The Multidisciplinary Management of Colorectal Cancer: Present and Future Paradigms

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Abstract

As treatment strategies for patients with colorectal cancer advance, there has now become an ever-increasing need for multidisciplinary teams to care for these patients. Recent investigations into the timing and duration of perioperative therapy, as well as, the rise of molecular profiling have led to more systemic chemotherapeutic options. The most efficacious use, in terms of timing and patient selection, of these therapies in the setting of modern operative and radiotherapy techniques requires the generation of care teams discussing cases at multidisciplinary conferences. This review highlights the role of multidisciplinary team conferences, advances in perioperative chemotherapy, current clinical biomarkers, and emerging therapeutic agents for molecular subtypes of metastatic colon cancer. As our understanding of relevant molecular subtypes increases and as data becomes available on treatment response, the treatment of colorectal cancer will become more precise and effective.

Keywords

- colon cancer
- rectal cancer
- chemotherapy

Despite advances in screening and treatment, colorectal cancer (CRC) remains the second-leading cause of cancer-related death and is responsible for approximately 50,000 deaths each year in the United States alone.¹ Depending upon the stage of disease, CRC treatment can involve multiple modalities including surgery, radiotherapy, interventional radiology approaches and systemic chemotherapy. The complex multidisciplinary planning for both early- and late-stage treatment is dependent upon patient and tumor characteristics, symptoms, and requires careful communication with patients. These factors all increase the complexity in decision making about the best therapeutic strategies and the timing of these modalities.

Surgical intervention alone is curative in many patients with early-stage disease. For patients with locally advanced disease (stage III), adjuvant 5-fluorouracil (5-FU)-based chemotherapy significantly enhances the relapse-free survival.² In the metastatic setting, the current standard first-line chemotherapeutic options for patients with metastatic CRC are 5-FU in combination with leucovorin and either oxaliplatin (FOLFOX) or irinotecan (FOLFIRI). These treatments have increased median survival from 10 to 14 months with 5-FU and leucovorin alone to 16 to 23 months with FOLFOX and FOLFIRI.^{3,4} Recently, in the CALGB 80405 study, further discussed below, the median survival was 29 months with modern therapy, including biological agents.⁵ In addition,

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CRC is one of a few cancers in which definitive treatments for oligometastatic disease can still be cured with definitive treatment, thereby increasing the rates of hepatic ablations and metastasectomies which requires the need for multiple disciplines to be involved in the care of these patients.⁶ The creation of multidisciplinary teams (MDTs) are central to the successful management of CRC treatment and are recommended for cancer patient management.⁷

In addition, the use of molecular analyses for subtyping CRC is becoming more common practice, especially in the metastatic setting. These molecular markers further discussed below are important for their prognostic and therapeutic implications. This review presents a brief overview of the multidisciplinary treatment of CRC including future directions in perioperative chemotherapy, as well as the current state of molecular profiling, and investigational treatment approaches for subtypes of CRC. As molecular profiling advances, the MDTs will also advance to include members of a molecular tumor board.

Multidisciplinary Team Conferences

Multidisciplinary team conferences are regularly scheduled meetings between surgeons, radiologists, pathologists, medical oncologists, interventional radiologists, gastroenterologists, and radiation oncologists. The goal of these meetings is to coordinate CRC treatment to: (1) provide seamless care throughout all stages of disease, (2) allow for individual evaluation of each patient from various specialties, (3) increase accuracy of staging, (4) decrease cancer recurrence rates, and (5) increase overall survival (OS) under a unified approach across specialties.

The greatest benefits for MDTs have been seen in rectal cancer patients. Burton et al evaluated the use of a MDT conference to discuss the magnetic resonance imaging (MRI) and preoperative treatment strategy for rectal cancer.⁸ They used reduction in positive circumferential resection margin (CRM) as a measure of successful rectal cancer treatment. They found that the patients that underwent surgery alone without an MDT conference had a positive CRM in 26% (16/62) as compared with 1% (1/116) for those whose MRI results were discussed at an MDT conference. Snelgrove et al investigated the use of a MDT for rectal cancer patients at Mount Sinai Hospital in Toronto, Canada.⁹ MDTs were discovered to lead to a change in treatment plan in 29% (12/42) of cases presented. This was thought to be largely related to reinterpretation of the MRI results and resulted in more appropriate preoperative assessment and referral for neoadjuvant chemoradiotherapy. This striking reduction in positive CRM along with a significant change in treatment plan has demonstrated the benefit of MDT conferences for the implementation of a preoperative treatment strategy for rectal cancer.

