Early-Onset Colorectal Cancer: From Genetic Discovery to Clinical Innovation

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OVERVIEW

The rising incidence of early-onset colorectal cancer (EOCRC) presents a growing challenge to traditional approaches in screening, treatment, and survivorship. EOCRC is increasingly recognized as a biologically distinct entity, driven by complex inter-related biological, genetic, behavioral, and socioenvironmental factors. This chapter reviews the molecular and clinical features that distinguish EOCRC, with attention to emerging precision oncology strategies, including germline testing, tumor genomic profiling, and biomarker-directed therapies. In metastatic disease, recent advances in targeting *BRAF* V600E, *KRAS* G12C, *HER2* amplification, and microsatellite instability-high (MSI-H)/mismatch repair deficiency tumors have reshaped therapeutic paradigms. Tumor sidedness and metastatic site patterns are now recognized as predictive and prognostic factors. In localized disease, neoadjuvant immunotherapy for MSI-H tumors and nonoperative management are redefining standard care, with special relevance to younger patients seeking fertility preservation or organ-sparing approaches. The chapter also addresses key gaps in EOCRC care, including underutilization of fertility preservation counseling and limited guidance for cancer management during pregnancy. A multidisciplinary, lifecycle-based framework is essential to optimize outcomes and improve quality of life for this unique and growing patient population.

INTRODUCTION

The landscape of colorectal cancer (CRC) is shifting, marked by a rising global incidence of early-onset CRC (EOCRC), defined as diagnosis before age 50 years. This trend challenges traditional paradigms in screening, risk stratification, and survivorship care (Fig 1). EOCRC often presents with advanced-stage disease, distal tumor location, and a growing proportion of nonhereditary cases. Emerging research reveals EOCRC as a biologically and clinically distinct entity, influenced by inherited risk, environmental exposures, microbial dysbiosis, and unique somatic and epigenetic alterations. Simultaneously, advances in biomarker-guided therapy have transformed metastatic CRC treatment, offering new opportunities for precision care in younger patients. This review highlights recent progress in understanding the molecular drivers of EOCRC, addresses its reproductive and survivorship implications, and summarizes evolving strategies in neoadjuvant and biomarker-based management that are reshaping care for patients with early-onset and advanced CRC.

ADVANCING OUR UNDERSTANDING OF EOCRC

In considering CRC from a lens of genetic discovery to clinical innovation, it is essential to call attention to the alarming rise in CRC incidence among adults age 18-49 years at diagnosis (EOCRC).[1] Approximately 20,000 new patients with EOCRC were diagnosed in 2023 across the United States—the equivalent of 53 young patients diagnosed with CRC per day.[2] Long-term projections suggest that nearly one in every four rectal cancer diagnoses and more than one in 10 colon cancer diagnoses in the United States will be among adults younger than 50 years by 2030.[3] Accumulating evidence also supports this rising tide of EOCRC being a global phenomenon.[4-6] Consequently, research studies and global scientific think tanks are ongoing to elucidate the causes for this worrisome trend, to advance clinical treatments, and to address the unique care needs for this growing patient population.

Molecular Drivers of Early-Onset Colorectal Carcinogenesis

Up to 25% of patients with EOCRC harbor a germline pathogenic variant associated with cancer risk.[7-15] Consequently, the National Comprehensive Cancer Network (NCCN) clinical practice guidelines were updated in 2023 to now recommend that all individuals who are diagnosed with EOCRC undergo germline clinical multigene panel testing (MGPT).[16] MGPT enhances detection of clinically actionable variants, enabling personalized treatment, informing surveillance, and supporting cascade testing in families.[17-19]

PRACTICAL APPLICATIONS

- All patients diagnosed with early-onset colorectal cancer (EOCRC) should undergo germline multigene panel testing, as recommended by current National Comprehensive Cancer Network guidelines, to inform treatment, surveillance, and cascade testing for at-risk relatives.
- Fertility preservation counseling must be routinely integrated into the initial treatment planning process for reproductive-age patients with colorectal cancer as early interventions can significantly affect future reproductive outcomes and quality of life.
- In patients with EOCRC with localized disease, neoadjuvant therapy decisions should carefully weigh long-term morbidity, fertility considerations, and organ preservation goals, with growing evidence supporting total neoadjuvant therapy and nonoperative management in appropriately selected patients.
- Tumor genomic profiling should be universally performed in metastatic CRC to guide biomarker-driven therapies, including anti-EGFR rechallenge, BRAF- or human epidermal growth factor receptor 2–targeted regimens, KRAS G12C inhibitors, and immune checkpoint inhibitors for microsatellite instability-high/mismatch repair deficiency tumors.

Notably, nearly 10% of patients with EOCRC carry a germline variant of uncertain significance, highlighting the need for pre- and post-test counseling to ensure informed care delivery.[20]

Although germline genetic predisposition is a contributor to EOCRC development, most patients have no underlying hereditary predisposition.[21] These so-called sporadic tumors in young patients are often characterized by advanced-stage diagnoses, more frequent signet ring cell histology, and poorer prognoses and are more commonly located in the distal colon/rectum.[22] Yet, the mechanisms underpinning this alarming rise in sporadic EOCRC development remain largely unknown and are complicated by the evolution of exposures, which includes changes in dietary patterns, obesity, sedentary behaviors, antibiotic use, and other lifestyle factors, across generations.[23,24] This is further complicated by our limited knowledge of how these exogenous factors (Fig 2)—amassed from conception to adulthood—may drive the accumulation of somatic mutations, epigenetic alterations, and cellular cross talk that may promote the dysbiosis of gut microbiota, alter immune responses, and influence the surrounding tissue microenvironment[25-27] and additional distinct carcinogenic processes in the colorectum of young patients that likely remain undiscovered thus far.

