CARE DELIVERY

Incorporating Reproductive Health in the Clinical Management of Early-Onset Colorectal Cancer

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The potential for long-term side effects of overtreatment on gonadal function and sexual health because of therapies designed for patients older than 50 years presents a clinical environment mismatch for young patients with colorectal cancer (CRC). This is of increasing importance as CRC incidence rates among adults age 18-49 years (early-onset CRC) have steadily increased over the past few decades with causes unexplained[1-3] and the number of young CRC survivors has also risen—nearly 60,000 adults are living in the United States with a previous early-onset CRC diagnosis.[4] Yet despite this alarming disease burden and demography, there remains a paucity of data to understand the effects of CRC therapies on reproductive health, including fertility and sexual health, within this population. Consequently, the distinct reproductive health needs that face patients after an early-onset CRC diagnosis as they attempt to maintain or return to normative lifestyles and to improve survivorship are poorly understood and are crucial to address to incorporate oncofertility and sexual health in the clinical management of early-onset CRC.

Reproductive Health as an Unmet Need Among Early-Onset CRC Survivors

The early-onset cancer experience is unique. In particular, the clinical management of early-onset cancers is comparatively *more demanding* than that for cancers diagnosed among individuals age 50 years and older. Among young patients, there is a greater need to treat the whole patient for whom multiple life domains (eg, sexual health and fertility)[5] are significantly affected by the cancer diagnosis.[6] Yet when asked about their experience of being diagnosed with cancer, lesser than two thirds of adolescent and young adult patients are informed that cancer treatment could pose an infertility risk.[7] McKay et al also recently illustrated the extent of unmet reproductive health care needs among 43 adolescent and young adult cancer patients, having observed that only 29% and 40% of patients had electronic health record–documented discussions about sexual health and fertility, respectively, with their provider.[8] Moreover, this care need is essential from early-onset cancer diagnosis and treatment to surveillance and survivorship as well as long-term outcomes for *all* patients. Although the traditional upper age bound for young adult cancer in the United States is 39 years, it is imperative to also include individuals between ages 40 and 49 years when evaluating reproductive health among patients with cancer given the current shift toward later motherhood and rising age of paternity.[9] Along with increasing family size, motherhood rates have nearly tripled in the past two decades among never-married women in their forties—across all racial and ethnic groups. Similarly, the birth rate for fathers age 30-49 years has increased 15% (30-34 years) to 52% (45-49 years).[10] The biologic potential for reproduction also continues for most of men's lives, as about 9% of fathers are older than 40 years and nearly 40,000 newborns have a father older than 50 years annually.[11]

Gonadotoxicity and sexual dysfunction are well-documented for patients with cancer across other tumor types (eg, lymphoma, breast, and germ cell).[12-20] However, the population of patients with early-onset CRC differs as rates of sexual dysfunction are higher in CRC (across all age groups, including early-onset CRC) compared with all cancer survivors.[21] This is because of altering physiology as a result of CRC-specific therapies—pelvic radiation, abdominoperineal resection, mesorectal surgery, and cytotoxic chemotherapies.[22,23] As a result of these CRC-specific treatment regimens, young patients with CRC may encounter unique survivorship challenges that can detrimentally affect fertility and/or sexual health. For example, patients with CRC may have an intestinal stoma after surgery[24] and/or may experience unique complications (eg, intra-abdominal sepsis)[23] that can lead to reproductive health complications. A qualitative analysis has identified impact on quality of life—including physical side effects (eg, sexual dysfunction)—as the highest area of concern resulting from an early-onset CRC diagnosis.[25] Results from the Colorectal Cancer Alliance cross-sectional survey[26] also tell us that two thirds of patients with early-onset CRC currently suffer from some level of sexual dysfunction because of CRC treatment. Nearly half (48%) of all respondents reported that sexual dysfunction put a strain on their relationships and one third of individuals felt they are not a complete person

ASSOCIATED CONTENT

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because of sexual dysfunction, including that stemming from anatomic reconfiguration.