Limited evidence for the benefits of MDT conferences exist for colon cancer patients, but a similar trend is seen with regards to increased use of neoadjuvant and adjuvant chemotherapy. MacDermid et al found that across stage II and III cancers, significantly more patients were prescribed adjuvant chemotherapy after the implementation of a MDT conference,

39% (43/109) versus 17% (23/136).¹⁰ This resulted in increased survival rates for stage III disease, 58% in the pre-MDT group, and 66% in the post-MDT group ($p = 0.023$) but was not significant for stage II disease. Furthermore, hazard regression analysis showed that MDT status was an independent predictor of survival ($p = 0.044$). While concerns exist about the implementation of MDT conferences, namely, lack of patient involvement,¹¹ potential for longer treatment intervals, and need for staff support, MDTs allow for consensus on complex cases across multiple disciplines and appear to improve patient outcomes.

Future Advances in Perioperative Chemotherapy

Length of Therapy

Around 6 months of postoperative FOLFOX has been the standard of care for the treatment of colon cancers at high risk of relapse. This duration of treatment was determined following multiple clinical studies showing that 6 months is equivalent to 12 months of adjuvant chemotherapy. This decrease in the duration of therapy also limits the adverse effects and toxicity associated with this treatment. While the investigations used to determine optimal length was based on dated therapy, mainly differing intensities of 5-FU/leucovorin calcium (LV), it has been adopted as the mainstay for length of treatment thus far.¹²

Currently, studies are ongoing to determine whether 3 month of adjuvant chemotherapy is a sufficient duration for patients with resected colon cancer compared with the standard 6 months. In 2003, Saini et al performed a multicenter study evaluating 716 patients with curatively resected Dukes' B or C colorectal cancer. Each was randomized to 3 versus 6 months of treatment, once again with 5-FU-based therapy, and showed no statistical survival benefit with a 3-year survival of 87.9 and 83.2%, respectively. As would be expected, the number of patients exhibiting severe side effects including grade 3 to 4 neutropenia, diarrhea, and alopecia was significantly decreased with the shorter treatment time ($p < 0.0001$).¹³ Expanding on that premise, the IDEA (International Duration Evaluation of Adjuvant Chemotherapy) collaboration is comprised of six clinical trials, including CALGB 80702, evaluating the efficacy of 3 versus 6 months of treatment with FOLFOX6, mFOLFOX, or XELOX, with the primary endpoint of 3-year disease-free survival. The stated objective of the collaboration is "reducing the treatment duration, cost, and toxicity of adjuvant chemotherapy in colon cancer."¹⁴

Therapy Escalation for High-Risk Patients

In 2004, the MOSAIC trial (Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer) first released data regarding the addition of oxaliplatin to standard therapy for colon cancer, which resulted in FOLFOX becoming the standard adjuvant chemotherapy regimen for patients with high risk of relapse.¹⁵ Follow-up data published in 2009 showed a significant improvement in disease-free survival for stage II and stage III patients (5-year disease-free survival rates were 73.3 and 67.4% in the FOLFOX4

and LV5FU2 groups) and an OS benefit for patients with stage III disease (72.9 vs. 68.7%, respectively).¹⁶

