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GERIATRIC ONCOLOGY (AR MACKENZIE, SECTION EDITOR)

# Treatment of Rectal Cancer in Older Adults

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**Abstract**

**Purpose of Review** Rectal cancer is predominantly a disease of older adults but current guidelines do not incorporate the associated specific challenges leading to wide variation in the delivery of cancer care to this subset of population. Here, we will review the current data available regarding the management of rectal cancer in older adults.

**Recent Findings** The greatest challenge arises in the management of stage II/III disease as it involves tri-modality treatment that can be harder to tolerate by frail older patients. Response to neoadjuvant treatment is being used as a new marker to tailor further therapy and possibly avoid surgery. Oxaliplatin can be omitted from the adjuvant treatment without compromising outcomes.

**Summary** Physicians should perform geriatric assessment utilizing many validated tools available to help predict treatment tolerability and outcomes in older adults that can help personalize subsequent management. Most older adults can undergo standard therapy for stages I, II, or III rectal cancer with curative intent. Increasing evidence suggests that patients with a clinical complete response to neoadjuvant treatment may be observed closely with the possibility of avoiding surgery. Studies are evaluating alternate systemic treatments for advanced metastatic disease with the hope of maintaining quality of life without compromising cancer outcomes.

**Keywords** Rectal cancer · Older adults · Neoadjuvant chemoradiation · Watch and wait · Pre-treatment risk assessment · Rectal cancer surgery

## Introduction

Rectal cancer is diagnosed in approximately 43,030 Americans each year. It is predominantly a disease of older adults with a mean age at the time of diagnosis of 68 years for men and 72 years for women [1]. As the global population ages, the incidence of this and many other cancers will likely become more pronounced. We cannot rely on chronological age alone to make complex cancer management decisions. Older adults comprise a heterogeneous population on a spectrum from very fit to frail patients. Clinicians need a better sense of the biologic age of the patient, and there are various published and validated tools that can be used to help do this [2, 3].

There is a dearth of clinical trial evidence specifically addressing the risks and benefits of all aspects of rectal cancer care in older adults. Trials designed for older patients can be challenging to complete because of poor accrual. The Alliance N0949 trial attempted to accrue over 300 patients over 70 years of age but could only recruit 32 patients. Concern for randomizing fit patients into a less aggressive arm (and vice versa) along with too strict eligibility criteria were cited by investigators as some of the reasons for not enrolling patients [4••]. Major guidelines do not yet incorporate optimal treatment recommendations for older adults, resulting in inconsistency and disparity in delivery of standard of care to older adults [5, 6]. The FOCUS2 trial from Cancer Research UK and the Medical Research Council demonstrates that it is possible for frail and elderly to participate in randomized clinical trials, if designed appropriately with dose-modified chemotherapy regimens [7]. In fact, older patient-specific trials can be more effective to inclusion of patients over 75 and can result in similar survival with fewer adverse events [8].

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## Rectal Cancer Is a Distinct Disease

Rectal cancer is often bundled with colon cancer though these are different diseases. Anatomically, the rectum has its own unique lymphatic and venous drainage, explaining why rectal cancer can metastasize to the lungs with the same frequency as the liver. Furthermore, the site of first failure after surgery for rectal cancer is equally distributed between local and distant sites. Significant morbidity is associated with local failure and carries a poor prognosis. Treatment of rectal cancer aims to prevent both local and systemic recurrence, resulting in a more challenging treatment regimen including radiation which is generally not used in colon cancer. Recent data also indicate that there are important intrinsic biological differences between right- and left-sided colorectal cancer [9], with rectal cancer being included in the left sided grouping.

