

AUTHOR'S VIEW

Size matters: Survival benefit conferred by intratumoral T cells is dependent on surgical outcome, treatment sequence and T cell differentiation

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ABSTRACT

Outcome of cytoreductive surgery, treatment sequence and the differentiation status of T cells are key factors to take into account when studying the prognostic value of tumor-infiltrating lymphocytes (TIL) in high grade serous ovarian cancer.

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It has become absolutely clear that the immune system exerts control over cancer growth and can even mediate tumor regression. Indeed, patients with so-called immunologically “hot” tumors—highly infiltrated with immune cells—generally have a better prognosis than patients with immunologically “cold” tumors. However, how conventional treatment affects this prognostic benefit of the immune system has remained underexplored.^{1–3} Recently, we addressed this question in a unique cohort of high-grade serous ovarian cancer (HGSC) patients.

HGSC patients included in our cohort were highly similar in terms of clinicopathological characteristics and were treated with an identical combination of cytoreductive surgery and platinum-based chemotherapy, in the adjuvant or neo-adjuvant setting. The outcome of primary and interval cytoreductive surgery (adjuvant and neo-adjuvant treatment, respectively) was standardized and registered as complete (no residual tissue), optimal (<1cm residual tissue) or incomplete (>1cm residual tissue) in line with international agreements. Interestingly, we observed that only those patients that had no residual macroscopic tumor lesions following primary surgery benefitted from high infiltration of CD8⁺ TIL. By contrast, CD8⁺ TIL infiltration in patients treated in the neo-adjuvant setting did not predict a better prognosis, even in patients in whom cytoreductive surgery was complete. These striking differences may in part be explained by the selection of patients for a given treatment regimen. Patients with a small chance of complete surgical cytoreduction at start of treatment—based in large part on considerable tumor dissemination—are more likely to receive neo-adjuvant chemotherapy. In this patient group, antitumor immunity may therefore be insufficient to constrain aggressive tumor growth even after complete cytoreduction. Patients with immunologically “hot” tumors treated in the neo-adjuvant setting

might therefore especially benefit from checkpoint inhibition to augment the existing antitumor immunity. Alternatively, one could speculate that these aggressive tumors reflect a distinct subset of HGSC with an underlying biology less conducive to immune-mediated tumor control. In line with this hypothesis, a specific gene expression signature was recently found to correlate with surgical outcome in ovarian cancer.⁴

We also observed no overall differences in median T cell infiltration in tissue obtained during primary or interval surgery, suggesting that chemotherapy does not exert a major effect on the absolute number of T cells infiltrating the tumor. A key next step would be to validate this finding by determining whether changes in TIL infiltration occur in individual patients during chemotherapeutic treatment using matched pre- and post-chemotherapy samples. One consideration herein remains that lesions available after chemotherapy may differ from lesions eradicated by chemotherapy and may therefore differ in key genomic/immunologic factors. Indeed, heterogeneity in both cancer cells and tumor microenvironment has frequently been reported between lesions.

In contrast to what we observed for the total CD8⁺ TIL population, a CD27⁺ subset of CD8⁺ TIL was not only predictive for better outcome in patients in whom complete removal of the tumor during primary surgery was achieved, but was also of prognostic benefit in patients with remaining macroscopic lesions.⁵ This CD27⁺ subset of TIL largely consisted of CD45RO⁺CCR7⁺ central memory and CD45RO⁺CCR7[−] effector memory T cell populations and were highly enriched for PD-1 and CD137 expression, a phenotype consistent with a naïve-like antigen-experienced tumor-reactive T cell subset.^{6,7} The association of this phenotype with tumor control is in line with results from various adoptive cell transfer studies in