Despite these improvements in OS, clearly advances in adjuvant treatment options are still clearly needed. Alternative adjuvant regimens, including FOLFIRI and the addition of targeted therapies, such as cetuximab or bevacizumab, have not improved outcomes for patients in the adjuvant setting.^{17–19} The triplet plus bevacizumab (TRIBE) study evaluated the efficacy of oxaliplatin, irinotecan, fluorouracil, and leucovorin (FOLFOXIRI) plus bevacizumab versus standard FOLFIRI plus bevacizumab in the metastatic setting. A significant difference in progression-free survival (PFS, 12.1 months with FOLFOXIRI vs. 9.7 months with FOLFIRI) was seen. A significant increase in OS (29.8 vs. 25.8 months, respectively) was observed with additional follow-up.²⁰ While there appears to be a significant survival advantage using FOLFOXIRI plus bevacizumab, as might be expected, there was significantly more toxicity associated with this intensified regimen. The number of patients experiencing grade 3 to 4 neutropenia was 50% in the FOLFOXIRI arm versus 20.5% in the FOLFIRI arm, peripheral neuropathy was 5.2 versus 0%, respectively, and diarrhea was 18.8 versus 10.6%, respectively. Of note, the TRIBE trial was comprised predominantly of asymptomatic patients with an Eastern Cooperative Oncology Group performance status of 0 (89.8% of included patients). The benefit of FOLFOXIRI in the metastatic setting has resulted in this regimen becoming an attractive option for the escalation of therapy in the adjuvant setting. This regimen deserves further investigation, especially in patients with particularly high-risk disease, including T4 or N2 disease.

Neoadjuvant Chemotherapy for Colon and Rectal Cancer

The utility of neoadjuvant chemotherapy has been widely accepted as the gold standard in several malignancies including certain breast, ovarian, and rectal cancers. The theoretical benefits of neoadjuvant chemotherapy include potential tumor downstaging with the potential for a complete response, eradication of micrometastasis, and initiation of therapy at a time when it will be better tolerated. It is already known that patients who have a delay in the initiation of adjuvant chemotherapy greater than 12 weeks postoperatively have worse survival.²¹ Neoadjuvant therapy also has the added benefit of informing providers of whether or not the tumor is sensitive to chemotherapy. The FOXTROT clinical trial is evaluating the efficacy of neoadjuvant chemotherapy for high-risk stage II and stage III colon cancer. Patients in the neoadjuvant arm receive 6 weeks preoperative chemotherapy and 18 weeks postoperative chemotherapy, while the adjuvant alone arm received 24 weeks postoperative chemotherapy. The study is still accruing and has recruited over 800 patients. In a preliminary report, the initial feasibility results were reported.²² A significant decrease in apical node involvement between the neoadjuvant versus adjuvant chemotherapy arms ($p < 0.0001$), significant increase in tumor downstaging ($p < 0.04$), and fewer positive margins at time of resection ($p < 0.002$) were seen. Of note, there was no difference in postoperative morbidity or mortality between the neoadjuvant arm and the adjuvant alone arm (14 vs. 12% with

prolonged hospital stays, $p = 0.81$). The trial also has a second randomization in each arm to evaluate anti-epidermal growth factor receptor (EGFR) therapy using panitumumab in *KRAS* wild-type patients.²²

The movement of chemotherapy to the neoadjuvant setting has multiple potential advantages, as noted above. It does, however, also rely on improved clinical staging for nodal involvement to determine which patients might benefit from such an approach. This approach is also being investigated in the setting of locally advanced rectal cancer, where there has been a national shift to the movement of chemotherapy into the preoperative phase. This change to a preoperative approach has largely been in response to the development of clinical trials in this setting. These clinical trials include the Alliance led PROSPECT trial and the NRG led total neoadjuvant therapy study. This shift in treatment paradigm opens the possibilities of dose escalation in the setting of resistant disease and is also an interesting platform for the development of perioperative treatment strategies for molecular subtypes of colorectal cancer.

Applications of Molecular Testing for Colorectal Cancer

In addition to the MDTs described above, molecular tumor boards, adding genomics and bioinformatics experts to the treatment team, are now being utilized to determine treatment strategies for cancer patients based on the driver mutations present in each cancer. This degree of precision medicine has previously not been realized in CRC, though numerous targeted therapies have been developed for this disease. The development of targeted agents has offered both additional treatment options as well as improved outcomes for the treatment of metastatic CRC (mCRC). The clinical application of these agents calls for optimized administration either as monotherapy or in combination with cytotoxic chemotherapy. To maximize therapeutic benefit while reducing the inherent risk of systemic toxicity, identification of the patient populations most likely to benefit from these therapies is critical. U. S. Food and Drug Administration (FDA) approved agents for mCRC include the vascular endothelial growth factor (VEGF) monoclonal antibody, bevacizumab, anti-EGFR monoclonal antibodies cetuximab and panitumumab, and antiangiogenic agents aflibercept and ramucirumab. The current standard of care use of molecular analyses for choosing treatment strategies and future precision medicine-based treatment options are reviewed here.

