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Decision-Making Strategy for Rectal Cancer Management Using Radiation Therapy for Elderly or Comorbid Patients

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Abstract

Rectal cancer predominantly affects patients older than 70 years, with peak incidence at age 80 to 85 years. However, the standard treatment paradigm for rectal cancer oftentimes cannot be feasibly applied to these patients owing to frailty or comorbid conditions. There are currently little information and no treatment guidelines to help direct therapy for patients who are elderly and/or have significant comorbidities, because most are not included or specifically studied in clinical trials. More recently various alternative treatment options have been brought to light that may potentially be utilized in this group of patients. This critical review examines the available literature on alternative therapies for rectal cancer and proposes a treatment algorithm to help guide clinicians in treatment decision making for elderly and comorbid patients.

Introduction

Modern day treatment for locally advanced rectal cancer (LARC) (T3 or higher or lymph node positive) in the United States historically consists of neoadjuvant chemoradiation (CRT), followed by radical resection of the tumor and adjuvant chemotherapy. The current treatment paradigm has evolved remarkably from surgical management alone, which led to unacceptably high rates of local recurrences (1–3). Studies in the 1970s and 1980s investigated the role of preoperative or postoperative radiation therapy (RT) in the treatment of rectal cancer and found that inclusion of RT on average decreased the rates of local recurrence by 50% in the absence of total mesorectal excision (TME) (4–10). The addition of concomitant 5-fluorouracil (5-FU) with RT in the preoperative or postoperative setting further reduced the likelihood of recurrence and enhanced the tumoricidal effect (11–

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16). The seminal German Rectal Cancer Study Group trial addressed the question of preoperative versus postoperative CRT and found several improvements in clinical outcomes with preoperative CRT, including decreased rate of local recurrence, fewer acute and late toxicities, and higher rate of sphincter-preserving surgery in patients initially requiring abdominoperitoneal resection, which helped establish the commonly accepted standard of care of neoadjuvant CRT (17, 18).

Although these findings formed the basis of preoperative CRT as the standard of care for LARC, it is widely recognized that adherence to such a regimen is oftentimes impractical in elderly patients, who may have suboptimal functional status or comorbidities. Rectal cancer predominantly affects patients older than 70 years, with peak incidences in the 80- to 85-year-old age group (19). Yet patients in this age group were underrepresented in the majority of trials that shaped the current treatment paradigm for LARC. Understandably, these trials were designed to maximize treatment efficacy with aggressive therapy in patients with high performance status (PS), but PS may be compromised in the elderly or comorbid population. Thus, one purpose of this review is to underscore the dilemma in the management of LARC in the elderly population—a difficult balancing act between oncologic outcomes and treatment-associated morbidity and mortality. Although several geriatric assessment and prognostic tools can be helpful in predicting the tolerance of elderly patients receiving antineoplastic therapies, there is little information to guide adapted treatment for rectal cancer in this population (20–27). Therefore, it is the goal of this critical review to explore the various alternative therapeutic options for elderly patients regarding LARC management. We also believe that the evidence presented here potentially could be applied to other ill patients with significant comorbidities, and will henceforth refer to the population group as elderly/comorbid patients (ECPs). Finally, owing to the paucity of elderly data regarding alternative therapies for LARC, as well as the extensive extrapolation required to bridge the gap between available literature and applicability in the ECPs, we have divided this review into several sections to highlight the unmet needs of the ECP population with rectal cancer.

Assessment and Issues Relevant to ECPs

Understanding the unique needs of ECPs with rectal cancer is the first critical step for providing optimal care for these patients. One challenge of treating ECPs with LARC is the heterogeneity within this population, with wide spectrums of tolerability for and willingness to accept each given available treatment modality. We advocate for comprehensive pretreatment evaluations of ECPs with LARC to assess their fitness level to better guide treatment. The classification of patient fitness as described below will also form the basis of our proposed treatment algorithm. We also encourage treating physicians to respect the wishes and priorities of the ECPs when formulating treatment plans through the concept of shared decision making.

Comorbidity assessment in ECPs

Anticancer treatment is a double-edged sword: although it may provide cure or palliation, it may often cause a decline in the patient’s overall health or PS. Although otherwise healthy individuals with sufficient functional organ reserve can recover from the toxicities of various treatment modalities, those with pre-existing comorbidities might succumb to their adverse

effects. Although comorbidities are more prevalent, on average, in older patients (19), chronological age is not an accurate predictor for treatment-related outcomes and toxicities on an individual basis.

Balducci and Extermann (20) proposed that categorizing elderly patients into 3 functional groups based on a comprehensive geriatric assessment (CGA) screening can better evaluate the balance between safety and effectiveness of treatment. These groups include *fit patients* who are functionally independent, who may receive the full treatment; *frail patients* who are candidates for only palliation; and *intermediate patients* in between the *fit* and *frail* groups, who may benefit from modified treatment with lower toxicity. Proposed factors for CGA include functional status, number and severity of comorbidities, socioeconomic conditions, cognitive function, emotional and mental health, medication reliance and requirement, nutritional status, presence of geriatric syndromes, and functional reserve of organs (eg, liver, kidney, bone marrow) (20, 28, 29).

The oncologic–multidimensional prognostic index is another prognostic tool that can accurately predict the 1-year mortality of older cancer patients to help guide treatment decisions. Of the 658 cancer patients aged ≥70 years prospectively enrolled, oncologic–multidimensional prognostic index scores were used to stratify the patients into low-, intermediate-, and high-risk patients, which translated into a significant divergence of 1-year mortality rate observed (2.1% vs 17.7% vs 80.8%, respectively), with high discriminatory power (21).

However, CGA is a time-consuming process, and much effort has been made to develop screening tests to identify frail patients who may benefit from full evaluation with CGA (30–32). Unfortunately, all of the proposed frailty screening methods lack either sensitivity or specificity, or both, to predict the outcomes of CGA, and the current recommendation is for all elderly cancer patients to undergo a full geriatric assessment (23).

A systemic review of studies that examined the outcomes of elderly surgical patients who underwent preoperative CGA assessment and patient-specific optimization substantiated a benefit in reducing postoperative adverse outcome (33). Studies also investigated assessment tools using various components of the CGA to predict tolerance and toxicity to chemotherapy for older cancer patients. A prospective study with 500 elderly patients with cancer generated a predictive model for risks of developing grade 3 to 5 toxicity using CGA variables, laboratory values, and tumor/treatment characteristics (26). Similarly, the Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score was developed to predict the risk levels of hematologic and nonhematologic toxicities with chemotherapy in this older patient population (25).

Geriatric assessment is currently still under-utilized, and the International Society of Geriatric Oncology task force recommends wider adoption by clinicians. Although there is increasing evidence of the predictive value of treatment-related risk with geriatric assessment, whether treatment adaptation guided by these predictions can improve outcome or quality of life is a question that remains to be answered. As such, we seek to better define the various treatment options to optimally manage ECPs with LARC in this review,

especially for non-fit/frail patients. We proposed a classification of ECPs (*fit, intermediate*, and *frail patients*) largely based on Balducci and Extermann to help guide management; however, we acknowledge that a spectrum of patients is to be expected within each fitness class (Fig. 1, Table 1).

Shared decision making

Given the complexity in optimally treating ECPs with LARC, to have the clinicians involve the patients directly in the treatment decision making is of paramount importance (34). Patients and physicians oftentimes have different preferences in the treatment options for rectal cancer. Significantly more patients with LARC are willing to trade survival or disease control for quality of life than clinicians, who tend to favor more aggressive treatments (35, 36). In reality, however, treating physicians often overlook the priorities and wishes of their patients. A systemic review demonstrated low rates of shared decision making in consultations across all specialties (37). Additionally, a patient value study from The Netherlands showed that in a mere 18% of rectal cancer consultations did physicians explicitly consider the patient's values or treatment preferences. If patients' values were considered, the study showed increased patient-perceived involvement in the treatment decision process (38). Another study from the same Dutch group observed that only 3% of rectal and breast cancer consultations conducted discussion on treatment decision with the patients (39).

Current evidence suggests that shared decision making is an under-utilized concept. Therefore, it is important to emphasize the need for frank discussion of various treatment options for LARC, with the associated risks and benefits, to allow the ECPs to make informed treatment decisions.

Data on LARC Management With Background from Non-ECPs and Supporting Data Specific to ECPs

As mentioned earlier, treatment outcome data from various treatment modalities for LARC are lacking in the ECP population. In this section, we aim to discuss specific management strategies that stem from studies involving younger cohorts, with supporting data on treatment tolerability and efficacy in the ECPs. The available elderly data in this section help shape our understanding on how we may apply the following treatment regimens in the ECPs.