## Standard Management

As with most cancers, management depends upon the TNM staging per AJCC [10]. Stage I is localized to rectum. If the cancer invades through muscularis propria into pericolorectal tissues and beyond, it is regarded as at least stage II and the presence of lymph node metastases is considered stage III disease. Any evidence of distant metastases, including peritoneal metastases, is classified as stage IV disease. MRI has become the diagnostic modality of choice due to its high degree of accuracy for determining the depth of invasion of the tumor, prediction of circumferential resection margin, and nodal status. In comparison to ultrasound, MRI allows for study of stenotic tumors and is less operator dependent [11]. Computed tomography helps to evaluate distant metastatic spread and should include abdomen, pelvis, and lungs. Stage I disease is primarily treated by surgery alone and for stage IV disease, systemic therapy is the mainstay of treatment with the important exception of a subset of patients for whom metastatic disease can be fully resected for cure. Stage II and III disease require multimodality treatment, which can be particularly challenging in frail, older adults. The current standard of care for stage II and III rectal cancer in the US is comprised of *three phases*: neoadjuvant chemoradiotherapy (nCRT), surgery, and postoperative adjuvant chemotherapy, lasting nearly 8 months in total (Fig. 1).

## Pre-treatment Risk Assessment in Older Adults

There is a growing recognition of the need for geriatric assessment to identify vulnerabilities in the older patients with cancer and several oncology societies are working to develop some guidelines. International Society of Geriatric Oncology (SIOG) has an active task force working to develop personalized treatment of elderly patients with rectal cancer [12]. ASCO just published geriatric oncology guidelines addressing practical assessment of vulnerabilities in this population. An expert panel was convened who performed a systematic review of the 68 relevant studies and came up with recommendations, but these are more generalized and not rectal cancer-specific [13]. Some highlights include assessment of function, comorbidity, falls, depression, cognition, and nutrition. It is suggested that after making a geriatric assessment, the results be shared with patients to guide treatment decision-making. The following are examples of a few targeted assessments:

(1) Comprehensive geriatrics assessment (CGA)

This provides an in-depth analysis of all domains of functioning including functional, physical, mental, emotional, pharmacotherapeutic, and socioeconomic status and can help in determining potential tolerance of intensive anti-cancer treatments. The down side is that it is somewhat labor-intensive and requires some extra time and resources [14].

(2) The Cancer and Aging Research Group (CARG) and Chemotherapy Risk Assessment Scale for High Age (CRASH) scores

The CARG and CRASH scores are validated tools which incorporate key elements of the CGA to predict risk of toxicity from chemotherapy in older adults [3]. In a validation cohort of patients > 65 years of age, low CARG scores correlated with reduced toxicity frequency [15]. Both scores can be calculated quickly using online tools [16•, 17].

(3) Frailty assessment

Frailty as a concept has been hard to define but encompasses a multidimensional medical syndrome characterized by decreased reserve and diminished resistance to stressors [18]. Frailty assessment, as distinct from a full geriatric assessment, can be used to identify elderly patients needing further optimization before major surgery. It incorporates weight loss, gait speed, grip strength, physical activity, and physical exhaustion. A prospective study revealed that the odds ratio of postoperative major complications was 4.083 when the patient satisfied the criteria for frailty [19]. Similar results have been shown in other cancers where frailty was found to be more predictive of outcomes after multimodality anti-cancer treatment than traditional risk factors [20].

(4) Age-adjusted Charlson Comorbidity Index score (ACCI)

The ACCI takes into account 19 medical conditions with their respective weights that constitutes the extensively



