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Multidimensional Visualization for the Immune System State Presentation in Breast Cancer Patients

M. Stakheyeva[1, a)], D. Eidenzon[2], N. Cherdyntseva[1], E. Slonimskaya[1], E. Cherdyntsev[3]

[1]*Tomsk Cancer Research Institute, Kooperativnyi str., 5, Tomsk, Russia.*
[2]*NovoSpark Corporation, 243 Pineland Court, Waterloo, Ontario, Canada, N2T 2S4.*
[3]*National Research Tomsk Polytechnic University, Lenina pr., 30, Tomsk, Russia*.

[a)]Corresponding author StakheyevaM@oncology.tomsk.ru:

Abstract. The immune system is a complex organization system possessing its hierarchical structure of morphological and functional elements united into an integral unity. Therefore the immune system state should be characterized as an integral unity. The use of the NovoSpark Visualisation approach (Canada) to multidimensional data visualization provides the visual image representing the immune system state as an integral unity. This uniform visual characteristic is formed by values of individual immunological parameters in every person. The curves appropriating the immune system states in breast cancer patients with and without cancer progression (hematogenous metastases) during a 3-year follow-up are located in disjoint areas of the multidimensional data space. The obtained data suggest that the immune system greatly influences the course and outcome of breast cancer. In prospect this approach can be useful for a breast cancer outcome prognosis.

INTRODUCTION

The immune system is a complex organization system possessing its hierarchical structure of morphological and functional elements united into an integral unity. Changes in any elements of this system through existing regulatory interaction provide impact on the state of the other elements. The immune system within a living body is autonomous and self-regulating. Therefore, the immune system state should be characterized as an integral unity [1].

A wide test variety is being used nowadays for an adequate immune state evaluation. Investigation of cellular, molecular and genetic mechanisms providing the immune system effects led to an increase in the parameter number used for the immunity state evaluation.

However, an increase in the number of rates results only in refinement of the system elements. When attempting to comprehend the entire process going on in the system, correlations between single mechanisms and elements are easiest to be detected. However, immune system evaluation as an integral unity of different elements and functions is rather unavailable.

An integrated approach would allow finding out differences in the immune system functioning, which are not obvious when investigating individual parameters. Evaluation of the immune system state as an integrated unity is especially challenging in situations when immune response is multiplied and complicated. One of such cases is ambivalent immune system functioning in cancer [2, 3]. It is supposed that tumor suppression or its progression are correlated to various scenarios of the immune system functioning [4, 5].

One of the possible solutions of this problem is an approach to present the immune system state as a multidimensional but integral observation.

The aim is to apply the new methodological approach — multidimensional data visualization — for presentation of the immune system state as an integral entirety on a visual image in breast cancer patients with different disease outcome.

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SUBJECTS AND METHODS

Subject Characteristics

65 breast cancer (BC) patients with stages $T_{1-4}N_{0-3}M0$ treated in the Tomsk Cancer Research Institute were enrolled into the study. Diagnosis of all patients was morphologically verified. Cancer treatment included neoadjuvant chemotherapy (2–4 courses of standard FAC, CAF, CMF regimens), surgery, 4–6 courses of adjuvant chemotherapy, radiotherapy, and hormone therapy if indicated.

BC patients were divided into 2 groups with respect to the disease outcome in order to detect differences in the immune system as an integral unity. The first group (n=31) included BC patients with no signs of the disease progression for more than 3 years. The second group (n=34) included patients with hematogenous metastases found within a 3-year follow-up.

The work has been approved by the Ethical Committee of the Tomsk Cancer Research Institute. The patients gave an informed consent to the study.