Surgery alone

Radical surgery remains the cornerstone for curative therapy in LARC (T3–4, N0–2, M0). The advent of TME has significantly improved local control with surgery alone and is the standard surgery for rectal cancer (40). However, an epidemiologic study showed that less-radical surgeries were performed for patients older than 70 years, likely attributable to known elevated risk of postoperative complications in the elderly, as well as patient or clinician preference (41). Nevertheless, for ECPs who are surgically fit, TME with curative intent alone is a viable option.

Trimodality therapy for LARC aims to optimize local and distant control of disease. However, treatment mortality and morbidity were shown to be higher in CRT compared with surgery alone in elderly patients (42, 43). Interestingly, studies have implicated that TME alone may result in excellent outcomes in select patients with LARC. Frasson et al (44) reported a 5-year local recurrence rate of 9.5% from an institutional cohort of 152 patients (mean age, 70 years) with cT2N+ or cT3N0/N+ rectal cancer who underwent TME alone without neoadjuvant or adjuvant therapies. Furthermore, patients preoperatively staged with free margin >2 mm from mesorectal fascia using MRI or endorectal ultrasound had a 5-year local recurrence rate of 5.4%, compared with 19.4% in those with threatened circumferential resection margins (CRM) (44). Indeed, CRM remains to be a significant prognostic factor for local recurrence, distant metastases, and overall survival in rectal cancer, and hence the need for neoadjuvant therapy for tumors involving the CRM (45, 46). A United Kingdom single-institutional study also demonstrated remarkable local control in patients with TME alone without residual disease, reporting an overall local recurrence rate (mean follow-up of 8.7 years) of 7.5% in Dukes C (lymph node-positive) patients (47). The local control rates from these retrospective data are remarkably comparable to those from large randomized trials using neoadjuvant radiation therapy or CRT, suggesting feasibility of TME alone in LARC patients with uninvolved CRM.

In contrast to the younger cohort, older patients who underwent TME surgery did not seem to have improved overall survival (OS) compared with non-TME surgery, owing to increased perioperative mortality, yet cancer-specific survival remained excellent (19, 42, 48, 49). Analyses from the Dutch TME trial and Comprehensive Cancer Centre registry showed that 1-month and 6-month postoperative mortality in patients aged ≥75 years were 4.5% to 7.8% and 14% to 16%, respectively, compared with 0.8% to 2.5% and 3.3% to 3.9% in those younger than 75 years (48). Furthermore, a systemic review of 28 studies with a total of 34,194 patients who underwent colorectal surgeries concluded that incidence of postoperative morbidity and mortality increased progressively with advanced age. When comparing patients with age groups of <65 years, 65 to 74 years, 75 to 84 years, and 85+ years, the median postoperative mortality rates reported were 3.0%, 6.4%, 8.6%, and 19.4%, respectively. Incidence of postoperative morbidities from anesthesia, such as respiratory complications, cardiovascular complications, cerebrovascular accidents, thromboembolism, and memory decline, all significantly increased with age (50, 51). Although not yet widely adopted, preoperative CGA assessment and appropriate interventions based on each patient's pre-existing comorbidities may improve postoperative outcomes in elderly patients (33).

Despite potentially increasing the morbidity and mortality of surgery for ECPs, open surgery remains the standard surgical technique for TME. Laparoscopic surgery for rectal cancer is gradually gaining awareness, given its better tolerability and faster recovery demonstrated in colectomy. A laparoscopic approach for TME surgery was recently shown in the COLOR II trial in patients with mean age of 66 years to have decreased blood loss, sooner return of bowel function, and shorter hospital stay compared with open surgery, without compromising locoregional control or survival for rectal cancer >2 mm from endopelvic fascia (52, 53). A single-institution, prospective, randomized trial demonstrated decreased surgical morbidity rate in elderly (age ≥70 years) patients undergoing laparoscopic surgery for colorectal cancer compared with open surgery (20.2% vs 37.5%, $P = .01$) (54).

Furthermore, a case-matched control study showed that, despite octagenarians (age ≥80 years) having expected higher American Society of Anesthesia score than middle-aged controls (age 60–69 years), there were no significant differences in both morbidity incidence or 5-year cancer-specific survival in both cohorts (55). Although data suggest feasibility and utility of laparoscopic surgery in elderly patients, future randomized studies in ECPs with LARC comparing laparoscopic versus open surgery with specific attention to the preoperative CRM status are warranted, to better select patients for the optimal surgical technique.

In the meantime, thorough preoperative workup, CGA assessment, and frank discussion with patients regarding pros and cons of radical surgery are recommended. Surgery alone remains an appropriate option for those who are low risk for surgery with favorable CRM status. However, for patients who are *fit* or adequate surgical candidates, implying potential longevity, it would be reasonable to consider (neo)adjuvant therapies as well. Ultimately, discussion with the *fit patients* must make clear that reducing treatment morbidity by omitting preoperative RT or CRT may come with the potential cost of higher risk of local recurrence, especially if CRM are positive. For *intermediate patients*, surgery alone is therefore a reasonable option to provide curative therapy without adding treatment toxicity from (neo)adjuvant therapies.

CRT in elderly patients

Although CRT for rectal cancer is most known for its use in the neoadjuvant setting, many of the ECP population may not be surgical candidates. Given the aforementioned possible risks of TME surgery in the ECP population, nonoperative management (NOM) with CRT is a suitable alternative in ECPs with significant comorbidities who may not tolerate surgery, whereas preoperative CRT may be considered in *fit patients.*

Concurrent CRT has been shown in non-ECPs to have greater therapeutic effect compared with radiation or chemotherapy alone and is the current standard for neoadjuvant or adjuvant therapy for rectal cancer. Although the pathologic complete response (pCR) rates in these studies are in the range of 10% to 15%, this evidence substantiates the tumoricidal effect of CRT as a feasible nonoperative treatment option for ECPs (11–13).

Extrapolation of the results of several retrospective studies on CRT for elderly patients suggests that both definitive and neoadjuvant CRT are effective in ECPs. A French study that aimed at analyzing the treatment efficacy for rectal cancer in elder patients found that patients with age ≥85 years were treated preferentially with CRT and nonsurgical management, which demonstrated a 5-year OS rate of 45% and disease-free survival (DFS) rate of 65%. Although the OS in this elderly cohort was inferior (owing to complications and comorbidities) to that of the younger patients enrolled in large randomized studies, the DFS was, in fact, similar or improved (56). In terms of the biological effect of treatment, Choi et al (57) described a single-institution retrospective experience, which demonstrated that of the 160 patients treated with neoadjuvant CRT, older patients (age ≥70 years) exhibit no differences in tolerance to CRT, pCR rate, and treatment-related complications compared with younger patients (age <70 years). Likewise, a small series of 36 patients with age ≥70 years with rectal cancer were categorized as “fit” or “vulnerable” according to the number

and severity of comorbidities, and all patients regardless of fitness were able to tolerate the full course of concurrent CRT (50.4 Gy with bolus or continuous infusion 5-FU), with similar rates of pathologic down-staging and without differences in toxicity (58). Finally, a Surveillance, Epidemiology, and End Results program analysis of 4121 elderly patients aged >75 years with LARC showed that the 5-year cancer-specific survival was best for those who underwent neoadjuvant CRT (70.4%), followed by adjuvant RT (60.4%), surgery alone (52.1%), and RT alone (27.7%) (59). Although these retrospective data are limited by the inherent bias of patient selection and inclusion of patients for whom CRT was successfully administered, they suggest that CRT remains to be an effective therapy in elderly patients who can tolerate treatment, and this likelihood of tolerance should be assessed by CGA.

Neoadjuvant CRT, however, can potentially cause greater toxicity in ECPs compared with their younger counterparts. In an unplanned subset analysis of the ACCORD12/PRODIGE2 phase 3 trial, in elderly patients (age ≥70 years) compared with those with aged <70 years, preoperative CRT led to more severe grade 3 or 4 toxicities (25.6% vs 15.8%) and more permanent stomas (33.3% vs 22.8%). The lower rate of stoma reversal in older patients was due, in part, to higher rates of anastomic fistula compared with younger patients (38.9% vs 10.9% of those who develop complications) (60). These outcomes indicate that ECPs may have lower tolerance for preoperative CRT, and thus careful selection of patients for neoadjuvant CRT and individualized tailoring of therapy are warranted to ensure treatment safety.