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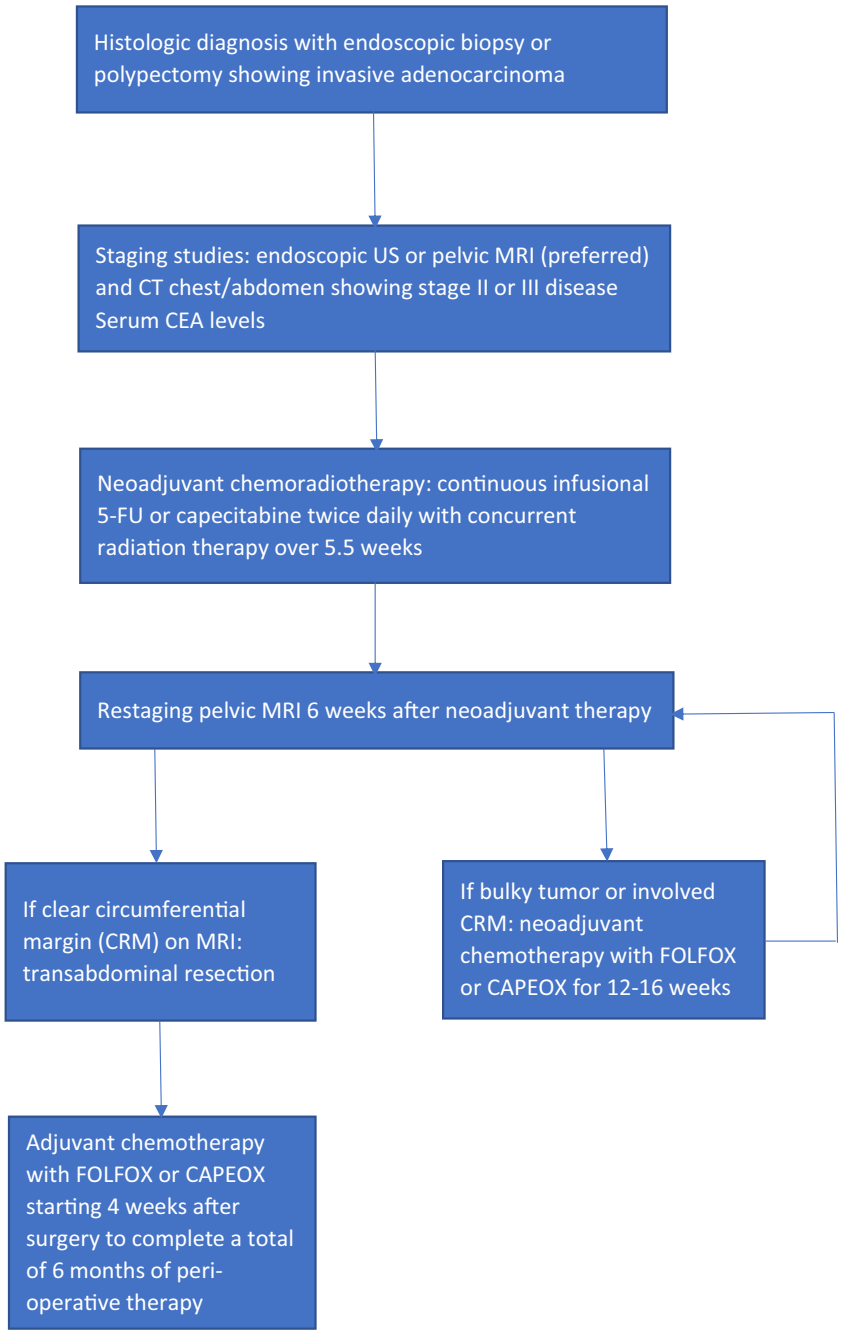


**Fig. 1** Management of stage II/III rectal cancer: a simplified algorithm

validated Charlson Comorbidity Index (CCI) plus age. It has been shown to predict increased risk for prolonged postoperative ileus (POI) in older adults undergoing rectal cancer surgery [21].

(5) American Society of Anesthesiologists score (ASA)

Park and colleagues recently showed that among patients undergoing laparoscopic colorectal surgery, those with an ASA score of 3 or higher had a higher risk of 30-day postoperative complications and mortality, ICU stay, prolonged hospitalization, and higher hospital charges. Independent risk factors affecting postoperative complications were older age (> 80 years), ASA score of 3, and the presence of rectal tumor [22].

