

or low. Patients whose tumors had an abundant infiltrate of T cells had a 5-year survival rate of 73%, compared with 30% for patients with low densities of T cells around the tumor. Thus, the nature of a patient's immune response to a given tumor can be a good prognostic marker, where the prognostic value of this particular marker may be greater than that provided by traditional staging methods.

Immune cells have been used as biomarkers for predicting survival to colon cancer in studies by other investigators, for example Pagès et al. (70) Pagès et al. (71) and Camus et al. (72).

8. Tumor infiltrating T cells as a prognostic biomarker for colon cancer – the Morris study

Morris et al. (73) evaluated the prognostic significance of lymphocytes as markers in colon cancer patients treated with surgery alone, or with surgery followed by 5-fluorouracil. Increased lymphocyte infiltration was associated with better survival in patients treated by **surgery plus 5-fluorouracil** (HR = 0.52). But increased lymphocyte infiltration was not associated with better (or worse) survival in patients treated by **surgery alone** (HR = 0.98). The study demonstrated that tumor-infiltrating lymphocytes are a parameter suitable for predicting efficacy of 5-fluorouracil. In this case, efficacy was measured according to the endpoint of overall survival.

The following concerns the hypothesis that chemotherapy creates a natural anti-cancer vaccine. The Morris study proposed that cytotoxic chemotherapy is a potent activator of anti-tumor immune responses, and referred to the hypothesis that chemotherapy creates a wave of dead or dying tumor cells that enters the antigen presentation pathway. To reiterate this scenario, antigen presentation involves uptake of antigen by dendritic cells, processing of antigen by DCs to peptides, presentation of the peptides by DCs to T cells, and activation of antigen-specific clones of T cells.

e. Lymphocytes can kill cancer cells, but lymphocytes can also cause cancer

As described above, tumor-infiltrating lymphocytes can be associated with favorable outcome, as documented above in the studies of Galon et al. (74) and Morris et al.

⁷⁰ Pagès F, Kirilovsky A, Mlecnik B, et al. In situ cytotoxic and memory T cells predict outcome in patients with early-stage colorectal cancer. *J Clin Oncol.* 2009;27:5944–5951.

⁷¹ Pagès F, Berger A, Camus M, et al. Effector memory T cells, early metastasis, and survival in colorectal cancer. *New Engl J Med.* 2005;353:2654–2666.

⁷² Camus M, Tosolini M, Mlecnik B, et al. Coordination of intratumoral immune reaction and human colorectal cancer recurrence. *Cancer Res.* 2009;69:2685–2693.

⁷³ Morris M, Platell C, Iacopetta B. Tumor-infiltrating lymphocytes and perforation in colon cancer predict positive response to 5-fluorouracil chemotherapy. *Clin Cancer Res.* 2008;14:1413–1417.

⁷⁴ Galon J, Costes A, Sanchez-Cabo F, et al. Type, density, and location of immune cells within human colorectal tumors predict clinical outcome. *Science.* 2006;313:1960–1964.