Concomitant CRT is effective in ECPs. Although the standard preoperative CRT consisting of RT doses of 45 to 50.4 Gy and concurrent 5-FU—based chemotherapy achieves rather low rates of pCR as mentioned previously, it forms the basis of various treatment combinations as discussed in later sections [see “CRT and observation (nonoperative management),” “CRT with dose escalation,” and “CRT with local excision”].

Brachytherapy

The 2 most common forms of brachytherapy for treatment of rectal cancer are Papillon contact X-ray 50-kV brachytherapy (CXB; also known as endocavitary brachytherapy) and high-dose-rate endorectal ^{192}Ir brachytherapy (HDREBT). The advantage of brachytherapy is that large doses of radiation can be delivered locally for excellent tumor control, while minimizing radiation-induced side effects to adjacent organs. For early-stage disease, brachytherapy is a feasible alternative to local excision (LE). For advanced disease, brachytherapy alone can achieve high rates of local control and/or pCR and is an alternative for ECPs who cannot tolerate CRT or surgery. Brachytherapy can also be used to salvage local recurrences after NOM or in the setting of reirradiation, as detailed below.

Advanced tumors with high T stage or nodal involvement often require multimodality therapy. However, for ECPs with poor performance status who cannot tolerate chemotherapy or a full course of external beam radiation therapy (EBRT), treatment or palliation with brachytherapy may be an option, as extrapolated from surgical evidence derived from non-ECPs. Vuong et al (61) at McGill University were one of the first groups to investigate the efficacy of neoadjuvant brachytherapy for LARC. Using HDREBT to 26 Gy delivered over 4 consecutive days, Vuong et al treated 49 patients with T2 to early T4 operable

tumors, followed by surgical resection after 4 to 8 weeks, and pathology revealed that 32% of patients had pCR and another 36% had only microscopic residual disease at the primary tumor site. The authors' follow-up study, which examined 100 patients with mostly T3 tumor using the same brachytherapy regimen, resulted in 29% of patients with ypT0N0–2 and 37% with micro-foci residual disease in surgical specimens. All of the patients developed acute proctitis, but 99% of them had grade 2 proctitis (62). Preoperative brachytherapy alone for LARC may be an excellent neoadjuvant option for *fit patients*. More importantly, the above evidence suggests that high doses of radiation delivered locally with brachytherapy, although they may not be curative owing to involvement of lymphatic spread or extent of primary disease, can still achieve high rates of local control at the site of primary disease for LARC. This notion is supported by retrospective data from investigations of the role of brachytherapy for advanced rectal cancer for which the patients were inoperable owing to old age with poor performance status, advanced disease, or presence of metastasis. With a median age of 82 years, these studies demonstrated high rates of local tumor control (local tumor response in 85% of patients, with complete response in approximately 60%) in elderly patients who were unfit for surgery or were treated with palliative intent. Definitive treatments were delivered via HDREBT up to 36 Gy in 6 fractions or as a boost of 12 Gy after conventional CRT, and the median survivals of those treated with radical intent were 18.5 to 25 months (63, 64). Late toxicities with rectal ulcers, strictures, and fistula were reported in 8% of patients (64). Altogether, evidence suggests that *frail patients* with LARC who cannot tolerate surgery or CRT may benefit from brachytherapy alone for local control and symptom palliation, with acceptable toxicity.

Brachytherapy is also a nonsurgical alternative for salvaging residual disease after NOM. Sun Myint et al (65) reported a series of 83 patients (median age, 72 years) with cT2–3 rectal cancer who had residual disease (≤3 cm) after CRT/EBRT and subsequently received salvage treatment with CXB. A total CXB dose of 90 Gy was delivered in 3 fractions over 4 weeks, and clinical complete response (cCR) was achieved in 53 (63.8%) patients. Several NOM studies [see "CRT and observation (nonoperative management)," below] also successfully used brachytherapy for salvage of disease progression after initial cCR (66–68). These results demonstrate that brachytherapy is a feasible alternative to surgical management in ECPs after appropriate down-staging of disease with CRT or EBRT.

Brachytherapy may also be a preferred mode of treatment for ECPs with rectal cancer who previously received pelvic irradiation. Additional EBRT is not recommended for patients who have had pelvic irradiation because of increased risk of long-term complications in adjacent organs or tissues. As such, reirradiation using HDREBT is dosimetrically more conformal to spare previously irradiated tissues while allowing dose escalation to the tumor. Currently, available data on reirradiation with brachytherapy are limited. Chuong et al (69) reported a retrospective analysis of a small group of patients (n = 10) with median age of 74 years receiving endorectal brachytherapy after previous radiation, with 3 patients achieving at least near-complete pathologic response and none with grade ≥3 acute toxicity. Future studies investigating brachytherapy for rectal cancer in the setting of reirradiation are highly encouraged.

Brachytherapy alone can be used in *frail patients* with LARC for both radical and palliative treatments. It is also a viable nonsurgical option for salvage therapy. Although additional data are needed, definitive or preoperative brachytherapy are likely feasible in the setting of reirradiation in ECPs.

Extrapolation From Non-ECP Studies for Clinical Application in ECPs

A major obstacle in optimizing LARC management in ECPs is the lack of high-level evidence supporting the use of various alternative therapies in this patient cohort. Ironically, these less-invasive treatment modalities are well suited to ECPs and are intended to minimize treatment toxicity while maintaining good oncologic outcomes. In this section we endeavor to explore the various treatment regimens studied in younger/healthier cohorts and extrapolate their clinical utility to ECPs.

CRT and observation (nonoperative management)

The knowledge that CRT can achieve pCR has prompted several investigations to query whether patients with LARC can be treated with up-front CRT, with surgery reserved only for salvage therapy, also known as nonoperative management (NOM). Nonoperative management aims to avoid or delay the complications and morbidity of radical surgery for treatment of rectal cancer. Although the majority of the NOM studies enrolled or analyzed patients in the younger cohort (median age of late 50s to mid-60s), the results are very encouraging for its application in ECPs with rectal cancer (Table 2), especially for those who wish to avoid perioperative surgical complications or who are at high risk for surgery (66–68, 70–78). Moreover, a decision-analytic model from the United Kingdom using Markov chain simulation found an absolute survival benefit in fit (10.1%) and comorbid (13.5%) 80-year-old patients at 1-year after treatment when NOM was implemented instead of radical surgery, underscoring a compelling adverse effect of surgical risks in ECPs (79).

In the setting of NOM, Habr-Gama et al (56) spearheaded this initiative and published their results on 265 patients with stage I-III potentially resectable adenocarcinoma of the distal rectum treated with neoadjuvant 5-FU, leucovorin, and 50.4 Gy of radiation concurrently. Patients were re-evaluated with endoscopic examination after 8 weeks from completion of CRT; those with gross residual disease or ulcer underwent immediate radical surgery, whereas those with cCR underwent strict observation. Seventy-one patients (26.8%) achieved cCR with CRT alone, with an overall recurrence rate of 7.0% (n = 5) at a mean follow-up period of 57.3 months. Of the 5 recurrences, 2 patients with local recurrence were salvaged with brachytherapy and LE. Interestingly, 8% of patients with incomplete responses who under-went surgery had pCRs. When comparing the observation cohort with cCR versus those with pCR after surgical resection, the 5-year overall survival was 100% and 88%, and DFS was 92% and 83%, respectively, with patients in the observation arm having similar, if not better, outcomes (66). Although the mean age of this cohort was only 54.8 years, these favorable results speak to the possibility of avoiding surgery in ECPs achieving cCR after CRT. Several studies, thereafter, reported similarly favorable outcomes of NOM, further providing credence for NOM as an alternative in ECPs (68, 71, 72).

Although NOM is an attractive alternative to surgical resection in the ECPs, careful selection of those who are likely to have true cCR is critical (76). Moreover, there is a considerable risk for patients with cCR to still harbor microscopic disease in the rectal wall and/or mesorectum and therefore remain at risk for developing local recurrence. An important question, consequently, is whether local recurrences after NOM can be effectively salvaged without compromising oncologic outcomes. Although most of the NOM studies demonstrate that most local recurrences were salvaged, albeit with limited follow-up data, this specific question was investigated only recently in a study by Habr-Gama et al (67). The study enrolled a total of 183 patients (mean age, 58 years) with T2–4N0–2 locally advanced distal rectal cancer who were treated with CRT (50.4–54 Gy RT with 5-FU-based chemotherapy), and 90 patients (49%) achieved cCR after 8 weeks from treatment completion. Of the cCR patients, 28 (31%) experienced local recurrences, with the majority of the recurrences developing within 12 months, and 26 patients underwent salvage therapy (mostly with TME surgery), with an overall salvage rate of 93%. The 5-year cancer-specific survival and DFS of the entire cCR cohort was 91% and 68%, respectively, and the 5-year local recurrence-free survival was 94% after salvage. For the 26 patients who were salvaged after local recurrence, the 3-year cancer-specific survival and DFS were 88% and 78%, respectively (67). This study demonstrated that salvage after NOM is effective without jeopardizing patient outcomes and can be applied to ECPs.

