility	Get Up and Go (16,17)
Emotional status	Geriatric Depression Scale-15 (18)
Pharmacy	Number of medications (≤3 or >3) (14)
Nutritional status	Mini-Nutritional Assessment (19)
Self-perception of health	G8 scale (14)

IADL, instrumental activities of daily living; ADL, activities of daily living.

the elderly population with rectal adenocarcinoma. For the purposes of this article, we employ the definition of elderly as ≥70 years, but we recognize that the definition of the elderly can vary from 70 to 75 years, depending on the study.

Geriatric assessment tools and predictors

Chronological age is not an accurate tool in predicting treatment-related outcome and toxicities. The International Society of Geriatric Oncology (SIOG) has strongly recommended the use of a systematic comprehensive geriatric assessment (CGA) in elderly patients with cancer (7). Multiple factors are included in the CGA: functional status including activities of daily living (ADL) and instrumental ADL (IADL), nutritional status, co-morbidities, polypharmacy, cognitive function and psychosocial status (8-10) (*Table 1*). A multidimensional geriatric assessment (MGA) identified three different categories of patients based on their life expectancy; "fit patients" who may receive the same treatments as younger patients, "vulnerable patients" who require tailored treatment approaches and "frail patients" who are only candidates for supportive care (20) (*Table 2*). The CGA is time and labor consuming; therefore, it is seldom used in clinical practice. Another prognostic tool is the multidimensional prognostic index (MPI) that has been validated recently as a predictor of mortality and length of stay during hospitalization in elderly patients. The MPI generates a score between 0 and 1 and identifies the risk of mortality; a higher MPI is associated with a higher mortality risk (21,22). A modified cancer-specific MPI has been developed and found to be an accurate predictive tool for 1-year mortality in older cancer patients (23). When compared to the MGA, the MPI has a greater discriminatory power for 12-month mortality than the MGA in a prospective study of 160 patients ≥70 years old with locally advanced or metastatic solid cancer (24).

Two studies have evaluated the impact of a geriatric assessment on treatment-decisions (25,26) and found that a CGA did significantly influence the decision-making in 30 to 80% of patients. Consequently, a systematic review assessed the diagnostic performance of seven different screening methods of frailty to predict the presence of impairment on a CGA in elderly patients. These frailty screening methods had insufficient discriminative power to refine patient selection; therefore, the authors recommended for elderly patients to receive a CGA (27).

Studies have attempted to elucidate the role of chemotherapy and factors contributing to inadequate delivery of chemotherapy in this patient population. Baseline depression and instrumental dependencies were associated with functional decline in patients who are ≥70 years receiving first line chemotherapy (28). To further assess the risk factors associated with increased toxicity in older patients with cancer, a number of tools incorporating geriatric assessment are under evaluation. In a prospective multicenter study, 562 patients ≥70 years of age were assessed based on twenty-four parameters including laboratory studies, instrumental ADL, performance status, chemotherapy regimen toxicity, etc. The Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score was found to be a useful predictive tool which could distinguish the risk of toxicity for this patient population (29). In another report, a predictive model for grade 3 to 5 toxicities was developed in a cohort of 500 patients aged ≥65 years who underwent comprehensive assessment that included socioeconomic setting, treatment modalities and geriatric assessment of function,

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Table 2 The three classes of elderly patients

Class	MGA parameters	Mortality rate at 2 years	Therapeutic indications
Class 1: fit patient	No functional dependence in ADLs and IADLs No relevant comorbidities No geriatric syndrome	8–12%	Same as younger patients
Class 2: intermediate patients	Dependence in one or more IADLs but not ADLs Comorbidities present but not life threatening Mild memory disorder and depression No geriatric syndromes	16–25%	Adapted or attenuated treatment
Class 3: frail patient	Age ≥85 years* Dependence in one or more items of ADL One or more geriatric syndromes† Three or more grade-3 comorbidities (CIRS-G) or one severe comorbidity with constant limitation of daily life	>40%	Only supportive care and palliation

*, age ≥85 years does not contraindicate treatment a priori, but extreme caution is required; †, Geriatric syndromes: delirium, dementia, depression, falls, neglect and abuse, spontaneous bone fractures. CIRS-G, Cumulative Illness Rating Scale's geriatric variant; IADL, instrumental activities of daily living; ADL, activities of daily living; MGA, multidimensional geriatric assessment.

