Review

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Diagnosis and Treatment of Metastatic Colorectal Cancer

A Review

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Abstract

Importance Colorectal cancer (CRC) is the third most common cause of cancer mortality worldwide with more than 1.85 million cases and 850 000 deaths annually. Of new colorectal cancer diagnoses, 20% of patients have metastatic disease at presentation and another 25% who present with localized disease will later develop metastases.

Observations Colorectal cancer is the third most common cause of cancer mortality for men and women in the United States, with 53 200 deaths projected in 2020. Among people diagnosed with metastatic colorectal cancer, approximately 70% to 75% of patients survive beyond 1 year, 30% to 35% beyond 3 years, and fewer than 20% beyond 5 years from diagnosis. The primary treatment for unresectable metastatic CRC is systemic therapy (cytotoxic chemotherapy, biologic therapy such as antibodies to cellular growth factors, immunotherapy, and their combinations.) Clinical trials completed in the past 5 years have demonstrated that tailoring treatment to the molecular and pathologic features of the tumor improves overall survival. Genomic profiling to detect somatic variants is important because it identifies the treatments that may be effective. For the 50% of patients with metastatic CRC with *KRAS/NRAS/BRAF* wild-type tumors, cetuximab and panitumumab (monoclonal antibodies to the epithelial growth factor receptor [EGFR]), in

combination with chemotherapy, can extend median survival by 2 to 4 months compared with chemotherapy alone. However, for the 35% to 40% of patients with *KRAS* or *NRAS* sequence variations (formerly termed *mutations*), effective targeted therapies are not yet available. For the 5% to 10% with *BRAF V600E* sequence variations, targeted combination therapy with BRAF and EGFR inhibitors extended overall survival to 9.3 months, compared to 5.9 months for those receiving standard chemotherapy. For the 5% with microsatellite instability (the presence of numerous insertions or deletions at repetitive DNA units) or mismatch repair deficiency, immunotherapy may be used in the first or subsequent line and has improved treatment outcomes with a median overall survival of 31.4 months in previously treated patients.

Conclusions and Relevance Advances in molecular profiling of metastatic CRC facilitate the ability to direct treatments to the biologic features of the tumor for specific patient subsets. Although cures remain uncommon, more patients can anticipate extended survival. Genomic profiling allows treatment selection so that more patients derive benefit and fewer are exposed to toxicity from ineffective therapies.

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