Altogether, the various studies on NOM have validated, albeit in younger patients, its feasibility and effectiveness as an alternative treatment option to standard of care for ECPs, with emphasis on minimizing treatment-related mortality and morbidity, which are particularly vital considerations when treating *intermediate* or *frail patients*.

CRT with dose escalation

While achieving cCR or pCR with CRT alone for LARCis the ideal outcome, the majority of patients, unfortunately, would be expected to have an incomplete clinical response (80). One contributing factor is the limited radiation dose with pelvic RT that can be safely delivered to the rectum and pelvis to avoid bowel toxicity. Patients with incomplete response after CRT can benefit from TME surgery as per standard of care. However, for ECPs not amenable to surgery, radiation boost with brachytherapy and/or EBRT can be used to increase local control of the disease to avoid surgery.

Numerous studies have evaluated the radiation dose—response effect on rectal cancer (Table 3) (74, 81–88). A higher radiation dose of 45 Gy has been identified as an independent factor for rectal tumor achieving pCR (84). Several phase 2 dose escalation studies have shown that pCR rates with doses from 46 to 50.4 Gy are significantly higher than that with <40 Gy (85–87). Moreover, modeling of radiation dose—response effect demonstrated that radiation dose of 92 Gy (equivalent dose in 2 Gy per fraction) is required to achieve pCR, whereas 72.1 Gy is required for major response, in 50% of patients (88).

Jakobsen et al (81) published one of the first studies that increased the radiation dose in concurrent CRT even higher, with dose escalation of the EBRT boost plus a brachytherapy boost. By treating the pelvis to 48.6 Gy and boost to gross disease to 60 Gy with concurrent tegafur-uracil, followed by a single 5-Gy endorectal brachytherapy boost to tumor bed, 27%

of the 48 patients with T3 rectal cancer had pCR, and another 27% had only microscopic tumor left after resection. The median age of the study cohort was 61 years, and only 6% of the patients had grade 3 nonhematologic toxicities. The same group later conducted a randomized trial comparing the standard CRT regimen of 50.4 Gy in 28 fractions with or without endorectal boost with brachytherapy (10 Gy in 2 fractions). Although the overall pCR rate was equivalent at 18% between the 2 arms, dose escalation with brachytherapy resulted in a significant increase in the rate of major tumor response (44%) compared with CRT alone (28%), including both complete response and residual microscopic disease. Toxicity rates between the 2 arms were shown to be similar (82). Outcomes and tolerability reported from these studies support the use of dose escalation and may be extrapolated to ECPs.

Using a similar dose-escalated regimen as Jakobsen et al, a Dutch study treated 51 patients with low-lying resectable rectal cancer (T2-T3, N0-N1) with 50 Gy to the pelvis and 60 Gy to the gross tumor using intensity modulated RT with concomitant boost, followed by a 5-Gy endorectal high-dose-rate brachytherapy boost with concurrent tegafur-uracil. Forty patients (78%) were found to have cCR and subsequently underwent observation, and the local recurrence rate at 1 year was 15.5% for the observation group. Interestingly, the cCR rate in this study seems to be higher than those of other NOM studies, potentially as a consequence of dose escalation, but it may also be due to a higher proportion of smaller tumors. The major late toxicity noted in this study was rectal bleeding, which occurred in roughly 80% of patients, although most cases were mild (<10% with grade 3 bleeding) (74). Although enrolled patients had a median age of 67 years, this regimen provides an opportunity to increase the rate of cCR and reduce the potential need for surgery in ECPs.

Dose escalation can lead to more tumor cell killing and greater tumor regression; but more importantly, to achieve an optimal balance between tumor control and treatment toxicity is crucial. Brachytherapy seems to be a feasible modality for delivering higher doses of radiation to improve local control while minimizing toxicity. The absence of increase in toxicity with dose escalation in the aforementioned studies is promising and supports this alternative option for ECPs. However, optimization of dose and fractionation of brachytherapy or EBRT boost done specifically in the elderly cohort may further refine this treatment concept to ECPs (similar to the HERBERT study discussed below in “EBRT with brachytherapy”).

CRT with local excision

Local excision is an acceptable alternative to TME surgery for early node-negative rectal cancer, such as select T1N0 tumors (size <3 cm, well to moderately differentiated, involving <30% of rectal circumference, and no lympho-vascular space invasion), because the survival outcome with minimally invasive surgery is similar to that of radical resection, albeit with higher rates of local recurrence (89–91). The benefit of LE, namely transanal excision and transanal endoscopic microsurgery, include organ preservation, lower rates of surgical morbidity, and improved quality of life. However, LE is not sufficient for T2 tumors or T1 cancers with high-risk features, owing to higher risk of local recurrence, higher risk of lymph node dissemination, and inferior survival outcome (92–94). As such, TME surgery is

the standard of care for T2 rectal cancer, whereas T3/T4 cancers often require the addition of neoadjuvant or adjuvant therapy. However, TME is associated with higher risk of long-term complications and postoperative mortality, especially in older patients (49). Alternatively, several retrospective and prospective studies have shown that neoadjuvant CRT before LE for T2 to T3 (mostly node-negative) rectal cancer can achieve similar local control compared with TME and therefore is a feasible treatment option for ECPs with these tumors to minimize surgical complications (Table 4) (95–101).

A single-institution prospective study in Italy compared LE with endoluminal locoregional resection versus standard TME surgery for select T2 rectal cancers (grade 1–2, tumor size <3 cm, and within 6 cm of the anal verge) after neoadjuvant CRT. One hundred patients with median age of 66 years were randomized to receive the 2 surgical approaches, and after a median follow-up of 9.6 years the local recurrence rates of the endoluminal locoregional resection (8%) and TME (6%) arms were similar (97). Additionally, the American College of Surgeons Oncology Group published results of their multi-institutional phase 2 trial, demonstrating the efficacy of CRT followed by LE in clinically T2 rectal cancer (ACOGSOG Z6041). With 79 eligible patients (cT2N0, size <4 cm, involving <40% circumference, and located <8 cm from anal verge), 72 patients (median age, 62 years) underwent RT to 50.4 to 54 Gy with concomitant capecitabine and oxaliplatin, and the 3-year DFS for the per-protocol group was 86.9%. Of note, 3 patients who underwent LE were found to have ypT3 tumor (excluded from per-protocol analysis), and 2 of the patients underwent salvage TME (99).

In some studies, this multimodality treatment was also used in cT3 rectal cancer. In the CARTS prospective multicenter study, 47 patients (median age, 64 years) with cT1–3 distal rectal cancer underwent CRT (50 Gy or 50.4 Gy with capecitabine) followed by LE. Significant down-staging of the tumor was observed, and those with ypT2 or higher after LE were offered salvage TME. After a median follow-up of 17 months, none of the ypT0 patients had recurrence, and only 1 patient with ypT1 developed local recurrence, with organ preservation in half of patients who would have required TME surgery (100).

Studies for LE after CRT for T2-T3 rectal cancer show promising results. In the era of increasing interest in NOM or less-invasive surgeries, adopting this regimen in the ECP population would be a reasonable consideration for those who would benefit from the addition of LE, albeit with certain challenges. Currently it is unknown whether patients with cCR after CRT would benefit from additional surgery with LE. Furthermore, if surgical pathology after LE demonstrates ypT2–3 or nodal involvement, the utility of LE may be present but requires additional data. Hypothetically, patients with residual ypT1 disease may benefit the most from LE after CRT. However, determining response or degree of residual disease after CRT may be challenging, given the limitations in staging techniques such as endorectal ultrasound, MRI, CT, or positron emission tomography (102–107). Indeed, this notion is exemplified by the results of the GRECCAR-2 prospectively randomized phase 3 study, in which 148 patients (median age, 61–64 years) with T2–3N0–1 rectal cancer with good response (residual tumor ≤2 cm) after CRT (50 Gy 3-dimensional conformal pelvic RT in 2-Gy fractions with concurrent capecitabine and oxaliplatin) were randomized to receive either LE or TME. Clinical response of CRT was assessed by pelvic MRI 6 to 8

weeks afterward. Of the 73 patients in the LE arm, 34 patients had unfavorable pathological response after LE (ypT2–3 or R1 resection), for which TME was recommended, and 26 of those patients received TME. Although the study hypothesized lower morbidity and side effects with LE, the intention-to-treat analysis showed no differences in all primary outcomes (death, tumor recurrence, morbidity, and side effects), presumably owing to a significant number of patients in the LE arm receiving TME. Furthermore, of the patients in the study who were considered as clinically inadequate responders after CRT and who were nonrandomly assigned to receive TME, 39% had good pathologic responses (ypT0–1) (108). These results underscore the importance of optimizing restaging assessment and patient selection for optimal use of LE after neoadjuvant therapy. Furthermore, the results suggested that few positive lymph nodes (8%) occurred in such small irradiated tumors, indicating that completion TME could be limited to less than 10% of patients who had been down-staged to ypT2N1 and ypT3. This notion will need additional prospective evaluation.

