Integrating Systemic and Surgical Approaches to Treating Metastatic Colorectal Cancer

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KEYWORDS

• Colorectal cancer • Liver metastases • Liver-directed therapy
• Antiangiogenic therapy • Antineoplastic therapy

KEY POINTS

- Median survival has increased substantially in recent years to nearly 30 months in patients with metastatic colorectal cancer treated with contemporary regimens.
- All patients with metastatic disease should undergo evaluation for potential resectability and/or liver-directed therapy, which can significantly improve outcomes and potentially cure a minority of patients.
- Chemotherapy regimens in initial and subsequent settings should be accompanied by a targeted agent, unless specific contraindications exist.
- RAS status should be checked in all patients with metastatic colorectal cancer. Anti–epidermal growth factor receptor antibodies should be only used in patients with "extended" RAS wild-type tumors.

INTRODUCTION

Metastatic colorectal cancer is an important contributor to the public health burden of cancer-related mortality. An estimated 136,830 people in the United States will be diagnosed with colorectal cancer in 2014. Approximately one-fifth of these patients will have distant metastatic disease at the time of presentation.[1] The spread of primary colorectal cancer can occur by lymphatic and hematogenous dissemination, as well as by contiguous and transperitoneal routes. The presence of right upper quadrant

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pain, abdominal distension, early satiety, supraclavicular adenopathy, or periumbilical nodules usually signals advanced metastatic disease. However, given extensive staging and surveillance protocols, it is also common to identify metastatic disease based on imaging studies. The first site of hematogenous dissemination is usually the liver, followed by the lungs and bone. An exception is rectal cancer, which may metastasize initially to the lung because the inferior rectal vein drains into the inferior vena cava rather than into the portal venous system.

Although the prognosis for patients with metastatic disease without specific treatment remains limited, multiple new treatment options developed during the past 2 decades are now available for the treatment of metastatic disease. As a result, median survival has increased to nearly 30 months in the latest large randomized study,[2] from approximately 6 months in the 1990s.[3] This improvement in survival has been driven not by a single "magic bullet" but by the sequential deployment of a variety of chemotherapy and so-called targeted therapy agents. This latter class includes monoclonal antibodies to vascular endothelial growth factor (VEGF) (bevacizumab) and epidermal growth factor receptor (EGFR) (cetuximab and panitumumab), aflibercept, a recombinant fusion protein also directed against VEGF, and regorafenib, an active inhibitor of multiple tyrosine kinases. Finally, a small but substantial minority of patients with isolated sites of metastases may potentially be curable with surgery and liver-directed therapies.

The availability of multiple therapeutic agents for the treatment of metastatic colorectal cancer therefore requires a strategic approach to maximize patient benefit, in terms of both life expectancy and quality of life. When determining initial treatment, the first step is to evaluate whether the patient is potentially curable by a surgical resection of metastases either at the time of diagnosis or after conversion therapy. This approach will guide the choice and timing of chemotherapy. Treatments with the potential highest response rates and the greatest potential to downsize metastasis are the most appropriate for potentially curable patients. If the patient does not seem curable, treatment regimens that offer the longest progression-free survival (PFS) and overall survival (OS) and that maintain quality of life as long as possible are to be preferred. This review focuses on describing systemic approaches to the treatment of patients with metastatic colorectal cancer, with notes on the incorporation of liver-directed and primary resection modalities in the appropriate context.

SYSTEMIC REGIMENS FOR METASTATIC COLORECTAL CANCER

In patients with unresectable metastatic colorectal cancer, who comprise most cases, systemic treatment is focused on tumor control, which is occasionally symptom-directed (palliative) and not curative. The treatment goals are to increase life expectancy while maintaining quality of life for as long as possible. In this context, the model of distinct lines of chemotherapy is being abandoned in favor of a continuum-of-care approach similar to that taken in other chronic illnesses.[4] Using currently available data, the authors propose an algorithm for treatment selection based on emerging clinical and molecular data (**Fig. 1**).

The 3 active conventional chemotherapy agents for metastatic colorectal cancer are fluoropyrimidines (including intravenous 5-fluorouracil or its oral prodrug equivalent, capecitabine), irinotecan, and oxaliplatin (**Table 1**). Patients clearly benefit from access to all active agents.[4,5] A variety of targeted therapy agents are also available (**Table 2**), which are incorporated into conventional chemotherapy regimens at various time points across the continuum of care.