

-Editorial-

Tumor infiltrating immune cells - potential powerful predictors in colorectal cancer patients

Stefan Riss, Rudolf Oehler

Medical University of Vienna, Department of General Surgery, Austria

Corresponding author: Stefan Riss, M.D., Medical University of Vienna, Department of Surgery, Währinger Gürtel 18-20, A-1090 Vienna, Austria.

Tel: ++43 1 404005621, Fax: ++43 1 40400 6932.

E-mail: stefan.riss@meduniwien.ac.at

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In the recent years, great effort was undertaken to elucidate prognostic markers after colorectal resection for malignancies. For example, tumor suppressor genes, DNA repair markers, markers for angiogenesis and several other potential parameters were intensively investigated. However, to date, present data do not provide sufficient evidence that warrants the majority of available prognostic markers to be used in daily clinical practice.

The primary goal is to define reliable parameters that could predict early relapse of cancer and reduced disease free survival in affected patients. Thus, individual risk stratification for each patient is the key stone to find out those patients who might benefit from a more intensive adjuvant treatment. On the other hand, those patients who have a considered low risk of disease recurrence may not require postoperative treatment modalities.

A number of studies focused on the prognostic value of immune cells that infiltrate colorectal cancer tissue.¹⁻³ Notably, several studies reported quite impressive results, demonstrating a potential link between prognosis and response to chemotherapy and tumor infiltrating immune cells. Pagès, *et al.*, observed that tumours with a high density of infiltrating CD45R0+ cells in combination with CD8+ cells were associated with a good clinical prognosis.⁴ Moreover, early metastatic invasion correlated with decreased levels of CD8+ T cells, ranging from early memory (CD45R0+CCR7-CD28+CD27+) to effector memory (CD45R0+CCR7-CD28-CD27-) T cells.³ Increased levels of messenger RNA (mRNA) for products of type 1 helper effector T cells were also found to be associated with no signs of early metastatic invasion. Similar results were reported by the same working group, showing that the type (CD3, CD8, GZMB and CD45R0), density, and location of immune cells (invasive margins and center of tumor) were a better predictor of patient survival in comparison to common histopathological methods.¹

Other reports underlined these findings by demonstrating positive correlation of tumour infiltrating immune cells and better prognosis.² In contrast, there exist controversial data in regard to regulatory T cells. For example, Sinicrope, *et al.* reported an increase in intraepithelial FoxP3+ cells was correlated with poor tumour differentiation.⁵

Another point of interest refers to the type of administered chemotherapy. In the light of controversial data, it becomes increasingly important to define parameters that could predict the clinical response to chemotherapy. Thus, a tailored treatment for individual patients can be offered, providing maximal benefit for each patient on the one hand, and economic cost reduction on the other hand. Chemotherapy induced tumor cell death results in the release of tumor-derived antigens as well as danger signals that could either be captured for triggering antitumor immune response or

ignored. There is an impressive amount of data from animal models showing that the high mobility group box 1 protein (HMGB1) released by dying tumor cells after chemotherapy or radiotherapy interacts with Toll-like receptor 4 (TLR4) on DCs, which are selectively involved in the cross-priming of anti-tumor T lymphocytes *in vivo*.⁶ A recently published clinical study revealed that the co-expression pattern of nuclear and cytoplasmic HMGB1 in colon cancer cells was inversely associated with the infiltration of both CD3+ and CD45RO+ T cells and the 5-year survival rates of patients with stage IIIB colon cancer.⁷ These data are in accordance with a study with 192 colorectal cancer patients. The HMGB1 expression was positively correlated with tumor invasion, lymph node metastasis, distant metastasis, and Duke's stage of CRC patients.⁸ These data suggest that HMGB1 protein is a potential marker for progression of CRC patients which interacts with tumor infiltrating lymphocytes.

The advantage of adjuvant chemotherapy in patients with stage III colonic cancer has been demonstrated by several studies.^{9,10} In contrast, the real impact of chemotherapy in stage II tumors, that penetrate the subserosa or deeper without involvement of lymph nodes, is still under debate.¹¹⁻¹⁴ Mamounas, *et al.* assessed the relative efficacy of adjuvant chemotherapy according to Dukes' stage in four sequential National Surgical Adjuvant Breast and Bowel Project trials (C-01, C-02, C-03, and C-04).¹² The authors concluded that independent of the occurrence of prognostic factors, chemotherapy in Dukes B cancer offers a survival benefit in affected patients. However, as the majority of randomized controlled trials found no significant survival improvement by administering chemotherapy after surgery of stage II colonic cancers, current guidelines do not recommend its routine use.¹⁵ The predictive role of tumor-infiltrating immune cells in these patients needs to be demonstrated in future studies.

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