Again, the above studies were conducted primarily in non-ECPs, but given the tolerability of the therapy and the potential to avoid TME, LE for ECPs could be a reasonable alternative when appropriately or sufficiently down-staged by CRT.

Short-course RT

Short-course RT (SCRT) before radical surgery for rectal cancer, similar to the effect of preoperative CRT, improves local control compared with surgery alone (Table 5) (109–112). Randomized trials also showed that rectal cancer patients receiving preoperative SCRT also have better local control than with postoperative CRT (113, 114). Preoperative SCRT has been shown to achieve locoregional control and OS comparable to that with standard conventional preoperative CRT. Both the Polish and the Trans Tasman Radiation Oncology Group 01.04 trials showed that SCRT (5 Gy × 5 delivered in 1 week) followed by immediate surgery can achieve outcomes similar to those with long-course CRT (50.4 Gy in 28 fractions with concomitant 5-FU) followed by surgery 4 to 6 weeks later (115, 116).

Neoadjuvant SCRT can be more convenient and with a higher compliance rate for ECPs who are surgical candidates. However, the Dutch TME subgroup analysis showed that although patients older than 75 years responded well to preoperative SCRT in terms of oncologic outcomes, it is also associated with significantly higher treatment-related mortality at 6 months compared with surgery alone (48). Another Dutch study of patients older than 75 years with T2–3N0–2M0 rectal cancer diagnosed between 2002 and 2004 reported a significant increase in postoperative complications in patients receiving preoperative RT (short or standard course) compared with those who underwent surgery alone (58% vs 42%), especially wound and deep infections (43). Although meta-analysis of trials comparing preoperative SCRT with standard CRT demonstrated large differences in rates of acute toxicity (which is largely due to patients undergoing SCRT receiving immediate surgery and bypassing the manifestation of acute radiation toxicity), rates of late toxicity between the 2 neoadjuvant regimens were similar (121). As such, patient selection for SCRT followed by surgery should be as rigorous as that for standard of care with preoperative CRT and TME surgery.

The Stockholm III trial results have broadened our knowledge of SCRT. In this multicenter, randomized, phase 3 noninferiority trial, patients with stage I-III resectable rectal cancer were randomized to 3 arms: (*1*) SCRT (5 Gy × 5) with immediate surgery; (*2*) SCRT with surgery 4 to 8 weeks thereafter; and (*3*) long-course RT (2 Gy × 25) with surgery after 4 to 8 weeks. After a median follow-up of 5.2 years, very few local recurrences occurred, without significant differences among the 3 arms. No difference in distant metastases was observed as well. However, when comparing SCRT with or without delay to surgery, patients who underwent delayed surgery experienced significantly lower rates of postoperative complications than those with immediate surgery (41% vs 53%). Although timing of surgery after SCRT did not affect local control of tumor, patients who underwent delayed surgery had higher rates of tumor down-staging and pCR (11.8% vs 1.7%), which was not unexpected given that there was more time for tumor regression to occur (117–119). This 1-week regimen could be applied to ECPs for purposes of convenience without apparent compromise in outcomes.

Although the Stockholm III trial demonstrated that SCRT with delayed surgery is a good alternative to conventional therapy, because it reduces treatment time while preserving effectiveness of tumor control, it also raises interesting questions that may be pertinent for ECPs who may not be able to tolerate surgery.

Is SCRT alone an effective treatment?—According to Stockholm III tumor regression data, the pCR rate 4 to 8 weeks after SCRT appears comparable to historic data with conventional CRT. Thus, it may be potentially beneficial to utilize SCRT in lieu of conventional CRT in NOM or a dose-escalation approach (see above, “CRT and observation” and “CRT with dose escalation”).

Could chemotherapy be integrated with SCRT?—In the Stockholm III trial in which patients did not receive concomitant chemotherapy with RT, and most did not receive adjuvant chemotherapy, the majority of disease recurrences were distant metastases. For patients planned for delayed surgery after SCRT, this waiting period provided an opportunity for neoadjuvant chemotherapy to be given to improve distant control of disease. Similarly, ECPs not fit for surgery may potentially benefit from chemotherapy after SCRT. In a phase 3 Polish trial, patients with fixed cT3 or cT4 rectal cancer were randomized to either: (*1*) SCRT (5 Gy × 5) followed by 5-FU—based chemotherapy; or (*2*) 5-FU—based concurrent CRT to 50.4 Gy in 28 fractions. Interestingly, SCRT with sequential chemotherapy compared with concurrent CRT demonstrated a similar R0 resection rate (77% vs 71%), pCR rate (16% vs 12%), and incidence of local failure (22% vs 21%) and distant metastases (30% vs 27%) but exhibited improved 3-year OS (73% vs 65%) and decreased rates of acute toxicity (75% vs 83%) (120). Although the primary endpoint of the study was rate of R0 resection, the overall findings can arguably be extrapolated to support the use of SCRT with sequential chemotherapy (preoperatively or definitively) as an alternative to standard CRT for ECPs.

Adjuvant local excision after SCRT

Despite that minimally invasive surgeries are potentially acceptable alternatives to radical surgeries in select cases (see above, “CRT with local excision”), current available literature does not recommend the use of LE after SCRT. A recent pilot study evaluating the efficacy of SCRT followed by LE 4 to 10 weeks after for T1-T2 rectal cancer revealed surprisingly high rates of major postoperative complications, including rectal suture dehiscence and enterocutaneous fistula, which prompted early closure of the trial (122). Although reasons are unclear, preoperative standard CRT seems to be associated with lower rates of major surgical complications after LE, without significant adverse effect on quality of life (99, 100). As such, LE should only be performed adjuvantly after standard long-course RT or CRT. For patients who received SCRT in the preoperative setting with the plan to undergo surgery, TME is recommended.

Palliation

Finally, given the convenience of the fractionation, SCRT alone can also be used in the palliative setting for symptomatic control. In a recently published phase 2 study with 18 patients with obstructive rectal cancer not amenable to curative treatment, 38.9% and 50% of patients had complete and partial symptomatic resolution after 4 weeks of completing the 5 Gy × 5 regimen, respectively. The study reported that the need for colostomy for obstructive symptoms was avoided in most patients, with 3-year colostomy-free survival of 47.6% and overall survival at 39.8% (123). Providing good local tumor responses for symptom palliation, the 5 Gy × 5 regimen is an excellent option for frail patients with advanced disease.

Adjuvant chemotherapy

The clinical benefit of adjuvant chemotherapy after definitive treatment with neoadjuvant CRT followed by surgery for LARC stage II-III has long been a controversial subject, given the lack of support with strong evidence. This is reflected in the large differences among guidelines throughout the world, ranging from National Comprehensive Cancer Network guidelines recommending adjuvant chemotherapy in stage II/III rectal cancer after receiving neoadjuvant CRT and surgery to the Dutch and Norwegian guidelines that do not recommend postoperative chemotherapy in patients who have received preoperative CRT (124). Results from large phase 3 randomized trials investigating the utility of adjuvant chemotherapy after preoperative RT (with or without preoperative chemotherapy) do not show survival benefits (125–128). In the largest of such studies to date, the European Organization for Research and Treatment of Cancer 22921 trial randomized 1011 patients with clinical T3–4 resectable rectal cancer to adjuvant chemotherapy or surveillance after preoperative RT (with or without concomitant chemotherapy) and surgery, but failed to show survival advantages in the adjuvant chemotherapy cohort compared with the surveillance cohort after a median follow-up of 10.4 years (10-year OS 51.8% vs 48.4%, $P = .32$; 10-year DFS 47.0% vs 43.7%, $P = .29$) (125). One argument for the lack of survival benefits in these trials was that the sample sizes were not large enough, but 2 independent meta-analyses of the randomized trials also failed to show significant benefit (129, 130).

