Critical Review

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

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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. © 2017 Elsevier Inc. All rights reserved.

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 (11-16). 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