Our current understanding of sporadic EOCRC biology has largely been limited to genomic panel testing results and/or studies conducted in smaller, selective cohorts—with sparse data on individual-level behaviors/exposures. Several studies have identified that sporadic CRCs in young patients are more likely to harbor somatic mutations in *TP53* and *CTNNB1* and less likely to harbor *BRAF* and *APC* mutations.[28-30] Nonhypermutated colorectal tumors from

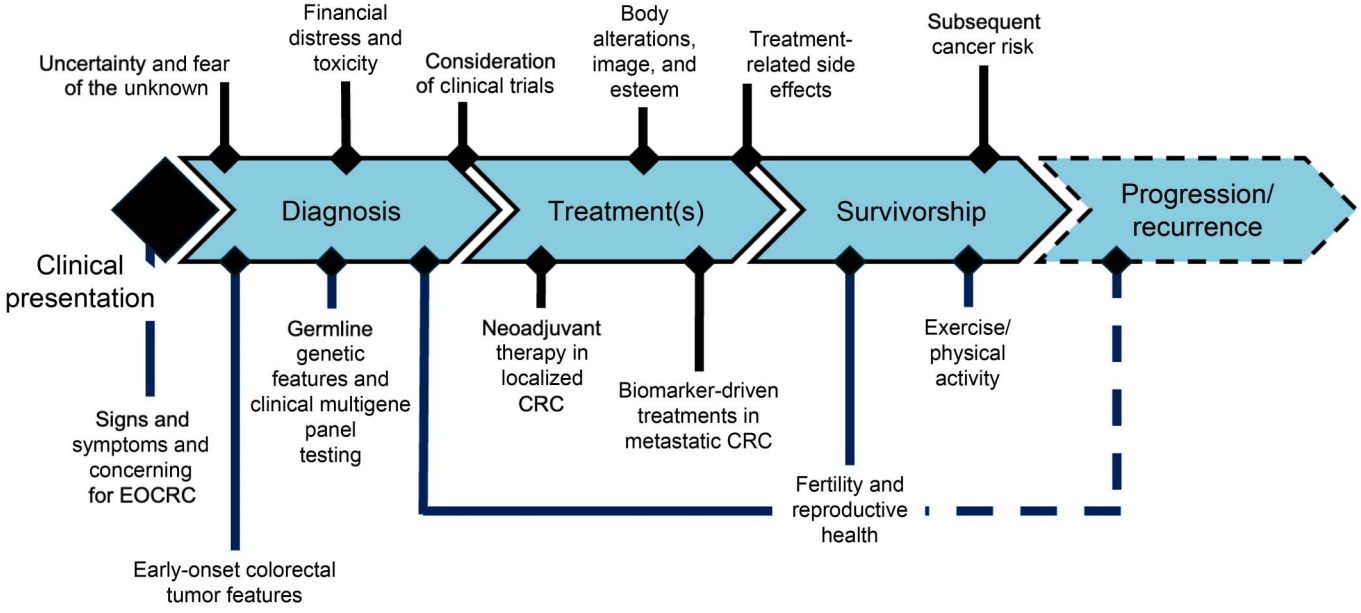

FIG 1. Considerations for EOCRC. Of note, the domains/considerations included herein across the cancer care continuum are representative examples and do not encompass all aspects of EOCRC. CRC, colorectal cancer; EOCRC, early-onset colorectal cancer.

FIG 2. Spectrum of potential exposures contributing to early-onset colorectal carcinogenesis. NSAID, nonsteroidal anti-inflammatory drug.

young patients are also significantly more likely to have nonsilent mutations in *LRP1B*, *TCF7L2*, and *FBXW7* when compared with tumors from older-age patients in adjusted models.[31] Integrated multiomic profiling of 233 patients with microsatellite-stable (MSS) CRC has implicated NRF2-mediated oxidative stress response, glutathione metabolism, and CXCL12-CXCR4 signaling as a distinct molecular signature of early-onset sporadic tumors.[32] Emerging international data further suggest that early-onset colorectal tumors may carry globally distinct mutation patterns.[33] Together, this body of evidence supports a potential distinct and/or accelerated molecular phenotype in EOCRC, emphasizes the growing need for universal CRC genomic testing for all young patients, and prompts the need for whole-genome and mechanistic studies to better understand how various exposures may drive the accumulation of these somatic mutations in young patients with CRC.