## Management of Stage I Disease

Stage I disease with T1 tumors can be treated with transanal excision in some favorable cases if coupled with close follow up, which is a less morbid option for older adults. T2 tumors



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require low anterior resection (LAR) or, if too close to the anal sphincter, abdominoperineal resection (APR). These surgeries also include total mesorectal excision (TME) due to increased risk of lymph node involvement. Means of avoiding APR and permanent colostomy in low lying rectal tumors are being studied with encouraging results [23•]. Neoadjuvant chemoradiotherapy (nCRT) followed by local excision or close monitoring is a consideration for patients unfit or unwilling to undergo the larger surgery.

## Management of Stage II and III Disease

### Neoadjuvant Treatment

The current standard was established by the landmark German rectal cancer trial published in 2004 that provided clear evidence of superiority of nCRT. This trial demonstrated improved disease-free survival, sphincter-preservation, better tolerability in both the short and long term, and better adherence to treatment when compared to postoperative chemoradiation [24].

An interim analysis of a phase II trial from China showed that for older adults (70 or above) who were fit as evaluated by CGA, it was safe and feasible to undergo nCRT [25].

Recent studies support the concept that patients 75 years and older with locally advanced rectal cancer have better survival with a combination of radiation and surgery as compared to either alone [26•] and that such patients can safely tolerate nCRT [27, 28]. Standard nCRT involves either oral capecitabine or infusional 5-fluorouracil concurrent with radiation, with the latter approach being useful in patients with renal insufficiency who cannot tolerate capecitabine. Recent trials have failed to show benefit to adding oxaliplatin during the chemoradiation [29–31].

Some studies are still assessing the role of FOLFOX before surgery with the objective to attain pathological complete response (pCR); the presence of which has a highly favorable prognostic impact. A phase-II trial in 17 institutions across the USA and Canada showed that the addition of 2, 4, or 6 cycles of mFOLFOX6 between nCRT and surgery improved the proportion of patients achieving pCR to 25%, 30%, and 38% respectively compared to 18% without mFOLFOX6. However, it did result in more neutropenia and lymphopenia. The authors concluded that this approach has the potential to increase the proportion of patients eligible for less invasive treatment strategies and is being tested in a phase-III trial [32]. Current NCCN guidelines also offer an option of giving 12 to 16 weeks of neoadjuvant induction chemotherapy with FOLFOX or CAPEOX prior to standard chemoradiation which allows for the possibility of skipping adjuvant chemotherapy after surgery. This approach is referred to as total neoadjuvant therapy (TNT) [33].

Neoadjuvant radiation therapy has been shown to decrease local recurrence, but also leads to more local issues including fecal incontinence. This can significantly affect quality of life both in the short and long term [34•]. It is also associated with local inflammation and pain, sexual dysfunction, vaginal fibrosis, urinary incontinence, and marrow suppression (secondary to pelvic radiation) (Table 1). The PROSPECT trial (NCT01515787) is a randomized controlled trial comparing neoadjuvant chemotherapy alone (FOLFOX) versus chemoradiotherapy to assess whether radiation can be entirely omitted from neoadjuvant regimens thus avoiding radiation-associated adverse events. The goal of all of these approaches is to maximize pCR.

It should be noted that another option for pre-operative therapy is a short course radiation treatment alone administered shortly before surgery [35]. This approach is used more frequently in Europe than the USA. If a delay is allowed after the short course radiation, it does not lead to pCR at the same rate as nCRT [36]. The concept which is gaining international popularity is the "Watch and Wait" strategy. A systematic review of literature of 17 studies showed that a clinical complete response after neoadjuvant chemotherapy when combined with robust surveillance allows early detection of recurrence and a high rate of successful salvage surgery (93% R0 resection)with no adverse effects on 3-year overall survival (93.5%) [37•].