This initial evidence illuminates the importance of addressing fertility preservation and offering counseling for sexual health, including function and satisfaction, to patients with CRC age 18-49 years. Concurrently, it also sheds light on our limited knowledge of the unparalleled challenges (eg, severity and type of sexual dysfunction) that patients face after an early-onset CRC diagnosis—which stands as a substantial roadblock in tailoring support strategies to this population. Coupled with the projection that 11% of colon cancers and 23% of rectal cancers in the United States will occur among adults younger than 50 years by 2030,[2] it will be imperative to differentiate this population of young patients with CRC from other malignancies to comprehensively evaluate the potential physiologic impact of CRC-specific therapies on gonadal function and sexual health.

Current CRC Treatment Modalities May Cause Gonadotoxicity Among Patients of Reproductive Age

The gonads are susceptible to deleterious effects of CRC therapy among *both men and women*. Compared with older age patients with CRC who have similar clinicopathologic tumor features, patients of reproductive age receive more adjuvant chemotherapy[27,28]—which carries potential gonadotoxicity and other detrimental effects on fertility and sexual health.[29-31] Chemotherapy can result in primordial cell death in the ovary, leading to premature ovarian failure and high infertility risk.[30,32] This risk is especially high among women who receive chemotherapy later in reproductive years as this treatment accelerates natural age-related decline in follicle reserve.[31] Retrospective pharmacy record review and questionnaires from 49 women with CRC who received adjuvant infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX) therapy observed that 41% of women had infusional fluorouracil, leucovorin, and oxaliplatin-induced amenorrhea—including one quarter of women age 41-50 years.[33] In men, fluorouracil may also cause a temporary reduction in male fertility.[34]

Abdominal and/or pelvic radiation therapy can also cause damage to the ovaries and/or testicles,[35,36] often leading to premature menopause and/or infertility.[37-39] Although shielding the gonads or adjusting the radiation field is possible to avoid direct irradiation to the gonads, in cases with pelvic involvement (eg, rectal cancers), pelvic radiation is unavoidable.[5,40] In men, the testes receive 3%-17% of the administered dose given for rectal cancer.[36,41,42] As a result, testicular exposure to radiation and testicular function in men with primary rectal cancer of all ages may cause impaired physical, psychologic, and sexual function after CRC treatment.[43] The limitations of these bodies of work are that the assessment of hormonal markers was conducted in small cohorts (fewer than 30 men) with median age more than 60 years. In women, pelvic radiation—as used in rectal cancer—exposes the ovaries to high doses of radiation.[44,45] This exposure is one of the highest risks for acute ovarian failure and premature menopause.[5,45,46] Thus, to fully understand the effects of CRC treatment on gonadal function among patients of reproductive age, a careful and *longitudinal* assessment of hormonal markers paired with reproductive health–related data is essential specifically *within* the early-onset CRC patient population to yield significant advances in delivering support strategies that improve survivorship for this patient population.

Path Forward

Despite the number of adults within their childbearing years diagnosed with, treated for, and surviving CRC, reproductive health care needs stand unmet among early-onset CRC survivors and their families. As of 2020, only 15 states (30%) have laws requiring private insurance coverage for infertility or in vitro fertilization procedures.[47] Twelve states (24%) have mandated some form of insurance coverage for infertility treatments—yet this coverage sharply varies from only reproductive health counseling and education to infertility assessment and laboratory tests or, rarely, fertility-preservation procedures. Furthermore, no federal legislature exists that addresses universal insurance coverage for these costly fertility-preservation procedures specific to patients with CRC facing potential iatrogenic infertility. In the absence of universal coverage of infertility treatment, and in light of the profound financial impact of a cancer diagnosis among young patients,[25] epidemiologic studies designed to primarily and comprehensively investigate fertility and sexual health specifically among patients with early-onset CRC are essential. Prospective cohort studies will allow us to address this gap by elucidating the impact of CRC therapies on psychosocial and physiologic dimensions of fertility and sexual health among individuals of reproductive age along the cancer continuum.[48] Together, such studies harbor immense potential to (1) deliver timely evidence that insurance coverage of fertility preservation for young patients with CRC is necessary, (2) drive significant advances toward concordant, comprehensive reproductive health care assessment and delivery of personalized resources and support (eg, physical, mental and social) strategies, and (3) improve long-term clinical outcomes for this growing population after cancer diagnosis.

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