Gene expression and tissue differentiation are also regulated by epigenetic mechanisms.[34] In the colorectum, aberrantly methylated genes and altered microRNA expression are key features, and even driver events, of carcinogenesis.[35,36] Specific to EOCRC, recent studies exploring the epigenome by CRC diagnosis age have found that colorectal tumors from young patients have a higher degree of LINE-1 hypomethylation as compared with tumors from older-age patients.[37] Recent whole-genome DNA methylation profiling of nonhypermutated colorectal tumors by Li et al[39] has also shown that methylation canyons[38]—extended regions of low DNA methylation that are flanked by sharp peaks of high methylation—preferentially occur over genes implicated in cancer-related pathways (eg, Wnt and TGF-B signaling) in early-onset, but not in late-onset (50+ years), colorectal tumors.[39] As DNA methylation is highly susceptible to the environment, the study of how environmental factors/exposures (Fig 2) influence DNA methylation and modulate EOCRC risk and development is crucial to fully appreciate the role of the epigenome in EOCRC carcinogenesis and to identify potential intervention strategies for this disease.[40,41]

The cross talk between the colorectal epithelium and gut microbiota supports a link between microbial dysbiosis in the human gut and early-onset colorectal carcinogenesis.[42-46] Indeed, paired metagenomic and metabolomic profiling of

CRCs and age-matched healthy controls has identified a unique multiomic signature of early-onset tumors that was associated with enriched Flavonifractor plautii and increased tryptophan, bile acid, and choline metabolism.[47] While not limited to EOCRC, data from the study by Kadosh et al[48] demonstrate how metabolites that are derived from the gut microbiota (ie, gallic acid) can inhibit gene function (eg, mutant tumor-suppressive *TP53*) and promote distal colon tumorigenesis in mice. A recent study by Díaz-Gay et al[49] has delivered fundamental evidence that early-life mutagenic exposures (eg, exposure to colibactin-producing bacteria) may in fact be a key contributor to the rise in EOCRC incidence over the past several decades. Their discovery of an association between colibactin-induced mutational signatures and EOCRC gives rise to a potential mechanism for colibactin-induced mutagenesis via somatic inactivation of one copy of *APC* via protein-truncating driver mutations and warrants further mechanistic investigation of microbial dysbiosis specific to early-onset colorectal carcinogenesis.

Taken together, EOCRC is hallmarked by a complex, intricate interplay[50] of biological and genetic features, together with environmental/early-life exposures and social, lifestyle/behavioral, and anthropometric factors[51]—that will be crucial to disentangle to elucidate EOCRC etiology, to develop precision therapeutic modalities, to improve patient outcomes,[52] and to reduce the burden of EOCRC worldwide.

EOCRC and the Reproductive Lifespan

As the number of young patients diagnosed with CRC continues to rise, this alarming trend is inevitably leading to generations of reproductive-age CRC survivors with distinct, and largely unmet, care needs. Consequently, an extensive framework for providing comprehensive cancer care in EOCRC, which considers each patient's individual needs from EOCRC diagnosis through treatment and into survivorship (eg, reproductive health, financial toxicity, quality of life, physical well-being, body esteem, genetic counseling; Fig 1), was developed by Eng et al.[26] This includes the essential need for discussions about fertility risks and preservation options, with patients involved as early as possible in the treatment planning process[53]—which is particularly important for all patients with CRC as the gonads are susceptible to deleterious effects of CRC therapy among men and women.[54] Chemotherapy may induce amenorrhea and reduce spermatogenesis.[55-57] A pilot study of 11 women and eight men with EOCRC reported that oxaliplatin may exert moderate transient gonadotoxicity between CRC diagnosis and 6 months after therapy completion.[58] Abdominal and/or pelvic radiation can lead to premature ovarian failure or infertility in women and sterility in men.[59-63] Surgery can also affect ejaculation through nerve damage in men or might involve removal of reproductive organs in women.[64,65]

Notwithstanding the recognized importance of fertility preservation in EOCRC and newly updated ASCO Clinical Practice Guidelines on Fertility Preservation,[53] a recent study by Keller et al[66] among 473 patients with early-onset cancer strikingly discovered that only 44.2% of the reproductive-age patients diagnosed with CRC reported having a health care provider involved in their cancer care who discusses fertility preservation options before cancer treatment. While prospective clinical cohort studies remain ongoing to deliver timely biological evidence on CRC treatment-related gonadotoxicity in support of insurance coverage for fertility preservation specific to patients with CRC (eg, ClinicalTrials.gov identifier: NCT05239338),[67] high-quality discussions about fertility risks and preservation strategies[68] as well as sexual health are also considered an essential component of clinical care toward tailored approaches that deliver concordant reproductive health care assessment and delivery. This is further supported by intraprofessional collaborations across medical specialties (eg, obstetrics and gynecology, urology), dedicated support staff, and timely referrals. This also supports the fact that patients with EOCRC have the opportunity to achieve control and retain some agency to make autonomous, informed decisions about their reproductive health while they cope with their diagnosis and treatment plan. Overall, and with the rising tide of CRC in young patients, it is imperative that reproductive care is part of the standard of care for *all* reproductive-age patients with CRC.

Alongside addressing fertility and sexual health care needs for all patients with EOCRC,[69,70] it is appreciable to highlight herein that the rising incidence of EOCRC—when combined with delayed childbearing among women in the United States[71]—is also increasing the likelihood of CRC development *during* pregnancy.[72] Overlapping symptoms between pregnancy and CRC also can contribute to delayed CRC diagnosis and advanced-stage disease in pregnant women,[72-76] which may lead to poorer maternal outcomes.[77] The paucity of clinical data and biological evidence on pregnancy-associated EOCRC is a gap that new clinical studies aim to begin to address.[78] However, there are currently no consensus recommendations regarding how to manage CRC during pregnancy.[79-81] Neoadjuvant therapy considerations are further discussed in the following section.

