

MEDICAL ONCOLOGY

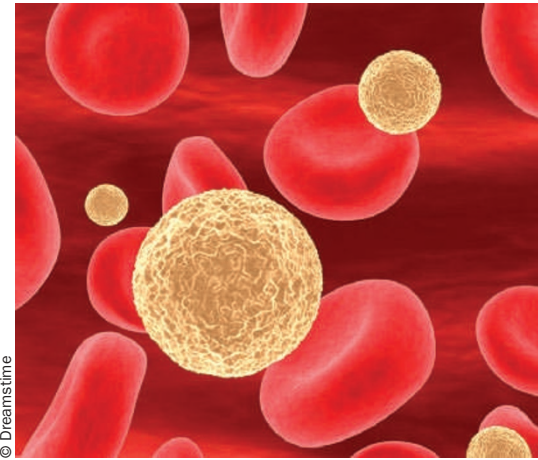
T-cell infiltrate predicts long-term survival in CRC

For patients with colorectal cancer (CRC) and liver metastases who are not surgical candidates, median survival is poor and most patients survive for less than 2 years. Features of the immune system are important in this setting: for example, tumor-infiltrating lymphocytes (TIL) are an independent predictor of survival in patients with primary colorectal cancer. Moreover, CD4⁺ and CD8⁺ cells are activated in patients with colorectal cancer and liver metastases; however, the prognostic importance of these cells in patients with resectable colorectal cancer liver metastases is unknown. A study by Katz and colleagues demonstrates that TIL are an independent predictor of long-term survival in patients who undergo surgical resection of colorectal cancer liver metastases. “This is the first report to demonstrate that the frequency and nature of T cells within colorectal cancer liver metastases are independent correlates of long-term survival”, states Steven Katz, first author of the paper.

The researchers characterized T-cell infiltrates from 162 patients with colorectal cancer liver metastases who had survived for ≤ 2 years or ≥ 10 years following liver resection. In total, 104 patients survived 2 years or less and 58 survived at least 10 years. Significantly more T cells were observed in patients who survived at least 10 years compared with those who died within 2 years.

Among the long-term survivors, 31% had high levels of CD8⁺ T cells compared with only 8% of those who survived less than 2 years. By contrast, levels of CD4⁺ T cells were significantly higher in patients who survived for only 2 years (69%) compared with those who survived for over 10 years (22%). A high CD4⁺:CD8⁺ ratio was also an independent predictor of poor outcome, and this parameter was a more powerful predictor of survival than either parameter alone.

“This is the first study to demonstrate an association between survival time and the degree of tumor T-cell infiltration following resection of colorectal cancer liver metastases,” note the investigators, in their paper. They comment, “Patients with a higher number of CD8⁺ T cells or a lower number of CD4⁺ T cells were more likely to survive 10 years following partial hepatectomy for colorectal cancer liver metastases.” The researchers postulate that high CD8⁺ T-cell levels in patients with colorectal cancer liver metastases might represent an effective immune response that leads to improved survival. By contrast, other studies have shown an association between high CD4⁺ T cell levels and improved survival. This apparent paradox might be explained by data from animal models, which suggest that liver CD4⁺ T cells produce greater amounts of immunosuppressive cytokines than do CD4⁺ T cells in other sites, and that these



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cells have a reduced ability to proliferate. High numbers of liver CD4⁺ T cells might, therefore, limit the efficacy of the intrahepatic immune response.

In conclusion, the researchers showed that in patients with colorectal cancer liver metastases who survive ≤ 2 or ≥ 10 years following hepatic resection, intratumoral levels of CD4⁺ and CD8⁺ cells are associated with outcome, and that this association is independent of other well-established prognostic factors, such as the tumor invasive margin.

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Original article Katz, S. C. *et al.* T cell infiltrate predicts long-term survival following resection of colorectal cancer liver metastases. *Ann. Surg. Oncol.* **16**, 2524–2530 (2009).