Because of the limited benefit, if any, of adjuvant chemotherapy in LARC, its risks and benefits of application in ECPs need to be carefully weighed. Quality of life for patients receiving adjuvant 5-FU chemotherapy significantly deteriorated during the length of the treatment in a prospective study (131). Postoperative chemotherapy can also cause significant late adverse effects that can have a negative impact on quality of life after treatment, as described in the quality-of-life evaluation of patients treated in the European Organization for Research and Treatment of Cancer 22921 trial (132). Furthermore, a Surveillance, Epidemiology, and End Results program analysis by Lund et al (133) reported no benefit of postoperative 5-FU or capecitabine in patients with age ≥75 years in terms of reduction of all-cause or cancer-specific mortality. In line with the minimally invasive approach in NOM, such as the Habr-Gama et al series, most patients in the NOM studies did not receive adjuvant chemotherapy, although may be largely reflected by institutional practices (Table 2). However, the incremental benefit of chemotherapy after NOM remains unclear; whether further chemotherapy after CRT could prolong the disease-free interval or improve the rate of pCR are questions that remain unanswered (134). Although adjuvant chemotherapy can be offered to *fit patients* with frank discussion of the risks and benefits, it may be avoided in most ECPs, unless there are poor prognostic features.

Data Specific to ECPs: EBRT With Brachytherapy

As previous sections have illustrated, evidence regarding the use of most alternative therapies for ECPs with rectal cancer is lacking, but clinical application of the aforementioned treatment modalities can be extrapolated to ECPs from non-ECP studies in these disciplines. However, the combination modality using EBRT alone with brachytherapy, as discussed below, was evaluated almost exclusively in ECPs on the basis of the available literature. This is not surprising, because this regimen is only suitable for *frail patients* with significant comorbidities who are unfit for surgery and cannot tolerate chemotherapy owing to poor performance status.

Recent efforts in formulating alternative treatment options have shown that standard RT is feasible for elderly patients with T2 to T4 rectal cancer. In the absence of chemotherapy, locoregional control of tumor, as well as control of disseminated disease, would be compromised. Therefore, achieving comparable local control would require higher doses of radiation than the standard 45 to 50.4 Gy of EBRT. Several studies, mostly retrospective, have shown that dose escalation beyond the standard pelvic radiation with EBRT is viable using brachytherapy for attaining reasonable rates of local control (see also above, “CRT with dose escalation”) (135–140).

A Washington University experience of treating 199 patients, with a substantial number of elderly patients (median age, 71 years), with most receiving EBRT (mean 45 Gy in 25 fractions) followed by endocavitary brachytherapy (most received 60 Gy to the mucosal surface in 2 fractions 2 weeks apart) without chemotherapy, showed a local control rate of 85% for cT2 and 56% for cT3 tumors after a median follow-up of 70 months. Of the patients treated, 54 had prior endoscopic removal of macroscopic disease; 71% of patients were treated with RT alone, whereas some underwent salvage surgery afterward (135). Similarly, the French experience at Lyon Sud reported a primary local tumor control rate of 60%

to 95% for T2-T3 rectal cancer in elderly patients with median age of 77 years treated with a combination of EBRT and endocavitary brachytherapy alone; approximately 27% of the patients treated were medically inoperable (136–139). Although these data are only retrospective, they provide a glimpse of a potential treatment regimen for *frail patients* for whom therapeutic options are otherwise limited.

The dose relationship between treatment efficacy and toxicity for HDREBT in ECPs has not been studied until recently. A Dutch group published the results of its phase 1 HERBERT study designed to identify the maximum tolerated dose, which is defined as the dose level below the dose at which 3 patients experienced grade ≥3 proctitis at <6 weeks after HDREBT. Thirty-eight patients with cT2–4N0–1M0–1 rectal cancer with a median age of 83 years were enrolled in this dose-escalation trial, and HDREBT dosed at 7 Gy per fraction per week for 3 weeks after EBRT (13 × 3 Gy) was concluded to be the maximum tolerated dose. Response occurred in 87.9% of patients eligible for response evaluation, and 60.6% of patients achieved cCR. The 2-year local progression-free survival and OS were 42% and 63%, respectively, and those with cCR showed significant improvement in local progression-free survival (60%) and trending improvement in OS (80%). However, because of high rates of severe late toxicity occurring in 10 of 32 evaluable patients with grade ≥3 toxicity (rectal bleeding, proctitis, and ulceration), the authors recommended further evaluation of risks and benefits to optimize this treatment regimen (140). At this time, if considering HDREBT boost after EBRT, clinicians would need to discuss with the patients regarding the benefit of improving tumor control weighing against the risk of late toxicity. Alternatively, endocavitary brachytherapy can be used for smaller tumors to minimize irradiated tissue to limit toxicity.

Both endocavitary brachytherapy and HDREBT can feasibly boost the radiation dose delivered to the gross disease after EBRT in *frail patients*, to increase tumor response. However, because of concomitant comorbidities, these patients may also experience greater a degree of adverse effects. Nevertheless, these treatment regimens may be effective for ECPs who are unable to tolerate surgery.

Conclusions

Clinicians are often faced with difficult decisions when treating LARC in ECPs, because many ECPs have medical contraindications to various aspects of the standard trimodality therapy. Optimization of the balance between oncologic outcomes and treatment morbidity/mortality in these patients is a challenge yet to be resolved. It is unlikely that large randomized studies evaluating various treatment modalities in ECPs will be conducted. Therefore, we have critically reviewed the literature on alternative therapeutic strategies that can be applied to ECPs and extrapolated pertinent findings to provide a basic treatment algorithm, presented in Figure 1. On the basis of the available evidence, we recommended the following treatment approach, depending on patient status. For *fit patients* without medical contraindications to therapy, the standard long-course CRT, or short-course RT with or without adjuvant chemotherapy, with standard TME will likely achieve optimal oncologic outcomes. Alternatively, for *fit or intermediate patients* with the goal of less-invasive therapy, NOM after CRT in the setting of cCR or minimally invasive surgery

(ie, local excision) after appropriate down-staging with CRT are acceptable options as well. Select patients with negative CRM preoperatively may opt for TME alone without neoadjuvant therapies. For *intermediate patients* who are medically inoperable, long-course CRT followed by NOM or dose escalation with brachytherapy boost can attain good local control of the tumor. For *frail patients* who cannot tolerate surgery or chemotherapy, EBRT with brachytherapy boost is an alternative option. In the palliative setting, *frail patients* may still benefit from brachytherapy or SCRT alone for symptomatic control. Finally, clinicians should embrace the concept of shared decision making to devise treatment plans that are considerate of the patient's values and priorities. Although these recommendations are not meant to serve as definitive guidelines, we hope to present an array of treatment options to help clinicians formulate treatment decisions for ECPs with rectal cancer.