Immune System State Analysis

The study included evaluation of the 55 immune system parameters before cancer treatment. Peripheral blood mononuclear cell (PBMC) subpopulations were assayed by immunocytochemistry using monoclonal antibodies to cluster differentiation antigens CD3, CD4, CD8, CD16, CD22, CD25, CD95, HLA-DR (Novocastra Laboratories Ltd., UK) [6]. PBMC apoptosis was tested by fluorescent microscopy with Hoechst 33342 nuclear staining [7]. Spontaneous and stimulated by mitogens secretion of interleukins (IL) 1, 2, 4, 10, tumor necrosis factor alpha (TNF-α), interferon gamma by PBMC were tested by ELISA-assay kits (Cytokine Ltd., Russia). PBMC proliferative activity was evaluated by ^{3}H-thymidine incorporation into cell DNA [8]. Neutrophil functional activity was tested by the nitroblue tetrazolium reduction test [9]. Immunoglobulins (Ig) of A, M, G classes in blood serum were detected by ELISA-assay kits (Vector-Best, Russia).

Multidimensional Data Visualization Method

In our study we used a novel data visualization approach of the NovoSpark Corporation (Canada). The core idea behind the NovoSpark's visualization technique is to present each multidimensional observation as a single observation curve. Within this approach, if two data observations are close, observation curves will have very similar shapes, whereas if records are different, curves will look significantly different as well. The approach establishes a one-to-one correspondence between data records and observation curves. An observation curve is a two-dimensional image of a multidimensional data observation [10, 11].

RESULTS

Presentation of the Immune System State in the Visual Image as an Integral Unity

The NovoSpark Corporation visualization approach allowed us to represent the immune system state as an integral unite. Figure 1 shows four sets of immunological parameters in different patients presented (a table in the low part of the figure) and visual images corresponding to them. Because there are differences in immunological parameters, visual images have different shape and location in multidimensional space.

Differences among the Immune System Visual Images in Breast Cancer Patients Depending on the Disease Outcome

To demonstrate the availability of our approach we used it for visualization of the immune system state in breast cancer patients; some of them lived 3 years without relapses (first group) and others had hematogenous metastases during this period (second group).

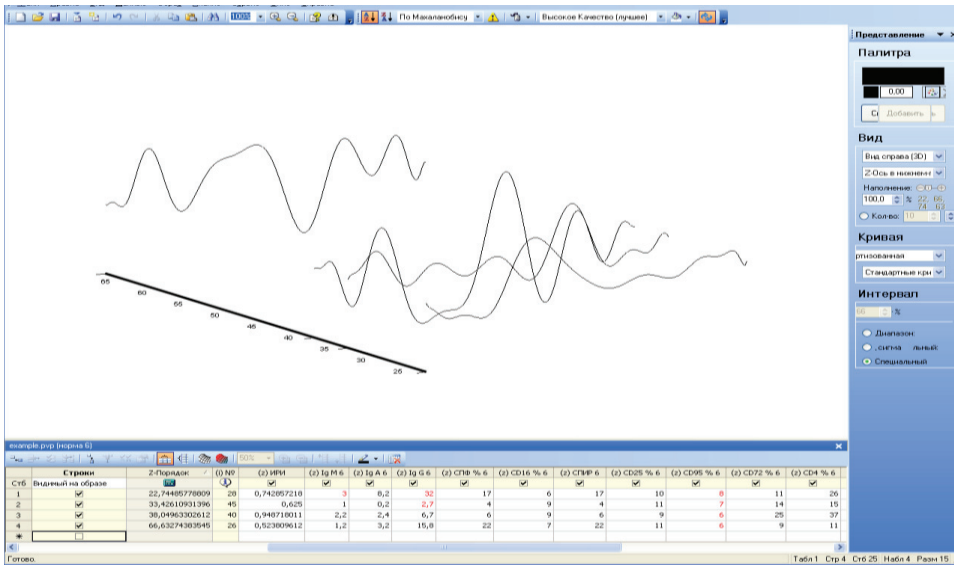

FIGURE 1. Visualization curves conforming different sets of immunological parameters in BC patients

When all estimated parameters of the immune system were included in the visualization model, there were not any statistically differences in visual image disposition for the remission and relapse groups. The curves of both groups overlapped in the three-dimensional space (Fig. 2).