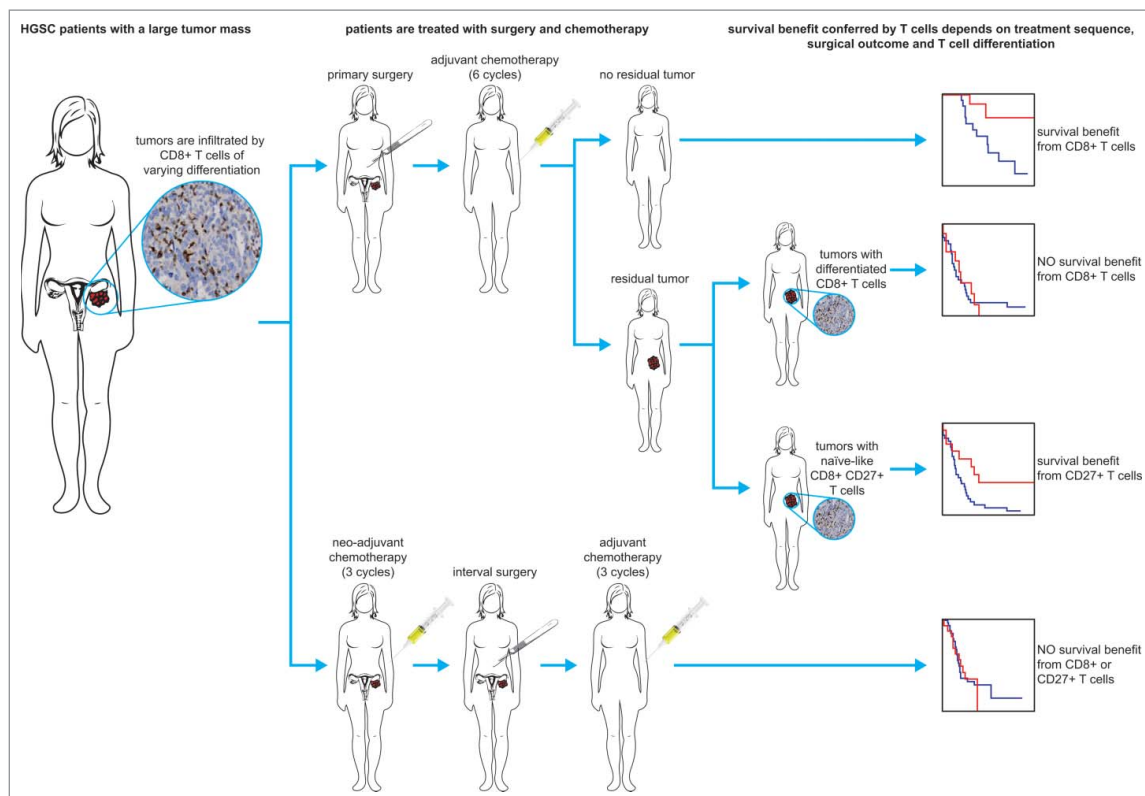


Figure 1. Surgical result and treatment regimen affect prognostic benefit conferred by tumor-infiltrating lymphocytes. CD8⁺ TIL confer a prognostic benefit only in HGSC patients whom received a complete surgical cytoreduction, whereas the CD27⁺ TIL subset also confers a prognostic benefit in patients with residual tumor after surgery. Patients treated with neo-adjuvant chemotherapy do not benefit from infiltration by CD8⁺ nor CD27⁺ TIL.

humans and mice where a high ratio of less-differentiated CD27⁺CD28⁺ cells in transferred TIL was strongly correlated with antitumor immune activity.⁸ Together, these data suggest T cell differentiation is a critical component of immune control *in situ*, but also in the therapeutic setting.

Finally, the finding that the co-stimulatory molecule CD27 is abundantly expressed in HGSC and is highly predictive for prognosis suggests CD27 to be an attractive target for therapeutic immunomodulation. In preclinical models, CD27 agonistic antibodies have proven highly effective and a fully humanized CD27 monoclonal antibody is undergoing clinical development with patients currently being enrolled for trials.^{9,10} Based on the strong co-stimulatory effect of this antibody, activation of TIL, IFN γ production and concomitant upregulation of PD-L1 on tumor and immune cells in the tumor micro-environment is to be expected. This combined with our work and that of others demonstrating that most intratumoral T cells in HGSC express PD-1, provides rationale for a combination strategy with checkpoint blockade targeting the PD-1/PD-L1 axis.

To conclude, outcome of surgical intervention and treatment with adjuvant or neo-adjuvant chemotherapy highly influence the prognostic value of TIL in HGSC. A naïve-like, less-differentiated CD27⁺ subtype of TIL can partly compensate for incomplete surgical removal of tumor and might be predictive for an immunologically “hot” tumor.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed

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