Current Clinical Application of Biomarker Status

KRAS/NRAS

Extensive studies have confirmed *KRAS* exon 2 (codon 12 or 13) mutations predict resistance to anti-EGFR therapies.^{23–30} Since approximately 65% of patients with wild-type *KRAS* exon 2 are resistant to anti-EGFR therapy,³¹ further investigation has been undertaken to determine additional biomarkers of response. Extended spectrum *RAS* mutations

including *KRAS* exons 2, 3, and 4, as well as, *NRAS* exons 2, 3, and 4 have also been identified as important predictors of resistance to these therapies. Retrospective analysis of patients with chemotherapy refractory mCRC, a high prevalence of *KRAS* mutations were observed including exon 2 (codon 12 or 13) at about 40%, with additional mutation rates of approximately 2% at exon 3 (codon 61) and exon 4 (codon 146).²⁸ When treated with cetuximab and chemotherapy, *KRAS* mutations were found to confer lower response rate (RR), shorter median PFS and OS versus wild type. Mutually exclusive of *KRAS* status, *NRAS* mutations were reported at 2.6% resulting in lower RR to cetuximab and chemotherapy, without significant reductions in PFS or OS limited by sampling size ($n = 17$).

In the first-line setting, the use of cetuximab in combination with FOLFOX4 was investigated as a function of biomarker status in the OPUS clinical study.²⁹ Patients with extended spectrum *RAS* mutations treated with cetuximab and FOLFOX4 resulted in no difference in RR or PFS compared with FOLFOX4.³² Similarly in the phase III CRYSTAL study, which analyzed the combination of cetuximab and FOLFIRI versus FOLFIRI alone, independent of locus, extended spectrum *RAS* mutations conferred no benefit in RR, PFS, and OS with addition of cetuximab.³³ Analysis of extended *RAS* status in the setting of panitumumab therapy also demonstrated no benefit to the addition of anti-EGFR therapy in the setting of these mutations.³⁴

To explore the use of targeted agents (cetuximab or bevacizumab) in addition to traditional therapy (FOLFOX or FOLFIRI) in the first-line setting, the phase III multicenter prospective CALGB/SWOG 80405 clinical trial was conducted. Follow-up genetic analysis of 1137 confirmed *KRAS* wild-type patients randomized to either cetuximab or bevacizumab was recently reported.⁵ There was no difference reported in serious toxicity between chemotherapy/cetuximab or chemotherapy/bevacizumab with one of the longest median OS reported to date at about 29 months. Further analysis was performed for extended spectrum *RAS* testing of the CALGB/SWOG 80405 clinical trial. For wild-type *RAS* patients treated with chemotherapy and targeted therapy, bevacizumab or cetuximab, median OS was improved to 31.2 and 32.0 months, respectively. Between groups, there are no significant difference in OS. Taken together, these results show that in selected *RAS* wild-type populations, agents targeted to VEGF and EGFR enhance clinical endpoints with improved RR, PFS, and OS.

BRAF

The *RAF* gene family includes *BRAF* a serine-threonine protein kinase included in the EGFR-mediated *RAS*-*RAF*-*ERK* signaling cascade with role in cellular growth, invasion, and metastasis.³⁵ *BRAF* mutations are highly variable with rates ranging from 5% in microsatellite-stable tumors with increase up to 51.8% in the setting of microsatellite instability.³⁶ Given constitutive *BRAF* activity would evade upstream inhibition at EGFR, it has been hypothesized that anti-EGFR agents would not be beneficial in this population. Multiple clinical investigations have confirmed that the presence of *BRAF* mutations is an independent predictor of poor prognosis^{37–40} and resistance to anti-EGFR therapies.^{28,37,38,40}