To achieve separate disposition of visual images we performed gradual removal of variables (immunological parameters). When an insignificant parameter was removed, visual images had no change in both the shape and location on the Z-axis, while removal of a significant variable led to a significant change, compared to the previous view. Thus, we can achieve significant differences in disposition for the remission and metastasis groups (Fig. 3). It should be noted that for small groups of patients with relapsed and simultaneous local recurrence and metastases the immune system state also had differences that are shown in different shapes of the visualization curves.

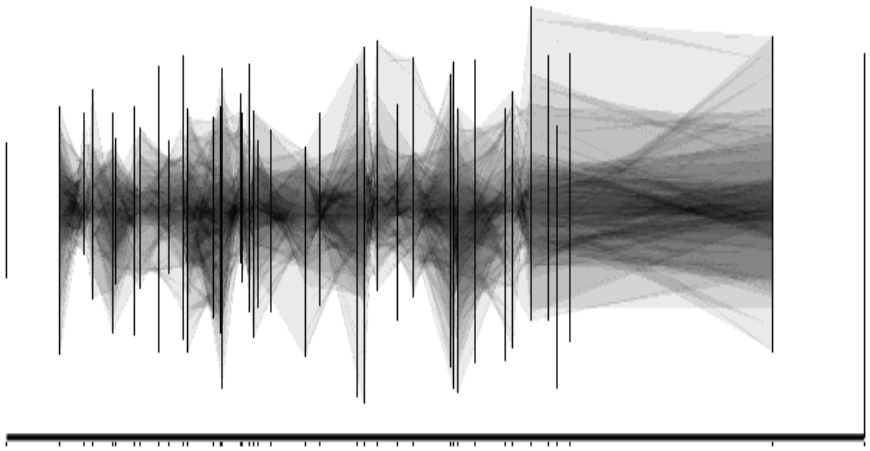

FIGURE 2. Immune system images in BC patients with different outcome immunological parameters. BC patients without signs of the disease progression for more than 3 years — grey area, BC patients with manifested hematogenous metastases — black lines

These data suggest that the immune system greatly influences the course and outcome of breast cancer. Since differences have been found in cancer patients before treatment and progression, in prospect this approach can be useful for a breast cancer outcome prognosis.

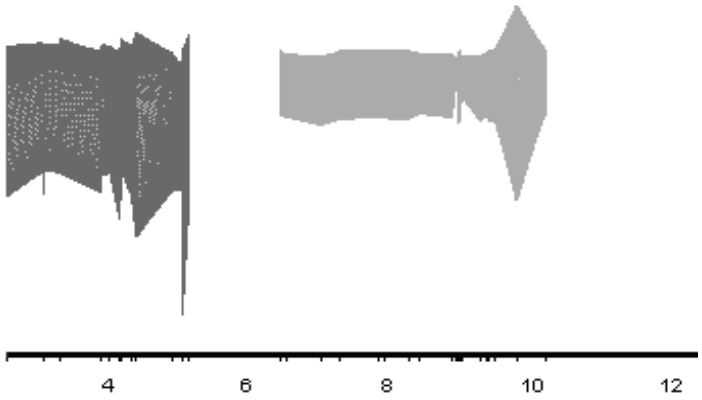

FIGURE 3. Differences in the visual images reflecting the BC patients' immune system state associated with the disease outcome in the 3-year follow-up. BC patients with no signs of the disease progression for more than 3 years — grey color, BC patients with developed hematogenous metastases — black color

CONCLUSION

The use of the NovoSpark approach to multidimensional data visualization provides the visual image representing the immune system state as an integral unity. This uniform visual characteristic is formed by values of individual immunological parameters in every person. The curves appropriating the immune system states in breast cancer patients with and without cancer progression (hematogenous metastases) during a 3-year follow-up are located in disjoint areas of the multidimensional data space.

The obtained data suggest that the immune system greatly influences the course and outcome of breast cancer. Since differences have been found in cancer patients before treatment and disease progression, in prospect this approach can be useful for a breast cancer outcome prognosis.

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