NEOADJUVANT THERAPY IN CRC

Challenges of Neoadjuvant Treatment of EOCRC

The rising incidence of EOCRC in recent years has posed several challenges for clinicians, and these include delivering effective treatments to younger patients with distinct preferences and values. In this regard, several studies confirm that young patients with both localized and metastatic disease receive more intensive treatments.[82-84] Despite this, the clinical benefit derived from such intensified treatments in this population remains unclear. Indeed, current guidelines acknowledge the lack of data to support or recommend changes to the existing therapeutic protocols for EOCRC, including extension of surgery and systemic treatment regimens.[85]

Over the past four decades, treatment algorithms for locally advanced rectal cancer have experienced several and profound changes. Some of these changes include moving chemoradiation (or short-course radiotherapy) and chemotherapy treatments toward the preoperative setting, an approach called total neoadjuvant therapy (TNT). This therapeutic strategy aims to target micrometastatic disease leading to better tolerability of systemic therapy and has been widely adopted worldwide. Recently, a multidisciplinary panel of experts conducted a systematic review and concluded that TNT was associated with increased pathologic complete response (pCR) rates (odds ratio [OR], 1.74 [95% CI, 1.45 to 2.10]) and better overall survival (OS; hazard ratio [HR], 0.78 [95% CI, 0.62 to 0.97]) versus standard neoadjuvant chemoradiotherapy.[86] Interestingly, no statistically significant benefit was found in disease-free survival (DFS; HR, 0.86 [95% CI, 0.71 to 1.04]). Another recent topic of interest has been the exploration of protocols to de-escalate the burden of treatment by omitting radiation therapy or surgery in a subgroup of selected patients with rectal cancer aiming to decrease short- and long-term morbidity. Furthermore, in patients with microsatellite instability-high (MSI-H) rectal cancer, immunotherapy with anti–PD-1 monoclonal antibodies has proven to be ablative with a high percentage of clinical complete response and long-term disease control.

In colon cancer, changes in the treatment approach have been more subtle; however, there is also a trend to consider neoadjuvant chemotherapy in patients with locally advanced disease (T4b or bulky nodal disease) based on multiple studies showing safety and benefits in these subgroups.[87,88] In MSI-H colon cancer, neoadjuvant immunotherapy has demonstrated high pathologic complete response and long-term DFS. Some of the pivotal trials that support these strategies are described in Table 1. Multiple narrative reviews have outlined their historical aspects, rationale, strengths, and shortcomings.[89,90] Herein, we will briefly discuss some of the most relevant aspects to consider when treating patients with EOCRC.

Nonoperative Management

Following the seminal work of Habr-Gama et al[91] that demonstrated favorable oncologic outcomes by using nonoperative management (NOM) in patients with rectal cancer with clinical complete response after neoadjuvant chemoradiation, this strategy has become a standard practice at most cancer centers. Indeed, several subsequent studies have confirmed adequate oncologic outcomes supporting the use of NOM (Table 1); however, to date, there are no randomized trials demonstrating equivalent disease and OS with both strategies. A systematic review that included 23 studies and 867 patients assessed the outcomes of patients with locally advanced rectal cancer using the NOM approach and found a 2-year local regrowth of 15.7%, of whom 95.4% underwent salvage therapy.[92] To replicate these outcomes in the real-world setting, it is essential to conduct careful surveillance after organ preservation at an experienced medical center with a high-quality multidisciplinary team. Interestingly, a study that interviewed 50 patients and surveyed more than 300 physicians found that NOM was consistent with patient's preferences and values at the expense of cancer outcomes.[93] Therefore, it is important to have a thorough discussion with every patient regarding all the implications of NOM, weighing the benefits in quality of life versus the risk of regrowth and the uncertainty of equivalent outcomes. This is even more relevant for younger patients who tend to be very active in terms of education, work, and family building.[94] Several studies have demonstrated that patients with local regrowth are more likely to suffer distant progression versus those without local regrowth, or those who achieved pathologic complete response after surgery, confirming this as a high-risk group.[95] However, these studies do not demonstrate that outcomes for this population would be better with mandatory total mesorectal excision (TME) after TNT. A recent pooled analysis of the multicenter phase II OPRA and CAO/ARO/AIO-12 trials showed that selective NOM and the mandatory TME strategy achieved equivalent rates of 3-year DFS and OS, providing further evidence on the safety of NOM.[96] In patients with oligometastatic rectal cancer, with limited liver, lung, or peritoneal disease, locoregional therapy with curative intent is often considered. It remains controversial whether these patients are good candidates for NOM, with some series showing high regrowth rate which was treatable without TME in most patients.

Neoadjuvant Immunotherapy in CRC

All patients with CRC should be tested for MSI or mismatch repair (MMR) status at diagnosis. MSI-H is a molecular signature of MMR deficiency; this phenotype is often associated with pathologic germline mutations in DNA-MMR genes known as Lynch syndrome which is more frequent in patients with EOCRC.[97] Both patients with MSI-H colon cancer and rectal cancer are candidates for therapy with immune checkpoint inhibitors (ICIs) in the locally advanced setting. A phase II trial that included 49 patients with MSI-H localized rectal cancer showed that treatment with the anti–PD-1 monoclonal antibody dostarlimab achieved 100% of clinical complete response at 12 months. Notably, none of the participants in the study required chemotherapy, radiation, or surgery. Updated results if this study have shown a 2-year recurrence-free survival of 96%.[98,99] Similar results were observed in an open-label single-arm phase II trial using the anti–PD-1 monoclonal antibody sintilimab.[100]