Pooled data from the OPUS and CRYSTAL studies⁴⁰ have revealed that *BRAF* mutation predicts overall reduced PFS and OS versus wild-type tumor regardless of treatment group. It has been shown that *BRAF* mutant tumors have significantly lower RR when compared with wild-type cancer when treated with anti-EGFR therapies with significant reduction in PFS and OS.²⁸ Retrospective analysis of PRIME data revealed no improvement in OS and PFS in patients with *BRAF* mutations when comparing treatment with FOLFOX4/panitumumab to FOLFOX4 alone.³⁰ In the second-line setting, *BRAF* mutation resulted in no significant difference in PFS or OS when patients were treated with FOLFIRI/panitumumab or FOLFIRI with study size and mutation status limiting overall conclusions.⁴¹

PIK3CA

Phosphoinositide 3-kinase is a lipid kinase heterodimeric with regulatory and catalytic role in cell growth, proliferation, survival, and apoptosis with downstream mTOR-AKT-PTEN signaling pathway. *PIK3CA* encodes the catalytic subunit p110 α which is made constitutively active by mutation in 10 to 20% of colorectal cancers.^{28,42–44} Of *PIK3CA* mutations, exons 9 and 20 are responsible for > 80% of the mutations found in CRC.⁴⁵ Initial studies remain unclear on the role of *PIK3CA* as a predictor of EGFR-targeted therapy response.

Evaluation of 15 patients carrying *PIK3CA* mutations treated with either panitumumab or cetuximab resulted in no response (0/15) to anti-EGFR therapies with statistically significant reduction in PFS when compared with wild-type *PIK3CA*.⁴⁴ Analysis of 44 patients treated with cetuximab or panitumumab, either alone or in combination with chemotherapy were analyzed as a function of *PIK3CA* status.⁴⁶ Wild-type *PIK3CA* was associated with improved PFS when compared with mutations found in 17.1% of patients with no difference observed in OS.

In contrast, analysis of 200 patients with chemotherapy-refractory mCRC were again analyzed for response to cetuximab monotherapy or in combination with irinotecan with baseline *PIK3CA* mutation rate of 12%.⁴³ This study revealed no difference in RR between mutation status, as well as, no difference in median PFS and OS as a function of *PIK3CA* mutation status. Subgroup analysis of mutation loci was included in data from the European consortium with similar prevalence reported of 14.5%.²⁸ *PIK3CA* mutations at exon 20 were associated with lack of response to cetuximab versus mutations at exon 9. The underlying mechanism for this resistance remains unclear given both mutations have been shown to result in constitutive activation regardless of domain motif. There remains many questions from the molecular to clinical application of *PIK3CA* in the regulation, activation, and integration within the EGFR-mediated cascade.

Development of New Therapeutic Options for Molecular Subtypes of mCRC

In 2012, the Cancer Genome Atlas Network reported a comprehensive molecular analysis of 276 CRC samples.⁴⁷ This study identified 24 genes for which many distinct targeted therapies are currently under investigation. Additional targets in the EGFR

signaling cascade have been identified with promise of precision-based application to mCRC. As multidisciplinary approaches to identifying and targeting malignancy advance, opportunity exist to apply bedside personalized medicine.

HER2

The avian erythroblastosis oncogene B is a family of growth receptors with complex interactions from receptor homology to a complex interplay of intracellular signaling. Toward the goal of improved efficacy, the use of combination therapies that differentially inhibit related molecular targets have been under investigation. Evaluation of patient-derived xenografts from mCRC identified as HER2 positive were found to have poor response to pertuzumab and cetuximab, with marked response noted in combination therapy of small molecule HER2 inhibitor lapatinib in combination with pertuzumab or cetuximab.⁴⁸

An initial phase II study of capecitabine and lapatinib in progressive mCRC did not reveal evidence of treatment response when there was no selection for *KRAS* or HER2 status.⁴⁹ The phase I trial of lapatinib and cetuximab was investigated with 2/6 (33%) CRC patients showing response versus a partial RR of 5/6 (83%) in disease controls.⁵⁰ The clinical application of pertuzumab and cetuximab was limited by 46% of patients dose-limited toxicities rash and mucositis with 1/7 (14%) evaluable patients showing a partial 6 month response.⁵¹ A phase II proof-of-concept study of HER2 Amplification for Colorectal Cancer Enhanced Stratification (HERACLES) was recently published for patients with therapy refractory mCRCs with HER2 amplification to evaluate the use of dual HER2 targeting with lapatinib and trastuzumab.⁵² Evaluation of 18 patients revealed overall response of 6/18 with stable disease over more than 4 months noted in 4/18 patients. Therapy was well tolerated with primary grade 2 diarrhea, fatigue, and skin toxicities with a single grade 3 skin toxicity noted.