Table 3 ASCO recommendations goals to improve the evidence-based treatments in the elderly population (32)

To improve the conduct of research
Use clinical trials to improve evidence for treating older adults with cancer
Leverage research designs and infrastructure for generating evidence on older adults with cancer
To improve the research environment
Increase US Food and Drug Administration authority to incentivize and require research involving older adults with cancer
Increase clinicians' recruitment of older adults with cancer to clinical trials
Use journal policies to improve researchers' reporting of age distribution and health risk profiles of research participants

ASCO, American Society of Clinical Oncology.

comorbidities, cognition, activity level and social support. Patients were stratified in three groups based on the risk of chemotherapy toxicity: low, intermediate and high risk (30). The main criticism of this study was lack of an in-office performance mobility test that could potentially add significant value to the scoring system (31).

Though data from these series and population-based studies provide some insight into factors to consider while making treatment decisions, widespread application of geriatric assessment still remains to be adopted. The American Society of Oncology convened a sub-committee to address lack of evidence for treating elderly patients with cancer and after analyzing the current evidence; a set of recommendations was formulated to address this question, which are detailed in *Table 3* (32).

Multiple dilemmas may exist in the decision-making for elderly patients with locally advanced rectal cancer, which center on underlying patient factors (comorbidities, functional status, geriatric assessments, and overall life expectancy) and the anticipated tolerance of the standard of care therapy (preoperative chemoradiation, subsequent surgery, and postoperative chemotherapy). Herein, we seek to evaluate the available evidence regarding treatment administration and provide an algorithm based on these data.

Neoadjuvant chemoradiation in elderly patients

Neoadjuvant long-course chemoradiation is the gold standard for locally advanced rectal cancer with no evidence of distant metastasis followed by surgical resection and

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adjuvant chemotherapy. Compared to post-operative chemoradiation, neoadjuvant chemoradiation was associated with improved local control and reduced toxicity (33). Combined modality therapy has been shown to decrease the risk of loco-regional recurrence (34-36).

Using the Surveillance, Epidemiology, and End Results (SEER) database, Chang *et al.* evaluated 21,390 patients with localized rectal cancer and found that with each 5-year increase in age ≥70 years, there was a 37% increase in the relative risk for cancer-related mortality and fewer cancer-directed surgeries, and less use of radiotherapy. The effect of age ≥70 years resulted in a 31% increase in cancer-specific mortality (37). Patients who were younger, had positive lymph nodes, comorbid condition and nonblack race were more likely to receive chemoradiation (38). Nevertheless, these data suggest possible under-treatment of the elderly.

An audit based on Swedish Rectal Cancer Registry was done to assess the impact of age on outcome in rectal cancer. A total of 15,104 patients with rectal cancer of which 42% were ≥75 years old were evaluated. Distant metastases were less frequently diagnosed in patients ≥75 years old, and patients were less likely to undergo preoperative radiotherapy and surgical resection. However, when surgery was performed, a Hartmann's procedure was more frequently used. The authors concluded that age had an impact on treatment decisions, but they did not find a significant difference in survival at 5 years or local recurrence rate between patients <75 years of age and ≥75 years (39). It is possible that such studies are subject to selection bias in patients ≥75 years who may not have been treated. Likewise, a large multi-institutional Canadian study including more than 1,100 patients treated with neoadjuvant chemoradiation followed by curative intent surgery found similar disease-free survival (DFS), cancer-specific survival and overall survival in patients <70 years of age and ≥70 years (40). Choi *et al.* evaluated 160 patients who underwent neoadjuvant chemoradiation did not observe a difference in tolerance to chemotherapy, complete pathological response rate or treatment related complications in older patients compared to a younger cohort (41).