In view of these encouraging results, the NCCN guideline has incorporated anti–PD-1 therapy in patients with MSI-H localized rectal cancer as a treatment option.[101] MSI is more frequent in localized colon cancer than rectal cancer, reaching up to 20% in stage II disease.[102] The NICHE trial is a platform study that has explored the efficacy of neoadjuvant ICIs across multiple colon cancer cohorts (Table 1). Collectively, these studies have demonstrated that a short-course

TABLE 1. Summary of Pivotal Neoadjuvant Treatment Trials in Colorectal Cancer

Study	Patient Population	No.	Treatment Arms	Main Results
Rectal cancer—TNT				
PRODIGE-23 (phase III; 38986769)	cT3/T4 under peritoneal reflection	461	mFOLFIRINOX → LCRT → TME → FOLFOX or cape Standard: LCRT → TME → FOLFOX or cape	7-year DFS 67.6% *v* 62.5%; RMST difference 5.7 months; $P = .048$ 7-year OS 81.9% *v* 76.1%; RMST difference 4.3 months; $P = .033$
RAPIDO (phase III; 33301740, 36661037)	cT4, EMVI+, cN2, involved MRF, or enlarged lateral lymph nodes	920	SCRT → FOLFOX or CAPOX → TME Standard: LCRT → TME → FOLFOX or CAPOX (optional)	3-year DRTF 23.7% *v* 30.4%; HR, 0.75; $P = .019$ LRR 10% *v* 6%; $P = .027$
STELLAR (phase III; 35263150)	cT3-4, cN+, distal or middle third rectal adenocarcinoma	599	TNT: SCRT → CAPOX → TME or NOM → CAPOX Standard: LCRT→ TME or NOM → CAPOX	3-year DFS 64.5% *v* 62.3%; HR, 0.88; $P < .001$ for noninferiority 3-year OS 86.5% *v* 75.1%; $P = .033$
CAO/ARO/AIO-12 (phase II; 34792531)	cT3 <6 cm from the anal verge, cT3 at 6-12 cm with invasion of mesorectal fat >5 mm, cT4 or cN(+)	311	Induction: FOLFOX → LCRT → TME Consolidation: LCRT → FOLFOX → TME	3-year DFS 73% *v* 73%; HR, 0.95; $P = .82$ 3-year LRR 6% *v* 5%; $P = .67$
OPRA (phase II; 37883738)	cT3-4 or cN+	324	Induction: FOLFOX or CAPOX → LCRT → TME or NOM Consolidation: LCRT → FOLFOX or CAPOX → TME or NOM	5-year DFS 71% *v* 69%; $P = .68$ TME-free survival 39% *v* 54%; $P = .012$
Rectal cancer—neoadjuvant chemotherapy				
PROSPECT (phase II/III; 37272534)	cT2N+, cT3N0, or cT3N+ amenable to sphincter-sparing surgery	1,194	FOLFOX → selective LCRT if tumor regression <20% → TME → FOLFOX Standard: LCRT → TME → FOLFOX	5-year DFS 80.8% *v* 78.6%; HR, 0.92; $P = .005$ for noninferiority Local recurrence 1.8% *v* 1.6%; HR, 1.18 (95% CI, 0.44 to 3.16)
Rectal cancer—neoadjuvant immunotherapy				
Cercek et al[98,99] (phase II; 35660797, 40293177)	cT3-T4 or N+ dMMR	49	Dostarlimab → LCRT (if no cCR) → TME (if no cCR)	cCR 100% 2-year recurrence-free survival 96%
Colon cancer—neoadjuvant chemotherapy				
FOxTROT (phase II/III; 36657089)	cT3-4 with extramural extension ≥1 mm, N0-2, M0	1,053	FOLFOX → surgery → FOLFOX Standard: surgery → FOLFOX	Residual or recurrent disease at 2 years 16.9% *v* 21.5%; rate ratio, 0.72; $P = .037$
OPTICAL (phase III; 38564700)	cT3-4 with extramural extension ≥5 mm, N0-2, M0	744	FOLFOX or CAPOX → surgery → FOLFOX or CAPOX Standard: surgery → FOLFOX or CAPOX	3-year DFS 82.1% *v* 77.5%; HR, 0.74; $P = .07$ 3-year OS 95.1% *v* 89.6%; HR, 0.44; $P = .01$
Colon cancer—neoadjuvant immunotherapy				
NICHE 2 (phase II; 38838311)	≥cT3 and/or N+ dMMR	113	Nivolumab and ipilimumab → surgery	Major pathologic response 95%; pCR 68% No disease recurrences with a median follow-up of 26.2 months
NICHE 3 (phase II; 39278994)	≥cT3 and/or N+ dMMR	59	Nivolumab and relatlimab → surgery	Major pathologic response 92%; pCR 68% One patient had disease recurrence with a median follow-up of 8 months

Abbreviations: cape, capecitabine; CAPOX, capecitabine and oxaliplatin; cCR, clinical complete response; DFS, disease-free survival; dMMR, mismatch repair deficiency; DRTF, disease-related treatment failure; EMVI, extramural vascular invasion; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; HR, hazard ratio; LCRT, long-course chemoradiation; LRR, locoregional recurrence; mFOLFIRINOX, modified folinic acid, fluorouracil, irinotecan, and oxaliplatin; MRF, mesorectal fascia; NOM, nonoperative management; OS, overall survival; pCR, pathologic complete response; RMST, restricted mean survival time; SCRT, short-course radiotherapy; TME, total mesorectal excision; TNT, total neoadjuvant therapy.

