Following colorectal cancer surgery, longer delay before chemotherapy associated with worse survival

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An analysis of data from previously published studies indicates that longer time to beginning adjuvant chemotherapy after surgery for colorectal cancer is associated with worse survival, according to a study in the June 8 issue of *JAMA*, a theme issue on cancer.

"Colorectal cancer (CRC) is the third leading cause of cancer mortality in the Western world. While surgical resection [removal] remains the cornerstone of management for patients with stage I-III disease, a considerable proportion of patients will ultimately relapse and die from their disease," according to background information in the article. "Adjuvant chemotherapy [AC; chemotherapy after surgery] improves survival among patients with resected colorectal cancer. However, the optimal timing from surgery to initiation of AC is unknown." There is also a question of the benefit of beginning chemotherapy after a certain time period, typically believed to be 12 weeks.

James J. Biagi, M.D., of Queen's University, Kingston, Ontario, Canada, and colleagues conducted a review and meta-analysis of studies that assessed the relationship between time to AC and survival in CRC. Studies were only included if relevant prognostic factors were adequately described and either comparative groups were balanced or results adjusted for these prognostic factors. The researchers identified 10 eligible studies involving 15,410 patients (7 published articles, 3 abstracts) that met study criteria for inclusion. Nine of the studies were

cohort or population based and 1 was a secondary analysis from a randomized trial of chemotherapy.

The researchers found that meta-analysis indicated that a 4-week increase in time to AC was associated with a significant decrease (14 percent) in both overall survival and disease-free survival. There was no significant heterogeneity (lack of uniformity) among included studies. Results remained significant after adjustment for potential publication bias and when the analysis was repeated to exclude studies of largest weight.

"The effect of AC on survival is thought to be eradication of micro-metastatic deposits in a proportion of patients who would otherwise be destined to have cancer recurrence. There is a substantial theoretical rationale to initiate AC promptly after curative surgery," the authors write.

Regarding the question of after what time period would beginning chemotherapy appear to be of limited benefit, the authors found that their results indicate survival of 48 percent if chemotherapy is administered at 12 weeks instead of 4 weeks, suggesting there may be some benefit to chemotherapy beyond a 12-week window, and that a reasonable limit may be more in the order of 4 to 5 months.

These findings suggest that timing of AC plays a critical role in the management and outcomes of patients with CRC and that it would be prudent for clinicians and jurisdictions to avoid delays in access to chemotherapy, the researchers write. "Our results indicate that at a population level, the effect of delays might be substantial. With approximately 140,000 new cases of CRC diagnosed in the United States in 2009, of which roughly 35 percent or 49,000 had stage III disease, the population at risk is sizeable."

"In conclusion, our results demonstrate a significant adverse association between time to AC and survival in CRC, supporting a position that clinicians and jurisdictions need to optimize patient flow logistics to minimize time to AC," the authors write. "Our results provide further validation of the intuitive concept of early time to AC. Physicians may need to more carefully consider timing when discussing AC with patients."

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