In a series of 56 patients with a mean age of 78 years, compliance rates for radiotherapy and chemotherapy were 91% and 41% respectively with adherence comparable to younger patients. The rate of grade gastrointestinal (GI) >3 toxicity was 14.3% (42). Another small series evaluated 36 patients >70 years with rectal cancer with a Cumulative Illness Rating Scale-Geriatric and categorized patients as "fit" and "vulnerable". All patients were able to complete a full course of radiotherapy (50.4 Gy with bolus and continuous infusion 5-FU) and "vulnerable" patients did not experience higher acute toxicity compared to "fit" patients and were able to similarly tolerate concurrent therapy compared to "fit" patients (43). As a result of perceptions, rather than objective scales to determine fitness, there may be disparities in administration of combined modality therapy in older adults as demonstrated by a series of 267 patients treated at the Boston Medical Center and Boston Veteran's Hospital. In this study, the odd of initiating therapy for patients >71 years was reduced by 22% after adjusting for comorbid status. In this study, only 56 of patients completed chemoradiation without dose reduction or delay, and completion of therapy was more likely with preoperative chemoradiation (44). A study from France also found disparities in the treatment of older patients (ages 80–84 years). Patients older than age 85 years were treated preferentially with primary chemoradiation and non-surgical management and demonstrated a 5-year overall survival rate of 45% and DFS rate of 65% (with the overall survival rate being inferior and the DFS being similar or improved compared to younger patients). The authors found that the differences in survival rates between elderly and younger patients were attributable to complications and co-morbidity, highlighting the need for a CGA (45). Disparities in care were also detected in a Canadian study that showed that age ≥75 year was the only factor impacting whether patients underwent surgery alone or surgery plus chemoradiation. Patients who received only surgery had a risk of death 2.35 times greater than elderly patients treated with trimodality therapy (46). Other series have also corroborated under-treatment of the elderly, which can be detrimental to quality of life due to recurrent disease (6,47).

A SEER analysis using data from 2004–2011 identified 4,121 elderly patients, >75 years, with locally advanced rectal cancer, which were divided into four groups: (I) surgery only (n=1,460); (II) radiation only (n=577); (III) neoadjuvant radiation therapy (RT) (n=1,498); (IV) adjuvant RT (n=586). The 5-year cancer-specific survival showed the best outcome for patients in the neoadjuvant RT group (70.4%), followed by adjuvant RT (60.4%), followed by surgery only (52.1%), and followed by RT only (27.7%) (48). A Mayo Clinic study of 160 elderly rectal cancer patients age ≥75 revealed that neoadjuvant chemoradiation did not provide a survival benefit for stage II (n=66) rectal cancer but did portend a benefit for stage III (n=94) rectal cancer

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compared to no neoadjuvant therapy (49). Another SEER study evaluating 2,886 stages II–III rectal cancer patients showed that completing postoperative chemoradiation resulted in a lower cancer-related mortality compared to their counterparts with no adjuvant therapy. Stage III patients were more likely to receive chemoradiation compared to stage II patients (50). The Mayo series may have been underpowered to evaluate the benefit of adjuvant chemoradiation in stage II patients.

Regarding the toxicities of neoadjuvant chemoradiation, in an unplanned subset analysis of the ACCORD12/PRODIGE2 phase III trial, preoperative chemoradiotherapy led to more severe grade 3/4 toxicities (25.6% *vs.* 15.8%, P=0.01) and more permanent stomas (33.3% *vs.* 22.8%, P=0.014) in elderly patients (≥70 years) who were less often operated on than younger patients (<70 years) (95.8% *vs.* 99.0%, P=0.008). The relative number of interventions per surgery type, treatment efficacy in terms of R0 resection rate, and complete pathological response (14.7% *vs.* 16.9%; P=0.55) were nearly identical between the two categories. Therefore, the treatment team must contemplate safe and individualized therapy for each patient (51).