neoadjuvant ipilimumab (anti-cytotoxic t-lymphocyte associated protein 4 [CTLA-4] ICI) plus nivolumab (anti–PD-1 ICI) or relatlimab (anti-lymphocyte-activation gene 3 ICI) plus nivolumab is not only feasible but also associated with high rates of pCR and DFS.[103-105] While these results are exciting, the clinical benefit of this strategy is not as clear as in MSI-H rectal cancer since surgery alone has excellent results in patients with localized MSI-H colon cancer, organ preservation is not a major concern for these patients, and immunotherapy is associated with toxicity that can be permanent and sometimes severe.[106]

Fertility Considerations in Patients With EOCRC

As mentioned above, infertility is a known complication derived from the treatment of CRC and may result from chemotherapy, surgery, or radiation therapy. Consequently, it is essential that all patients with EOCRC (both male and female) receive fertility counseling before the start of treatment. Unfortunately, this rarely occurs in most countries.[107] Ideally, female patients with rectal cancer interested in preserving their fertility should avoid neoadjuvant therapy whenever possible. However, only a subset of patients with locally advanced rectal cancer, for example, middle/upper T3a tumors, with clear mesorectal fascia and no extramural vascular invasion, might be candidates for up-front surgery.[108] In this regard, the phase II QuickSilver trial included 82 patients with rectal cancer categorized as good prognosis according to MRI criteria (mostly T2/early T3 or T3 with an extramural depth of invasion of <5 mm) who underwent primary surgery. While this study achieved its primary outcome reaching a positive circumferential resection margin rate of 4.9% (95% CI, 0.2 to 9.6), a significant group of these patients will still require adjuvant chemotherapy.[109] As such, a more reasonable alternative is neoadjuvant folinic acid, fluorouracil, and oxaliplatin (FOLFOX) chemotherapy as per the PROSPECT trial.[110] This study included 1,194 patients with rectal cancer (median age 57 years) with low-risk tumors (T2 node–positive, T3 node–negative, or T3 node–positive who were candidates for sphincter-sparing surgery) and demonstrated that neoadjuvant FOLFOX followed by selective use of pelvic chemoradiotherapy was noninferior to neoadjuvant chemoradiotherapy in terms of DFS. Furthermore, local recurrence in this study was very low (<2%). Although FOLFOX can induce persistent amenorrhea in 4%-16% of patients, this compares favorably with pelvic radiation that causes infertility in almost 100% of patients.[55,56] The PROSPECT trial also demonstrated that neoadjuvant FOLFOX was associated with better sexual function for both men and women 12 months after surgery than neoadjuvant chemoradiotherapy, which is particularly relevant for patients who desire fertility (37270691). Finally, uterine transposition has emerged as an additional alternative to preserve fertility and ovarian function in patients who cannot avoid pelvic radiation. However, the evidence on the efficacy and safety of this procedure is still scarce.[111]

Neoadjuvant Treatment of CRC During Pregnancy

Although the estimated risk of CRC during pregnancy is low (0.002%), its incidence is rising given the trends in EOCRC overall and delayed childbearing.[77] Unfortunately, CRC symptoms tend to be overlooked in the context of pregnancy, which leads to late diagnosis. Indeed, some patient series have reported a higher proportion of more advanced stage.[75,76] However, the impact of pregnancy on cancer prognosis is still unclear. Similarly, because of its low prevalence, treatment recommendations for these patients are mostly based on low-quality evidence. In patients with early-stage disease, up-front surgery can be performed before 20 weeks without increasing the risk of miscarriage significantly.[112,113] In locally advanced tumors, neoadjuvant therapy is recommended; however, radiation therapy is contraindicated during pregnancy. On the other hand, chemotherapy with fluorouracil with and without oxaliplatin appears to be safe during the second and third trimester.[114,115] Therefore, induction chemotherapy with FOLFOX followed by radiotherapy after delivery could be a feasible approach for these patients. Another option to consider is neoadjuvant folinic acid, fluorouracil, irinotecan, and oxaliplatin which is a good alternative in rectal cancer patients in whom radiation therapy is contraindicated and has showed very good results in the UNICANCER-PRODIGE23 study as part of a perioperative approach (Table 1). While there are case reports suggesting safety with the combination of FU, oxaliplatin, and irinotecan during second and third trimester, the evidence using a three-drug regimen is still very limited, and therefore, this approach should include a thorough discussion weighing the potential risks and benefits.[116]

RECENT ADVANCES IN BIOMARKER-BASED MANAGEMENT OF METASTATIC CRC

With the rising incidence of EOCRC and its poorer outcomes, biomarker-driven treatment and continuous innovation are critical. A multicenter study of 1,272 patients found that EOCRC is associated with worse prognosis than late-onset CRC (median OS, 34.7 *v* 43.0 months; $P < .0001$), regardless of the molecular subtype, suggesting age as an independent prognostic factor.[117] Routine testing for key alterations (eg, *RAS*, *BRAF*, MSI, *HER2*) now informs standard of care treatment.[118,119] New biomarkers and assays—including liquid biopsies—are emerging to detect residual disease, monitor resistance, and identify rare targets. Herein, we summarize recent advances in biomarker-guided management of metastatic colorectal cancer (mCRC), with attention to both well-established and emerging molecular targets and the evolving understanding of tumor sidedness and metastatic patterns.