### Surgery

Surgery (i.e., LAR or APR with TME) remains the main pillar of rectal cancer treatment and is usually carried out between 7 and 10 weeks after the completion of neoadjuvant treatment. Older adults are at relatively higher risk of surgical morbidity and mortality. Issues related to the ostomy, such as fluid and electrolyte imbalances, increased risk of postoperative ileus, urinary dysfunction, longer hospitalizations and an increased rate of discharge to an institutional care facility [38] are all associated with older patients undergoing surgery for rectal cancer (Table 1). The increased risk of postoperative complications predict for higher 1-year mortality [39••] and negatively impacts physical and role functioning [34, 40]. These findings have led to studies of alternative surgical approaches (e.g., laparoscopic or robotic surgery or even transanal TME) with hopes of reducing morbidity [41–43].

There is increasing interest in identifying patients who could effectively be treated with chemotherapy and radiation alone. If patients have achieved a pCR based on direct examination and biopsy, they may be managed [44] by local excision or even just observation. It is applicable to highly selected tumors with clinical complete response (cCR) to nCRT and requires intensive follow-up by an experienced colorectal surgeon using digital rectal exam, proctoscopy, and measurement of carcinoembryonic antigen (CEA) level at frequent



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**Table 1** Challenges in the management of rectal cancer in older adults

| |
|---|
| General |
| Increased frailty, loss of muscle mass, decreased performance status |
| Psychosocial issues, financial issues |
| Surgery related |
| Permanent colostomy if APR performed |
| Ostomy-related issues (daily management, fluid and electrolyte imbalance) |
| Postoperative ileus |
| Urinary dysfunction |
| Wound complications (dehiscence, infection) |
| Prolonged hospital stay |
| Radiation related |
| Local skin reaction/ulceration |
| Radiation proctitis |
| Fecal incontinence |
| Diarrhea |
| Pelvic fractures |
| Marrow suppression |
| Sexual dysfunction, vaginal fibrosis |
| Strictures, stenosis, fistulae as late complications |
| Secondary malignancies |
| Chemotherapy related |
| 5-FU and capecitabine-related toxicity including diarrhea, mucositis, marrow suppression, and rare neurotoxicity |
| Cardiac toxicity with 5-FU and capecitabine |
| Capecitabine cannot be used in severe renal impairment (CrCl < 30 ml/min) |
| Dose-limiting peripheral neuropathy with oxaliplatin |
| Irinotecan-related diarrhea and hepatotoxicity (contraindicated in severe liver dysfunction) |
| Severe myelosuppression with irinotecan particularly with UGT1A1 mutation |

intervals. To overcome the problem of inter-observer variability, novel MRI techniques and PET/CT may be effective [45–47]. Another investigational approach that may aid detection of residual disease or risk of recurrence in the future is analysis of circulating tumor DNA in blood [48•, 49].

If surgery is not performed or postponed, strict follow-up is the key to achieving equivalent oncological outcomes to those who undergo upfront surgery. In one study, about 31% of patients with initial cCR developed recurrence and more than half of those occurred within 12 months of follow-up. Salvage therapy is possible in ≥ 90% of recurrences, leading to 94% local disease control, with 78% organ preservation [37•, 50]. A study using decision-analytic modeling conducted with three patient cohorts (60-year-old men with mild comorbidities, 80-year-old men with mild comorbidities, and 80-year-old men with significant comorbidities) assigned to watch and wait versus surgery after neoadjuvant treatment found that survival was significantly better in the 80-year-old patients (both fit and comorbid groups) at 1 year in the watch and wait arm as compared to the surgery arm [51]. For tumors that respond poorly to nCRT, local excision is insufficient and associated with high rates of local recurrence [52]. It is hoped that more prospective data will be available in the near future from ongoing non-operative management (NOM) trials which involve initial chemotherapy followed by chemoradiation and careful documentation of cCR.