Other series have identified comorbidity indices as a reasonable method to preemptively assess patient toxicity and outcomes in the elderly rectal cancer population being treated with chemoradiation (52,53). In contrast, multiple other series have advocated for trimodality management of locally advanced rectal cancer, citing similar outcomes to younger patients (54-58).

Short-course radiation

Short-course radiation has been shown to be an appropriate option for patients with stage III rectal cancer with effective local control and comparable overall survival to long course chemoradiation (59-61).

In a subgroup analysis of the Dutch total mesorectal excision (TME) study, which showed an improvement in overall survival with addition of short course radiation (5 Gy ×5 fractions) before surgery, patients >75 years of age did not gain a survival advantage, and the mortality rates during the first 6 months were higher compared to younger patients (62). Similarly, treatment related complications were significantly higher in 455 patients ≥70 years old treated with short course radiation or long course chemoradiation ± intraoperative radiotherapy. On multivariate analysis, age >70, comorbidity and having ≥ two complications were significantly associated with worse survival (63). A study from the Netherlands analyzed a total of 642 patients aged 75 years and older with stage pT2–T3, N0–2 rectal carcinoma treated with surgery alone (n=296) and pre-operative radiation followed by surgery alone (n=346). When compared to surgery alone, short-course preoperative radiotherapy resulted in a decreased rate of local recurrence in patients ≥75 years (6% *vs.* 2%). However, postoperative complications occurred more frequently in the irradiated group especially deep infections and local wound problems but the 30-day mortality rate was similar between the two groups. Severe comorbidity, chronic obstructive pulmonary disease (COPD), diabetes and cerebrovascular disease were associated with a 4-fold increase in the 30-day mortality. On multivariate analysis, postoperative complications predicted 5-year survival (64).

Short-course radiation is not uniformly suitable for elderly patients who are surgical candidates as available studies suggest increased complication rates and lack of a survival advantage. For those with severe comorbidities and poor performance status, it should be considered with caution since the side effects and post-operative complications are not trivial.

Brachytherapy

Brachytherapy has been used as primary preoperative therapy for T1 or T2/T3, node negative or small node positive rectal cancer, as a dose escalation boost and in the palliative setting.

Papillon popularized contact X-ray brachytherapy (CXB) 50 kVp in the 1950s–1960s in Europe. It has been widely used in the treatment of early stage rectal cancer as a definitive treatment or in the adjuvant setting after surgery with excellent outcomes (65-68). Local treatment with radical radiotherapy is an alternative to radical surgery in patients with T1N0M0 rectal cancer. Sun Myint has established selection criteria for suitability of radical contact radiotherapy; mobile, non-ulcerative, exophytic tumors <10 cm from the anal verge, tumor size <3 cm or occupying less than 1/3 of the rectal circumference, T1 well to moderately differentiated tumors with no lymphovascular invasion (69). In patients with T1/T2 rectal cancer treated with radical radiotherapy including contact radiotherapy, local failure and overall survival were 7–25% and 60–96%, respectively (66,69-74). Myint strongly encouraged the consideration of contact radiotherapy as an alternative to surgery in elderly patients and those with a high anesthetic risk with low early stage cancer (75).

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Others reported their experience with the combination of CXB brachytherapy with external beam RT in patients with early stage and advanced T2–T3 rectal tumors and achieved good local control (60–70% at 5 years) (76-78).

Endoluminal high-dose rate (HDR) Ir-192 is gaining popularity in North America. In a study by Corner *et al.* HDR Ir-192 brachytherapy was used in 79 patients with locally advanced rectal tumors of whom 52 were unfit for surgery and were treated radically. In this study, the patient population was predominantly elderly with a median age was 82 years. Objective local tumor response was achieved in 85% of patients of whom 58% had a complete response and 27% had a partial response. The median survival of patients treated with a palliative intent was 6 months and 18.5 months for patients treated radically (79). In conclusion, contact radiotherapy or HDR brachytherapy are appropriate treatment options for early stage and locally advanced rectal tumors in patients unfit for surgery and in the elderly population.