Established Biomarkers Guiding Therapy

RAS mutations (*KRAS* and *NRAS*), found in 40%-50% of mCRC, predict resistance to EGFR inhibitors like cetuximab and panitumumab.[120-124] *RAS/RAF* wild-type tumors respond

favorably to anti-EGFR agents and have a relatively favorable prognosis.[123,125,126] Notably, recent advances have highlighted the dynamic management of *RAS/RAF* wild-type mCRC through the use of circulating tumor DNA to guide therapy rechallenge. The CHRONOS trial demonstrated that in patients with *RAS/RAF* wild-type tumors who previously progressed on EGFR inhibitors, plasma clearance of MAPK pathway activation mutations could identify candidates for effective anti-EGFR rechallenge. Cetuximab rechallenge led to disease control in more than 60% of patients.[127] This study underscores how molecular dynamics, rather than static baseline mutation status, can guide treatment in *RAS/RAF* wild-type mCRC.

BRAF V600E mutations, identified in approximately 8%-12% of patients, portend poor prognosis and are often right-sided in origin with a predilection for peritoneal dissemination.[128] Standard chemotherapy is suboptimal.[129] The BEACON study validated encorafenib and cetuximab as a second-line option.[130] This dual regimen achieved an objective response rate of 20% and an improvement in median OS by 3 months compared with second-line chemotherapy (8.4 *v* 5.4 months). BREAKWATER moved this combination to first-line, adding modified FOLFOX and achieving an overall response rate of 60.9% compared with 40% with chemotherapy alone.[131] Responses were also more durable in the triplet arm (68.7% of patients maintained response ≥6 months *v* 34.1%). This led to accelerated Food and Drug Administration approval in 2024, making it the first targeted regimen available for frontline use in *BRAF*-mutant mCRC.

MSI-H/mismatch repair deficiency (dMMR) tumors (approximately 4%-5% of mCRC), enriched in Lynch syndrome, exhibit high mutational burden and strong responses to immune checkpoint blockade.[128,132] KEYNOTE-177 trial established pembrolizumab as a first-line Standard of Care for MSI-H/dMMR mCRC, with a median progression-free survival (mPFS) of 16.5 versus 8.2 months, higher overall response rate (ORR) (43.8% *v* 33.1%), and better safety.[133,134] CheckMate 8HW trial evaluated the efficacy of nivolumab and ipilimumab as first-line therapy in MSI-H/dMMR metastatic CRC.[135] Patients were randomly assigned to receive nivolumab monotherapy, nivolumab plus ipilimumab, or standard chemotherapy. Nivolumab plus ipilimumab significantly improved OS compared with chemotherapy, with a hazard ratio for death of 0.58. Combination immunotherapy demonstrated superior mPFS versus chemotherapy (54.1 *v* 5.9 months; HR, 0.21 [95% CI, 0.14 to 0.31]) and versus nivolumab monotherapy (not reached *v* 39.3 months; HR, 0.62 [95% CI, 0.48 to 0.81]).[136] The ORR for nivolumab plus ipilimumab was 58% versus 38% for chemotherapy. The complete response rate with combination immunotherapy was notably high at 18%. The combination regimen was associated with a higher incidence of immune-related adverse events; grade 3-4 treatment-related adverse events occurred in approximately 32% of patients, primarily diarrhea, colitis, hepatitis, and endocrinopathies, but were largely manageable with immunosuppressive therapy. Together, these data from KEYNOTE-177 and CheckMate 8HW firmly establish immunotherapy as the first-line approach for MSI-H/dMMR metastatic CRC.

HER2 amplification (3%-5% of *RAS/BRAF* wild-type) is an actionable target. Routine HER2 testing by immunohistochemistry and/or fluorescence in situ hybridization is advised for all patients with RAS/BRAF wild-type mCRC, particularly those with left-sided primary tumors, to guide appropriate therapeutic selection. Based on accumulating clinical evidence, multiple HER2-directed treatment strategies are now recommended for this biomarker-defined subgroup. Early-phase trials demonstrated promising activity for dual HER2 blockade. Several dual HER2-targeted approaches have demonstrated efficacy. The MyPathway basket trial studied trastuzumab plus pertuzumab, achieving an ORR of 32% (95% CI, 20 to 45) and a median OS of 11.5 months (95% CI, 7.7 to not estimable).[137] Antibody-drug conjugates offer an additional therapeutic option. The DESTINY-CRC02 phase II trial evaluated trastuzumab deruxtecan (T-DXd) in patients with previously treated HER2-positive mCRC.[138] Among those receiving 5.4 mg/kg of T-DXd every 21 days, the confirmed objective response rate was 37.8%, compared with 27.5% in the 6.4 mg/kg every 21 days group. The 5.4 mg/kg every 21 days dose also demonstrated a more favorable safety profile, supporting its selection as the optimal dose for this patient population. Most recently, the phase II MOUNTAINEER trial established tucatinib plus trastuzumab as another active HER2-targeted regimen.[139] In this study, the ORR was 38.1% (95% CI, 27.7 to 49.3), the mPFS was 8.2 months (95% CI, 4.2 to 10.3), and the median OS reached 24.1 months (95% CI, 20.3 to 36.7). Tucatinib was well tolerated, with low rates of grade 3 or higher adverse events (approximately 13%) and manageable diarrhea and fatigue.