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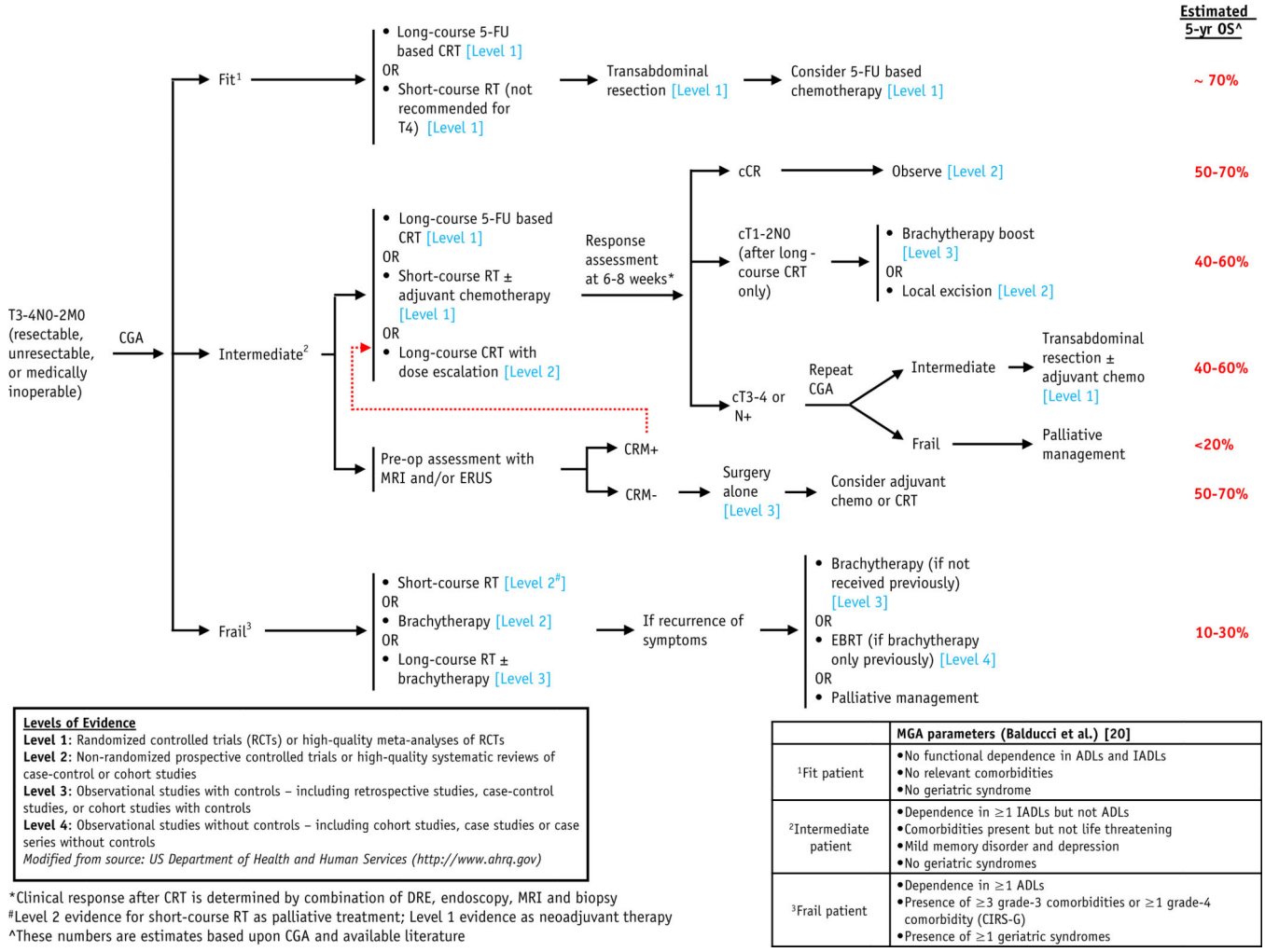

Levels of Evidence
Level 1: Randomized controlled trials (RCTs) or high-quality meta-analyses of RCTs
Level 2: Non-randomized prospective controlled trials or high-quality systematic reviews of case-control or cohort studies
Level 3: Observational studies with controls – including retrospective studies, case-control studies, or cohort studies with controls
Level 4: Observational studies without controls – including cohort studies, case studies or case series without controls
Modified from source: US Department of Health and Human Services (http://www.ahrq.gov)

*Clinical response after CRT is determined by combination of DRE, endoscopy, MRI and biopsy
#Level 2 evidence for short-course RT as palliative treatment; Level 1 evidence as neoadjuvant therapy
^These numbers are estimates based upon CGA and available literature

	MGA parameters (Balducci et al.) [20]
[1]Fit patient	•No functional dependence in ADLs and IADLs •No relevant comorbidities •No geriatric syndrome
[2]Intermediate patient	•Dependence in ≥1 IADLs but not ADLs •Comorbidities present but not life threatening •Mild memory disorder and depression •No geriatric syndromes
[3]Frail patient	•Dependence in ≥1 ADLs •Presence of ≥3 grade-3 comorbidities or ≥1 grade-4 comorbidity (CIRS-G) •Presence of ≥1 geriatric syndromes

Fig. 1.

Proposed treatment algorithm for locally advanced rectal cancer in elderly/comorbid patients. *Abbreviations:* 5-FU = 5-fluorouracil; ADLs = activities of daily living; cCR = clinical complete response; CGA = comprehensive geriatric assessment; CIRS-G = Cumulative Illness Rating Scale–Geriatric; CRM = circumferential resection margins; CRT = chemoradiation; EBRT = external beam radiation therapy; DRE = digital rectal examination; ERUS = endorectal ultrasound; IADLs = instrumental activities of daily living; MGA = multidimensional geriatric assessment; RT = radiation therapy.

Table 1

Elements of a comprehensive geriatric assessment from Balducci et al

Parameter assessed	Elements of the assessment
Functional status	Performance status ADLs IADLs
Comorbidity	No. of comorbid conditions Severity of comorbid conditions
Socioeconomic conditions	Living conditions Presence and adequacy of a caregiver
Cognitive function	Folstein's mini-mental status
Emotional status	Geriatric depression scale
Pharmacy	No. of medications Appropriateness of medications Risk of drug interactions
Nutritional status	Mini-nutritional assessment Body mass index Albumin, hemoglobin, transferrin
Geriatric syndromes	Dementia Delirium Depression Falls Neglect and abuse Spontaneous bone fractures

Abbreviations: ADLs = activities of daily living; IADLs = instrumental activities of daily living. See reference 20.

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Table 2

Chemoradiation and observation (nonoperative management)

Authors (reference)	N	Age (y)	f/u (mo)	Stage	RT	Chemotherapy	cCR, n (%)
Habr-Gama et al (2004) (66)	265	Mean 54.8 (range, 25–92)	Mean 50.5	Stage I-III, resectable	50.4 Gy @ 180 cGy/fx	5-FU and folinic acid	71 (26.8)
Dalton et al (70)	49	Median 64	Mean 25.5	T3–4N0–2	45 Gy in 25 fx	Capecitabine	6 (12.2)
Maas et al (71)	192	Mean 65	Mean 25	Stage I-III	50.4 Gy @ 180 cGy/fx	Capecitabine	21 (10.9)
Smith et al (72)	N/A	Median 70	Median 28	T2–4N0–2	50.4 Gy (median dose)	5-FU or capecitabine	32
Habr-Gama et al (2013)(73)	70	Mean 60.2	Median 56	T2–4N0–2	54 Gy @ 180 cGy/fx	5-FU and folinic acid	47 (68)
Appelt et al (74)	51	Median 67	Median 23.9	T2–3N0–1	60 Gy in 30 fx + 5 Gy brachytherapy boost	Tegafur-uracil	40 (78.4)
Araujo et al (75)	N/A	Median 63.6	Median 47.7	LARC	45–50.4 Gy	5-FU and leucovorin	42
Renehan et al (68)	N/A	Median 66.9	Median 33	Stage I-III	45 Gy	Capecitabine	129

Response assessment (timing*)	Adjuvant chemotherapy after cCR, n (%)	LF after cCR, n (%)	DF after cCR, n (%)	Salvage after LF, n (%)	Survival (cCR cohort) (%)
Proctoscopy, rebiopsy, DRE, CT A/P, chest X-ray (8 wk)	None	2 (2.8)	3 (4.2)	2 (100)	10-y OS, 97.7; 10-y DFS, 84
MRI, EUA, rebiopsy, PET/CT (6–8 wk)	None	0	0	N/A	N/A
MRI, DRE, endoscopy, rebiopsy (6–8 wk)	17 (81)	1 (4.8)	0	1 (100)	2-y OS, 100; 2-yDFS, 89
DRE, endoscopy, selective biopsy (4–10 wk)	17 (53)	6 (18.8)	3 (9.4)	6 (100)	2-y OS, 97; 2-y DFS, 88
DRE, proctoscopy, CEA, MRI, and/or PET/CT (10 wk)	None	12 (25.5)	3 (6.4)	11 (91.7)	3-y OS, 94; 3-y DFS, 75
DRE, endoscopy, rebiopsy, MRI pelvis (6 wk)	None	9 (22.5)	3 (7.5)	9 (100)	N/A
MRI, DRE, endoscopy (not stated)	2 (4.8)	8 (19.0)	7 (16.7)	4(50)	5-y OS, 71.6; 5-y DFS, 60.9
MRI pelvis, DRE, endoscopy (≥8 wk)	8(6)	44 (34.1)	7 (5.4)	37 (84.1)	3-y OS, 96; 3-y DFS, 88

Abbreviations: 5-FU = 5-fluorouracil; cCR = clinical complete response; CEA = carcinoembiyonic antigen; CT A/P = computed tomography abdomen and pelvis; DF = distant failure; DFS = disease-free survival; DRE = digital rectal examination; EUA = examination under anesthesia; f/u = follow-up; fx = fractions; LARC = locally advanced rectal cancer; LF = local failure; OS = overall survival; N/A = not available; PET = positron emission tomography.