Surgical management of rectal cancer in the elderly

The combined effects of an aging population and rectal cancer as an age-related disease will continue to increase the need for surgery in the elderly population (80,81). Surgical treatment of rectal cancer remains fundamental in the management of colorectal cancer. However, with multimodality treatment approaches for rectal cancer, alternative options and even non-surgical approaches become possible definitive treatments for older patients who are perceived to be at a higher surgical risk than younger patients. The risks for surgery alone in the elderly need assessment, independent of chemotherapy and radiation. Due to age and fragility, additional surgical options may be considered. Furthermore, in patients with multiple medical comorbidities, preoperative optimization and an interdisciplinary effort among anesthesiology, cardiology, and primary medical providers can help to better determine postoperative risks. Multiple tools also can be used to determine risk scores for complications and may help to inform surgical choices (82).

The first question therefore is whether age alone is a relative contraindication to surgical management of rectal cancer. Elderly patients make up an increasingly higher percentage of patients presenting with rectal cancer, but the percentage of patients in this age group undergoing curative surgery is lower and emergency surgery is more often the indication compared to younger patients (83,84). Studies evaluating age as an independent risk factor for complications have not been conclusive, with some studies finding an association with age, and others finding increased comorbidities without a specific effect on post-operative course (85-89). The SEER Database has been helpful in clarifying the impact of age on rectal cancer surgery. Chang *et al.* found that for patients over 70 years, there was a decrease in cancer related surgery with more local excision and less radical surgery across all stages of rectal cancer (37). A second SEER analysis compared survival in elderly patients based on operative *vs.* non-operative approaches. Elderly patients had improved cancer-specific survival as well as overall survival when treated with surgical management of their rectal cancers. The elderly population did show divergence in cancer-specific survival and overall survival suggesting that the mortality in the elderly was due to non-cancer related causes, supporting the use of radical therapy in the elderly (90). Operative approaches to rectal cancer are unique in the multiple options available for management of tumors. In general, earlier stage tumors can be addressed by either abdominal or transanal surgery with different risks and benefits to each.

Transanal surgery (local excision)

Transanal surgery in general offers the advantage of decreased operative morbidity, but a higher recurrence rate. Transanal endoscopic microsurgery (TEM), allows removal of rectal lesions through a 40-mm operating proctoscope with rectal insufflation (91). Advantages of the TEM system include improved visualization of tumors, decreased recurrence rates compared to standard transanal excision and access to more proximal tumors (92-95). Many studies have evaluated the efficacy of TEM in addressing rectal cancer (95-99). A meta-analysis evaluated 860 patients with early stage rectal cancer of which 303 underwent a TEM and 557 received standard surgical approaches including total mesorectal dissection. No significant difference was identified for DFS or distant metastatic disease. However, there was an increase in local recurrence with TEM compared to standard surgery (100). In general, TEM is best for low-risk cancers, well to moderately differentiated T1, without lymphovascular invasion that are less than 3–4 cm in size (101). Although there is limited data specific to the elderly, the relative increased safety of the TEM approach, faster operative time, decreased blood loss, shorter hospital-stay, and decrease in stoma formation make

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it an attractive approach to an elderly patient with more comorbidities (97).

A second area where local excision of a rectal tumor has been employed is in patients that have been treated with neoadjuvant chemoradiation as a means of evaluating for complete pathologic response or for resection for cure of the downstaged tumor. Two large prospective trials, the ACOGSOG Z6041 and the CARTS study have evaluated the role of local excision following chemoradiation therapy with promising results (102,103). There is currently no study of this technique specific to the elderly population.

TME

Current standard therapy for rectal surgery includes performing a TME for improved local control of disease and survival (104,105). However, Rutten *et al.* evaluated the impact of TME on the elderly and found that older patients did not have improved survival compared to younger patients and that the mortality within the 6-month period following treatment was significantly higher in patients over 75 years compared to a younger cohort (14% *vs.* 3.9%) (62). A subsequent evaluation by the same group again revealed no improvement with TME in the elderly population prompting them to suggest alternate methods of treatment for the elderly population (106).

