Invited Commentary

Primary Tumor Resection and Patients With Asymptomatic Colorectal Cancer and Nonresectable Metastases
Results of Recent Randomized Trials

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The role of up-front surgery for primary colorectal cancer (CRC) in patients who have nonresectable metastases has been long debated. Small retrospective studies have demonstrated an association between primary tumor resection (PTR) and longer survival.[1] However, without random assignment to resection vs not receiving resection, it is impossible to eliminate patient-selection biases.[2] Advocates also argue that PTR may prevent obstruction, bleeding, and other complications during chemotherapy. Thus, PTR has been common clinical practice even in the setting of unresectable metastatic disease.[1]

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Two large randomized clinical trials, both published in 2021, offer important data supporting the use of chemotherapy alone in this setting.[3,4] In a multicenter trial from the Japanese Colorectal Oncology Group, Kanemitsu et al[3] tested the hypothesis that PTR followed by chemotherapy is superior to chemotherapy alone. A total of 165 patients who had unresectable stage IV asymptomatic CRC were randomly assigned to chemotherapy alone (84 patients) or PTR plus chemotherapy (81 patients). With a median follow-up of 22.0 months, the median overall survival was 26.7 months in the group that received chemotherapy alone and 25.9 months in the group that received PTR plus chemotherapy (hazard ratio, 1.10; 95% CI, 0.76-1.59; $P = .69$). Three postoperative deaths occurred in the group that received PTR plus chemotherapy. PTR was associated with more frequent and severe chemotherapy-related nonhematologic adverse events. The authors concluded that PTR should no longer be considered a standard of care for patients with CRC who have asymptomatic primary tumors and synchronous unresectable metastases.[3]

Similar findings from a larger multicenter, randomized clinical trial from medical centers in the Netherlands and Denmark are reported in this issue of *JAMA Surgery*.[4] The CAIRO4 trial, conducted by the Danish and Dutch Colorectal Cancer Group, included 196 patients who had histologically proven CRC, unresectable metastases, and a primary tumor with few or absent symptoms. These patients were randomized to systemic treatment only (fluoropyrimidine-based chemotherapy with bevacizumab) vs PTR followed by systemic treatment. Within 60 days from randomization, there were 3 deaths (3%; 95% CI, 1%-9%) in the systemic treatment arm and 11 deaths (11%; 95% CI, 6%-19%) in the PTR arm ($P = .03$). The primary cause of 60-day mortality was disease progression. Thus, PTR can no longer be considered the standard of care for asymptomatic colorectal tumors in the setting of unresectable metastases.

In this randomized clinical trial reported by van der Kruijssen et al,[4] patients who had elevated serum levels of lactate dehydrogenase, aspartate transaminase, alanine aminotransferase, and/or leukocytosis who were randomized to PTR had a significantly higher 60-day mortality than patients without these conditions. These data would make us wonder if patients who have transaminitis, leukocytosis, and primary tumors with obstructive symptoms should be considered for stenting rather than PTR.

The favorable outcome of systemic therapy alone is because of the effective oxaliplatin-based chemotherapy and irinotecan-based chemotherapy regimens available for CRC treatment.[5] FOLFOX (folinic acid, 5-fluorouracil, oxaliplatin) chemotherapy or FOLFIRI (folinic acid, 5-fluorouracil, irinotecan) chemotherapy plus bevacizumab results in an approximately 50% tumor response rate with another 30% chance of stable disease. The use of FOLFOX-based chemotherapy can render nonresectable metastatic disease resectable in 10% to 20% of patients.[6] In many of these patients, the primary tumor becomes clinically imperceptible and may be a complete pathologic response in 15% to 40% of cases.[5] More recent data on FOLFOXIRI (folinic acid, 5-fluorouracil, oxaliplatin, and irinotecan chemotherapy) demonstrate even higher response rates and higher conversion of nonresectable disease to resectable disease.[7] A recent meta-analysis found that 39% of patients who had initially unresectable metastatic disease may be downstaged to resectable by FOLFOXIRI with R0 status achieved in 28% of cases.[7]

These data support systemic therapy with oxaliplatin-based chemotherapy as standard for asymptomatic CRCs in the setting of nonresectable metastases and encourage reevaluation of patients after 2 to 4 chemotherapy cycles to determine if the metastatic disease has been converted to resectable. Less surgery up front may result in more effective surgery later with a possible curative outcome.

ARTICLE INFORMATION

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