Rare Molecular Subtypes With Targeted Therapy Opportunities

Comprehensive genomic profiling has revealed several rare but actionable genomic alterations, including mutations in the DNA polymerase genes *POLE* and *POLD1*. These define a hypermutated subset characterized by ultramutator phenotypes and extremely high tumor mutational burden, often exceeding 100 mutations per megabase, despite being MSS.[140] *POLE* mutations occur in approximately 1%-2% of metastatic CRCs, whereas *POLD1* mutations are less common[141,142] Notably, emerging evidence suggests that *POLE/POLD1* mutations confer strong sensitivity to ICIs, with retrospective analyses and basket studies reporting durable responses and the ORR exceeding 50%.[141,143,144]

KRAS G12C mutations, found in approximately 3%-4% of mCRC patients, are now targetable using selective KRAS G12C inhibitors in combination with EGFR inhibition to overcome adaptive resistance mechanisms.[145-147] The phase III trial by Fakih et al demonstrated that sotorasib plus

panitumumab significantly improved PFS compared with standard therapy (trifluridine–tipiracil or regorafenib) in patients with refractory *KRAS* G12C–mutated metastatic CRC (mPFS, 5.6 *v* 2.2 months; HR, 0.49; $P < .001$). In addition, a phase I/II study of adagrasib plus cetuximab demonstrates similar activity with a mPFS of 6.9 months. These findings support dual-targeted inhibition of KRAS G12C and EGFR as an emerging standard of care for this molecularly defined subset of refractory mCRC.

Similarly, *NTRK* gene fusions, though exceedingly rare (<1%), confer remarkable sensitivity to NTRK inhibitors like larotrectinib, entrectinib, and repotrectinib.[148-150] *RET* fusions, while also rare, respond to selective RET inhibitors such as selpercatinib.[151] These rare molecular subsets highlight the importance of broad-based next-generation sequencing at diagnosis and disease progression to identify all actionable targets.

Impact of Tumor Sidedness and Anatomic Patterns of Metastasis

Past evidence from the CALGB/SWOG 80405 and FIRE-3 studies illustrates that tumor sidedness is a significant prognostic factor that influences treatment selection.[152,153] Right-sided colon cancers, which originate from the cecum, ascending, and transverse colon, are often characterized by MSI-H, hypermethylation, and a poor response to anti-EGFR therapies such as cetuximab and panitumumab.[154] By contrast, left-sided tumors, arising from the descending colon and rectum, are associated with better prognosis and greater responsiveness to anti-EGFR therapy.[120,155,156] The PARADIGM trial prospectively validated the clinical significance of primary tumor sidedness. In this Japanese phase III study, patients with left-sided RAS wild-type tumors treated with panitumumab plus chemotherapy demonstrated superior OS compared with those receiving bevacizumab-based regimens.[126] These findings firmly establish sidedness as a critical biomarker guiding selection of first-line biological therapy.

Metastatic patterns also influence prognosis. Patients with disease confined to the liver or lung generally have more favorable outcomes than those with peritoneal or multiorgan metastases.[157] The site of metastatic disease in CRC significantly influences both prognosis and response to therapy. Patients with lung-only metastases have consistently demonstrated more favorable survival compared with those with liver involvement; a large SEER analysis showed a lower risk of death for lung-only disease (HR, 0.82 [95% CI, 0.71 to 0.94]) and the median OS exceeding 4 years in selected cohorts.[158] This pattern has potential therapeutic implications, as demonstrated in the phase I trial of botensilimab (a novel Fc-enhanced anti-CTLA-4 antibody) plus balstilimab (anti–PD-1 ICI) in relapsed/refractory MSS mCRC.[159] In this study, patients without active liver metastases (including those with lung-only disease) achieved an objective response rate of 22% and a median OS of 20.9 months, compared with 0% and 7.4 months, respectively, for those with liver involvement. These results highlight that lung-only metastases not only confer a better natural history but may also predict enhanced benefit from emerging immunotherapy strategies in MSS mCRC, whereas liver metastases remain a barrier to effective immune response. Overcoming immunotherapy resistance in MSS mCRC with liver metastases is an active area of investigation. Approaches under evaluation include targeting the TGF-β pathway (eg, NIS793 plus PD-1 inhibitors), using CD40 agonists to reprogram the tumor microenvironment, and combining angiogenesis inhibitors like cabozantinib with anti–PD-L1 therapies to enhance immune infiltration.[160-162]

CONCLUSIONS

As the global burden of EOCRC continues to rise, a deeper understanding of its distinct molecular features, clinical behavior, and reproductive implications is urgently needed. Precision oncology approaches—including germline testing, tumor genomic profiling, and biomarker-driven therapy—are central to optimizing care for this growing population. Advances in neoadjuvant strategies, organ preservation, and immunotherapy have opened new frontiers in both localized and metastatic disease, with promising data supporting tailored interventions for molecularly defined subgroups. However, significant gaps remain, particularly in addressing disparities in fertility counseling, managing CRC during pregnancy, and overcoming resistance to therapy in MSS tumors with liver involvement. A multidisciplinary, lifecycle-based approach—one that spans from diagnosis through long-term survivorship—will be essential to improve outcomes and quality of life for the current and future generations of patients with EOCRC.

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