Laparoscopic surgery

One area that has been evaluated specifically with respect to the elderly population is laparoscopic surgery. Laparoscopic approaches to rectal cancer have increased over the past 20 years with laparoscopy providing decreased narcotic intake, shorter hospital stays, faster return to activity compared to those undergoing open surgery (107-109). A number of studies have specifically looked at this comparison in the elderly population (110-113). Manceau *et al.* evaluated 446 consecutive patients grouping them into 10-year intervals from under 45 to older than 64 years. Elderly patients had a higher American Society of Anesthesiologists (ASA) score and higher Charlson comorbidity index preoperatively with higher cardiovascular, pulmonary and neurological comorbidities. Despite these differences, there was no difference in post-operative complications and age was not a significant independent risk factor for post-operative morbidity (111). Otsuka *et al.* evaluated short and long-term outcomes in patients undergoing laparoscopic surgery and compared octogenarians to case matched controls between the ages of 60–69. They similarly found that the ASA score was significantly higher in the octogenarian group but this did not correlate with increased post-operative complications and long-term cancer specific survival (91% in the octogenarian group and 95.7% in the case matched controls). There was an increased rate of permanent stoma in the elderly group from either abdominoperineal or Hartmann's procedure compared to the middle-aged group (112). Recently, comparison between laparoscopic and open surgery has been evaluated in two large multicenter trials, ALACART and ACOSOG Z6051 with both showing that laparoscopic surgery did not meet non-inferiority for rectal cancer patients (114,115). These results should prompt further study and evaluation of the role of laparoscopic surgery in the management of rectal cancer.

Robotic surgery

Robotic surgery is an emerging technology in the surgical management of rectal cancer and is another option for a minimally invasive approach to rectal surgery. A number of small studies have evaluated the role of robotics in the treatment of rectal cancer (116-118) and the ROLAAR trial (NCT01736072) was established to compare the role of robotics in rectal cancer surgery. No published series exist regarding the elderly and robotic approaches to rectal cancer.

Stoma rates

Another significant difference in the elderly population compared to the younger population is the use of stomas as part of the surgical management (119). This is likely related to concern about fecal incontinence following low pelvic reconnection in the elderly population. One study out of the Netherlands did show significantly worse quality of life based on Wexner and fecal incontinence quality of life scores. However, in a number of other studies, elderly patients that do have a low pelvic anastomosis are generally satisfied with their control and functional results (120-122). In general, after a preoperative assessment of fecal continence, and a discussion of the potential risks of fecal urgency and soiling, elderly patients should be offered option of sphincter-sparing surgery for low rectal tumors.

While surgery remains integral in the management of the elderly patient with rectal cancer, multidisciplinary and patient specific factors need to be considered when developing the optimal treatment plan.

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Adjuvant chemotherapy for the elderly rectal cancer patient

Specifically, with regards to the elderly patient, there is a paucity of data about the use of postoperative chemotherapy for rectal cancer patients treated with chemoradiation. In a study by Margalit *et al.* evaluating the tolerability of combined modality therapy for elderly rectal cancer patients (n=36, ages ≥75 years), only 39% of patients were able to complete ≥4 months of adjuvant chemotherapy (123). Lund *et al.* examined the comparative effectiveness of postoperative chemotherapy using the SEER Medicare database. Two groups of patients were compared in terms of mortality rates: (I) postoperative 5-FU or capecitabine to no treatment (n=666) and (II) postoperative oxaliplatin +5-FU/capecitabine (n=341) to 5-FU capecitabine alone (n=309). For patients <75 years, the use of post-operative 5-FU/capecitabine demonstrated a reduction in mortality in the post-operative setting but oxaliplatin did not provide additional survival benefit. For patients ages ≥75, there was no mortality reduction for 5-FU/capecitabine (124). In another SEER analysis, investigators found that the use of postoperative oxaliplatin with 5-FU after neoadjuvant chemoradiation and curative resection could prolong survival in those <73 years of age with pathologically positive lymph nodes, but oxaliplatin did not improve survival rates in the postoperative setting for those patients ≥73 years (125). These studies were unable to evaluate the rates or patterns of recurrence based on the nature of the SEER database.