BRAF-Targeted Combination Therapy

Future approaches to targeting *BRAF* mutations have been developed for metastatic melanoma, although single agent targeting of *BRAF* has been shown to result in poor RRs in colorectal cancer. In vitro models of CRC treated for vemurafenib for direct *BRAF* inhibition have triggered compensatory EGFR activation.⁵³ A recent phase 1B study of combinatory therapy including *BRAF* inhibitor vemurafenib with irinotecan and cetuximab was reported.⁵⁴ Patient with refractory *BRAF*-mutated cancer received escalating doses of vemurafenib with combinatory cetuximab and irinotecan. The phase 1b cohort reported therapy tolerance with partial response noted in 6/17 evaluable (RR, 35%). The randomized phase II trial (SWOG1406) will provide insight into the addition of vemurafenib to cetuximab and irinotecan in *BRAF* mutant mCRC with evidence of disease progression following initial therapy.

Microsatellite Instability

Detection of microsatellite instability (MSI) or the presence of mismatch-repair deficiency has become standard for CRC.

This information is useful in the adjuvant setting for early-stage patients due to its ability to predict an improved prognosis and resistance to 5-FU chemotherapy.⁵⁵ This information is also important for the identification of patients with Lynch syndrome.^{56,57} In the metastatic setting, MSI testing is also proving to be beneficial for predicting with CRC patients might benefit from immunotherapy approaches.

The programmed death 1 (PD-1) pathway is known to repress Th1 cytotoxic immune responses, which when unregulated results in tumor proliferation across a varied of malignancies. Initial therapies targeted to PD-1 blockade in CRC revealed a response in only 1 of 33 patients.^{58,59} Mismatch-repair deficiencies are also observed in a small fraction of CRC and are associated with increased frequency of somatic mutations as well as a significant immunologic response to malignancy. Notably, the single patient found to be responsive to targeted PD-1 blockade was found to have mismatch-repair deficiency. Given this observation, a small phase II study was conducted to evaluation patients with CRC treated with immune checkpoint blockade with pembrolizumab for RR and PFS as a function of mismatch-repair status.⁶⁰ Mismatch-repair-deficient patients were observed to have improved RR (40 vs. 0%) and PFS (5.4 vs. 2.2 months). This work suggests that immune infiltration in mismatch repair-deficiency can be targeted at neoantigens when targeted therapies blocking known immunologic repression.

Conclusion

As further knowledge is gained regarding tumor biology and as treatment options advance, the need for a multidisciplinary approach to the treatment of patients with CRC continues to evolve. Patients with locally advanced rectal cancer benefit significantly from review at MDT conferences, primarily through improved staging and therapeutic planning. In the future, this is also likely to be important for locally advanced colon cancers as well. This will depend upon improvements in the prediction of node positive disease using imaging modalities. If patients at high risk of recurrence can be predicted before operative management, this would allow for the use of neoadjuvant therapies with the potential benefit of reduction in tumor size, improvements in operative margins, and the potential ability to adjust therapies depending on cancer response.

In the metastatic setting advances are leading to a better understanding of CRC as a collection of multiple subtypes distinguished by their molecular profile. It is already standard of care to subtype all CRC cancers for the presence of *KRAS*, *NRAS*, and *BRAF* mutations to determine patients eligible for anti-EGFR-directed therapies. Clinical trials now are investigating markers of sensitivity for targeted and immune-based treatments, including HER2 overexpression, *BRAF* mutations and MSI status as outlined above. These investigations are likely to lead to the identification of new treatment strategies for CRC subtypes. Studies like these are encouraging for the future development of precision medicine strategies for CRCs. Genomics and other biomarkers are to likely play a larger role in the multidisciplinary approach to CRC in the future expanding the scope and importance of the multidisciplinary team.

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