* Timing of clinical response assessment after completion of chemoradiation.

Table 3

Chemoradiation with dose escalation

Authors (reference)	Accrual year	N	Median age (range) (y)	Median f/u (mo)	Stage	RT	Chemo	pCR (%)
Jakobsen et al (2006) (81)	N/A	50	61	N/A	T3N0–2	60 Gy @ 1.8–2 Gy/fx + 5 Gy ERB boost	Tegafur-uracil + leucovorin	27
Jakobsen et al (2012) (82)	2005–2010	120	64 (38–78)	N/A	T3–4, resectable	50.4 Gy in 28 fx + 10 Gy in 2 fx ERB boost	Tegafur-uracil + leucovorin	18
Appelt et al (74)	2009–2013	51	67	23.9	T2–3N0–1	60 Gy in 30 fx + 5 Gy ERB boost	Tegafur-uracil	cCR 78.4

Abbreviations: ERB = endorectal brachytherapy; pCR = pathologic complete response. Other abbreviations as in Table 2.

Table 4

Chemoradiation with local excision

Authors or study (reference)	Accrual year	N	Age (y)*	Median f/u (mo)	Stage	RT
Kim et al (95)	1994–2000	26	Mean 63 (44–90)	19	T2–3N0–1	45 Gy in 25 fx
Bonnen et al (96)	1990–2002	26	60	46	T3N0–1	45 Gy in 25 fx ± boost to 52.5 Gy
Lezoche et al (97)	1997–2004	50	66 (58–70)	9.6 y	cT2N0	50.4 Gy in 28 fx
Nair et al (98)	1994–2006	44	69 (43–89)	64	T2–3N0–1	50.4 Gy in 28 fx
ACOSOG Z6041 (99)	2006–2009	79	62 (30–83)	56	T2N0	54 Gy @ 180 cGy/fx
CARTS (100)	2010–2012	55	64 (39–82)	17	cT1–3N0	50 Gy in 25 fx; 50.4 Gy in 28 fx

Chemo	LE criteria†	LR, n (%)	DM, n (%)	OS (%)	DFS (%)
5-FU	ypT0	1 (3.8)	0	N/A	N/A
5-FU	N/A	2 (7.7)	3 (11.5)	N/A	5-y = 80
5-FU	ypT0–2	4 (8)	2 (4)	OS = 72; CSS = 89 (at end of f/u)	N/A
5-FU	N/A	4 (9.1)	5 (11.4)	5-y = 81–84	N/A
Cape-ox	ypT0–2	3 (3.8)	5 (6.3)	N/A	3-y = 88.2
Capecitabine	ypT0–1	4 (7.3)	1 (1.8)	N/A	N/A

Abbreviations: Cape-ox = capecitabine/oxaliplatin; CR = complete response; CSS = cancer-specific survival; DM = distant metastases; LE = local excision; LR = local recurrence. Other abbreviations as in Table 2.

*Age expressed as median unless otherwise noted. Values in parentheses are range.

†Acceptable pathologic staging after neoadjuvant chemoradiation and local excision without recommendation for radical surgery.

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Table 5

Short-course radiation therapy

Study (reference)	Accrual year	N	Age (y)*	Median f/u	Stage	Study arms
Stockholm I (109)	1980–1987	424	Mean 69	107 mo	Any stage resectable	Arm 1: 5 × 5 Gy with immediate surgery
		425	Mean 67			Arm 2: surgery alone
Stockholm II (110)	1987–1993	272	66 (30–80)	8.8 y	Any stage resectable	Arm 1: 5 × 5 Gy with immediate surgery
		285				Arm 2: surgery alone
Swedish trial (111)	1987–1990	585	69 (50–78)	13 y	T1–3	Arm 1: 5 × 5 Gy with immediate surgery
		583				Arm 2: surgery alone
Dutch TME trial (112)	1996–1999	924	65 (26–88)	12 y	Any stage resectable	Arm 1: 5 × 5 Gy with immediate surgery
		937	66 (23–92)			Arm 2: selective postoperative RT for positive margins, 50.4 Gy in 28 fx
Uppsala (113)	1980–1985	235	N/A	>5 y	Dukes A-C	Arm 1: 5 × 5.1 Gy with immediate surgery
		236				Arm 2: selective postoperative RT for Dukes B/C, 60 Gy in 30 fx
MRC CR07 (114)	1998–2005	674	65 (38–87)	4 y	Stage I-III	Arm 1: 5 × 5 Gy with immediate surgery
		676	65 (36–87)			Arm 2: selective postoperative CRT for positive margin, 45 Gy in 25 fx + 5-FU
Polish trial (115)	1999–2002	155	Mean 60 (30–75)	48 mo	T3–4, resectable	Arm 1: 5 × 5 Gy with immediate surgery
		157	Mean 59 (34–73)			Arm 2: 50.4 Gy in 28 fx and 5-FU/leucovorin followed by surgery at 4–6 wk
TROG 01.04 (116)	2001–2006	163	63 (26–80)	5.9 y	cT3N0–2	Arm 1: 5 × 5 Gy with immediate surgery
		163	64 (29–82)			Arm 2: 50.4 Gy in 28 fx and 5-FU followed by surgery at 4–6 wk
Stockholm III (3-arm) (117–119)	1998–2013	129	67 (62–74)	5.2 y	Any stage resectable	Arm 1: 5 × 5 Gy with immediate surgery
		128	67 (62–75)			Arm 2: 5 × 5 Gy with surgery at 4–8 wk
		128	66 (61–73)			Arm 3: 25 × 2 Gy with surgery at 4–8 wk
Stockholm III (2-arm) (117–119)		228	67 (61–74)			Arm 1: 5 × 5 Gy with immediate surgery
		227	67 (61–74)			Arm 2: 5 × 5 Gy with surgery at 4–8 wk
Bujko et al. (120)	2008–2014	261	60 (54–66)	35 mo	cT3–4	Arm 1: 5 × 5 Gy followed by FOLFOX
		254	60 (56–65)			Arm 2: 50.4 Gy in 28 fx with concurrent 5-FU/leucovorin

pCR (%)	Acute toxicity (%)	Late toxicity (%)	Local control	OS (%)
N/A	26 s 19 ($P < .01$)		86 vs 72 $P < .01$)	30 vs 31 (NS)

pCR (%)	Acute toxicity (%)	Late toxicity (%)	Local control	OS (%)
N/A	41 vs 28 ($P < .01$)		88 vs 75 ($P < .001$)	39 vs 36 ($P = .2$)
N/A	32 vs 19 ($P < .01$)	56 vs 49 ($P = .01$)	91 vs 74 ($P < .001$)	38 vs 30 ($P = .008$)
N/A			95 vs 89 ($P < .0001$)	48 vs 49 ($P = .86$)
N/A	33 vs 18 (sepsis, $P < .01$)	19.4 vs 18.2 (NS)	87 vs 78 ($P = .02$)	No difference
N/A	35 vs 22 (nonhealing perineum)		95.6 vs 89.4 ($P < .0001$)	5 yr OS: 70.3 vs 67.9 ($P = .4$) 5 yr DFS: 73.6 vs 66.7 ($P = .013$)
0.7	3.2 vs 18.2 (grade ≥3, $P < .001$)	10.1 vs 7.1 (grade ≥3, $P = .36$)	91 vs 85.8 ($P = .17$)	67.2 vs 66.2 ($P = .96$)
15.2				
1.2	N/A	5.8 vs 8.2 (grade ≥3, $P = .53$)	92.5 vs 95.6 ($P = .24$)	74 vs 70 ($P = .62$)
14.7				
N/A	46.6 vs 40 vs 32 ($P = .164$)	50 vs 38 vs 39 ($P = .075$)	97.7 vs 96.9 vs 94.5 ($P = .48$)	73 vs 76 vs 78 ($P = .61$)
N/A				
N/A				
1.7[†]	N/A	53 vs 41 ($P = .001$)[‡]	97.8 vs 97.2 ($P = .58$)[‡]	N/A
11.8[†]				
16	75 vs 83 (all events, $P = .006$)	20 vs 21 (NS)	3-y: 78 vs 79	3-y: 73 vs 65 ($P = .046$)
12				

Abbreviation: NS = nonsignificant. Other abbreviations as in Tables 2 and 3.

[*] Age expressed as median unless otherwise noted. Values in parentheses are range.

[†] Pooled analysis of both 2-arm and 3-arm randomization of Stockholm III trial (20).

[‡] Pooled analysis of both 2-arm and 3-arm randomization of Stockholm III trial.

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