Given the similarities in the use of postoperative chemotherapy for colon cancer, one may consider appraising the data for non-rectal colon cancers and consider extrapolating those data to rectal cancer. Sargent *et al.* incorporated data from seven phase III randomized trials (n=3,351) and compared the effects of postoperative 5-FU -based therapy (with leucovorin or levamisole) to the effects of surgery alone in resected stages II and III colon cancer. The 5-year overall survival was 71% for those treated with adjuvant therapy versus 64% for surgery alone and the toxicity effects were not increased among those >70 years (126). The addition of oxaliplatin to 5-FU and leucovorin did not show an overall or DFS benefit for patients over 70 years in the NSAPB C-07 study possibly related to higher rates and grades of toxicities compared to younger patients (127). Although 5-FU and oxaliplatin combinations have seemed to demonstrate a limited benefit for elderly patients, a study using the ACCENT database suggested that for patients >70 years, fluoropyrimidine monotherapy with either 5-FU plus leucovorin or capecitabine is an appropriate adjuvant therapy (128). A SEER study linked to the New York State Cancer Registry suggested that the addition of oxaliplatin for stage III colon cancer in patients >75 years offered no more than a small incremental benefit compared to non-oxaliplatin regimens (129). The authors recommended that consideration be made for the use of adjuvant chemotherapy with discussions evaluating individual risks and preferences. Given the variation in underlying medical comorbidities, performance status and pathological risk factors for elderly patients, adjuvant chemotherapy should be considered. Oxaliplatin may increase the toxicity of adjuvant therapy, and as such, may be avoided to provide a more tolerable yet efficacious postoperative chemotherapy regimen using 5-FU therapies with or without leucovorin.

Conclusions

Thus, data for the optimal treatment strategy for rectal cancer in the elderly remains mixed along with significant limitations inherent to retrospective and population-based analyses in the absence of prospective randomized studies.

Based on these recommendations and on the literature review detailed above, a treatment algorithm has been established to help guide the oncologist in treatment decision-making when facing an elderly patient with non-metastatic rectal cancer (*Figure 1*). For the fit patients with acceptable sphincter tone, standard of care therapy should be employed. For fit patients with unacceptable sphincter tone and cT2+ or N1–2, an APR should be favored. For the class 2 patients with cT3+ or N1–2, both neoadjuvant long-course chemoradiation and short-course radiation are appropriate. Regarding the surgically inoperable or frail patients with more advanced disease, more intensive radiotherapy options could be considered.

We strongly suggest that the patient undergo a CGA or other multi-dimensional assessment and the case should be discussed at multidisciplinary tumor board with a medical oncologist, GI surgeon, radiation oncologist, physician extenders, nutritionist, nurse and geriatrician. Although it is important to adequately treat the patient, clinicians should attempt to optimize treatment to maximize patient safety and avoid under- or over-treatment. Most studies suggest that elderly patients can tolerate standard courses of therapy with no interruptions; however, clinicians must be vigilant to quickly identify and address toxicities and make appropriate adjustments to therapy, which supports the