### Adjuvant Treatment

The current standard of care in stage II and III rectal cancer is to administer 4 months of postoperative adjuvant chemotherapy to complete a total of 6 months of perioperative treatment comparable to the total treatment course used (up until recently) in colon cancer. Since this recommendation is based mainly on extrapolation from colon cancer clinical trials, it is important to review recent findings in colon cancer. A pooled analysis from seven prior RCTs in colon cancer showed that adjuvant 5-FU-based chemotherapy (without oxaliplatin) improved survival even in patients > 70 years of age with no added toxicity compared to younger patients [53]. Addition of oxaliplatin is standard in stage III colon cancer but was not shown to add survival benefit to patients over 70 years of age. Results from the MOSAIC and NSABP C-07 trials also showed no overall survival benefit of adding oxaliplatin to 5-FU in the adjuvant setting in colon cancer [54, 55]. Similar results seem to be obtained in older adults with rectal cancer based on recent studies [56••, 57]. However, a trial comparing adjuvant capecitabine and oxaliplatin with 5-FU/LV in stage III colon cancer did show improved DFS across all age groups [58].

A recent pooled analysis of multiple concurrent trials in colon cancer evaluating a shortened course of oxaliplatin-based chemotherapy (combined with either capecitabine or infusional 5-FU) from 6 to 3 months of treatment found that for low risk patients (fewer than four positive nodes and T1-T3 tumors), 3 months of therapy may provide equivalent benefit with less peripheral neuropathy [59]. These trials are undergoing further follow-up but similar results may be relevant to rectal cancer. Investigation of the approach of administering all therapy before consideration of surgery in rectal cancer [60], may be of special value in older adults since chemotherapy and radiation are better tolerated in the pre-operative setting and successful completion of therapy may be increased in this manner.

## Management of Stage IV Rectal Cancer

A significant subset of patients with oligometastatic colorectal cancer can be cured through resection of liver or lung metastases along with the primary tumor. If this is not feasible, then systemic therapy is the main approach with goals of life extension but not cure. The primary tumor generally responds



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well to systemic chemotherapy. However, if this is large and causing immediate or impending complications, surgical resection, radiation, or stenting could be considered as an adjunctive/palliative approach. Stenting has a high short-term success rate [61]. A recent meta-analysis compared palliative surgery versus stenting showing that stents were less effective at relieving the obstruction but were associated with lower 30-day mortality rates [62] thus making this a reasonable option for older adult patients who may be poor surgical candidates due to their age and/or comorbid conditions.

The overall goal for unresectable stage IV disease is to deploy available agents sequentially to maximize survival extension while minimizing quality of life impacts (Table 1). Standard regimens include FOLFOX or FOLFIRI. An EGFR inhibitor cetuximab or panitumumab can be added to the chemotherapy backbone if the tumor is wild type for KRAS, NRAS, and BRAF. Use of these antibodies appear to show the most benefit in patients with left-sided colorectal cancer (including rectal) compared with right-sided colon cancer [63]. The vascular endothelial growth factor (VEGF)-inhibiting antibody bevacizumab is another option that can be added to the chemotherapy backbone in the upfront setting [64]. Treatment which combines bevacizumab with a fluoropyrimidine may be a better option for older adults based on a recent meta-analysis which showed that both overall and progression free survival was improved if bevacizumab was added to a fluoropyrimidine in older adults instead of irinotecan or oxaliplatin [65]. If a good response is obtained with induction treatment, continuation of maintenance treatment with bevacizumab and capecitabine could be considered as reported in the CAIRO3 study which showed improved progression-free survival with this maintenance strategy compared to observation alone. However, on age stratified subgroup analysis, this benefit did not reach statistical significance in the > 70-year patient cohort [66]. Of note, a recent study found that reduced dose capecitabine can result in improved quality of life in older adults with metastatic colorectal cancer without compromising the efficacy [67]. Capecitabine, being an oral agent unlike 5-FU, avoids the need for IV access and frequent clinic visits. This needs to be balanced with the patient's ability to manage oral medications and report symptoms.

Other VEGF targeting drugs can be used upon disease progression or bevacizumab can be continued [68, 69]. Two oral drugs have been recently approved based on survival extension for patients progressing after the various standard chemotherapy regimens: regorafenib [70] and trifluridine-tipiracil, also known as TAS-102 or Lonsurf [71]. Regorafenib has significant side effects which may limit its use in older adults, including hand-foot skin reaction, fatigue, diarrhea, hypertension, and rash. Encouragingly, a small trial with 23 older patients (> 75 years) published in 2018 with modified 2 weeks on 1 week off schedule of regorafenib showed that it may be a good alternative [72]. Further exploration of regorafenib [73] and another oral VEGFR-2 inhibitor, apatinib, are ongoing in refractory metastatic colorectal cancer [74]. Trifluridine-tipiracil is an anti-metabolite and its most notable toxicity is neutropenia. The pivotal trial of this agent included significant number of patients above age 65, who actually showed better response with a delay in the drop of performance status compared to placebo [71].

Increasingly, subsets of colorectal cancer patients are being identified who can respond to immunotherapy or targeted therapies. Anti-PD1 antibodies (nivolumab and pembrolizumab) are now approved in the second line for colorectal patients with microsatellite instability (MSI) based on high response rates and durable remissions in some patients [75, 76]. Although patients with Lynch Syndrome (genetic loss of mismatch repair genes) generally present at younger ages [77], sporadic MSI tumors actually occur at higher frequency in older adults [78, 79]. These results with immunotherapies are exciting given their overall effectiveness and reasonable toxicity profile in older adults [80•, 81]. However, it must be noted that the majority of colorectal cancers do not demonstrate loss of these genes/MSI. Given recent results showing high levels of effectiveness of adjuvant or neo-adjuvant immunotherapy in other cancers [82, 83], trials are ongoing including antibodies targeting the PD-1/PD-L1 pathway in adjuvant therapy of colon cancer or in combination with nCRT in rectal cancer [84]. Adding anti-VEGF therapy to nCRT has also been reported in a phase II trial [85]. These approaches may be particularly valuable for older patients if increased pCR rates can be achieved allowing less extensive surgery. Another potential avenue is targeted therapy against the HER2 receptor which is overexpressed in a minority of metastatic colorectal cancer patients [86].

## Conclusion

Rectal cancer is predominantly a disease of the older adult population. Treatment regimens are more challenging to tolerate compared to colon cancer, involving multimodality therapy especially for stage II and III disease. For older patients, instead of relying on chronological age alone, a geriatric assessment should be performed using the various available validated tools and those results used in shared decision-making. For the fitter older adults based on these analyses, the multimodality treatment including nCRT, surgery, and postoperative chemotherapy (possibly excluding oxaliplatin) is still the standard of care. For those at higher risk of toxicity or who refuse surgery, response to neoadjuvant treatment is emerging as a new prognostic marker and acts as a segue to next steps. Advances in imaging techniques like high-resolution MRI or assay of circulating tumor DNA may have the ability to more accurately detect cCR. "Watch-and-wait" may be reasonable strategy for carefully selected group of patients with complete



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clinical response to neoadjuvant treatment, without compromising oncologic or functional outcomes. Inclusion of additional pre-operative therapies (e.g., immunotherapy) may allow increased CR rates and reduction in need for radical surgery. Results of further prospective trials of this approach are awaited with interest. This is especially relevant to older and frail adults who have the greatest adverse quality of life impacts with key aspects of the current standard rectal cancer management (i.e. surgery and radiation). Although, there are some recently published geriatric oncology guidelines, they need to be bolstered further with the help of more randomized controlled trials tailored towards older adults with wide range of vulnerabilities. Efforts continue in the task of refining cancer-specific guidelines for this vulnerable but growing segment of the population worldwide. The overall goal for older adults with rectal cancer, as with all cancer therapy, is to maximize cure or disease control rates while minimizing adverse impacts on quality of life dictated by the patient's physical health, potential for treatment related toxicity, as well as his/her expectations and personal goals from the treatment. After a period of little change in the treatment of rectal cancer, recent new advances suggest that significant progress towards these goals is likely.

## Compliance with Ethical Standards

**Conflict of Interest** Ayesha R. Sheikh, Hassan Yameen, and Kevan Hartshorn declare they have no conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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