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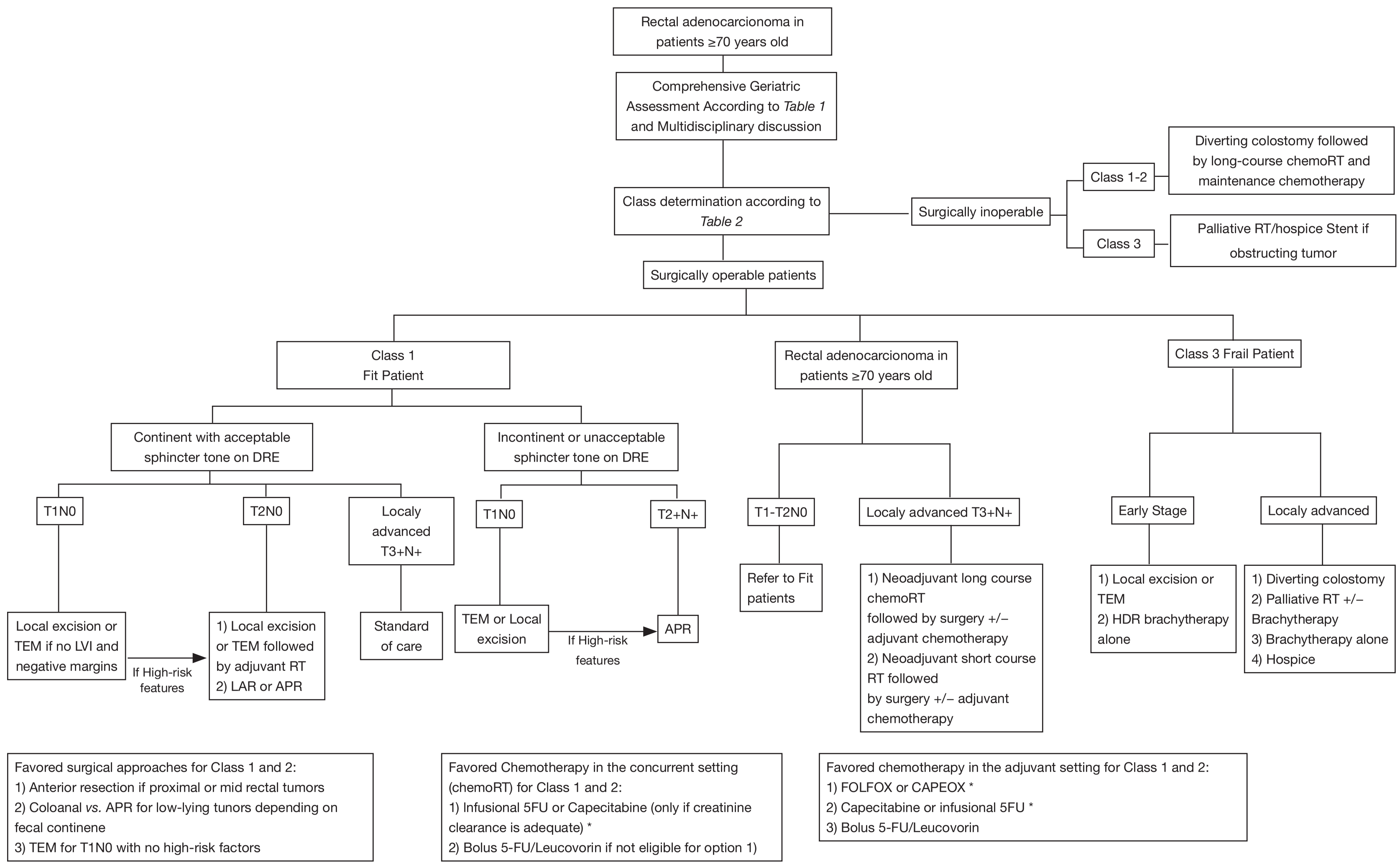

Figure 1 Treatment algorithm for elderly patients with rectal cancer. *, consider infusional 5-FU if polypharmacy or difficultly with adherence with medications. APR, abdominoperineal resection; LAR, lower abdominal resection; TEM, transanal endoscopic microsurgery; LVI, lymphovascular invasion; RT, radiation therapy; HDR, high-dose rate.

need for a team approach for care.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Hathout L, Maloney-Patel N, Malhotra U, Wang SJ, Chokhavatia S, Dalal I, Poplin E, Jabbour SK. Management of locally advanced rectal cancer in the elderly: a critical review and algorithm. J Gastrointest Oncol 2018;9(2):363-376. doi: 10.21037/jgo.2017.10.10

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