



## Endometrial cancer: Importance of tumor infiltrating lymphocytes as a prognostic factor

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### INTRODUCTION

In the last issue of the *Archive of Oncology* I wrote about importance of our immune system against ovarian cancer. Maybe such a thoughts were only illusions in the past, but nowadays many laboratories worldwide examine the possibilities of our own immune system to recognize tumor cell and become active against it. Recently, another paper about a tumor infiltrating lymphocytes and their importance as a prognostic factor in endometrial cancer has been published in the *Clinical Cancer Research*. I would like to present this article as another important news in this field of immuno-oncology.

In developed countries, adenocarcinoma of the endometrium is the most common gynecological cancer; however, in developing countries, it is much less frequent than carcinoma of the cervix. It accounts for only 2% of all cancer-related deaths; the number of women dying of this disease is still significant (1). The median age of patients at the diagnosis of endometrial carcinoma is 63 years (2). The incidence of endometrial carcinoma is highly dependent on age; there are 12 cases per 100,000 women at 40 years of age and 84 per 100,000 at 60 (3). Seventy-five percent of women with endometrial carcinoma are postmenopausal (4). Ninety-seven percent of all cancers of the uterus arise from the glands of the endometrium and are known as endometrial carcinomas. Endometrioid adenocarcinoma is the most frequent histopathologic subtype.

Christopherson et al. described adenocarcinoma, adenoacanthoma, adenosquamous carcinoma, clear-cell carcinoma, and papillary serous carcinoma, which occurred in 60%, 22%, 7%, 6%, and 5% of the cases, and found five-year survival rates of 80%, 88%, 53%, 44%, and 68%, respectively, for stage I disease (5,6).

Multiple prognostic factors exist for endometrial cancer. These prognostic factors are:

- \* Stage of the disease
- \* Histopathological type of tumor,
- \* The degree of histological differentiation,
- \* Myometrial invasion,
- \* Peritoneal cytology,
- \* Lymph node metastasis

Where is the place of the immune system in this story about prognostic factors?

The functioning of the antigen-specific immune system is based on a division of labor

between T cells and antibody-producing B cells (7). Tumor-infiltrating lymphocytes (TILs) are one of the major immune components infiltrating solid tumors. The majority of TILs in endometrial carcinomas express the CD8+suppressor/ cytotoxic phenotype, and minor subsets express B-lymphocyte and macrophage markers (8,9). Natural killer cells are virtually absent in endometrial tumors (9). Svetlana Kondratiev et al. investigated intratumoral CD8+T lymphocytes as a prognostic factor of survival in endometrial carcinoma (10).

They examined paraffin blocks containing tissue samples that had been obtained from 90 patients with endometrial carcinoma between the years 1991 and 1999 and were retrieved from the archives of the Carmel Medical Center. All tissues had been obtained by hysterectomy. None of the patients had undergone radiation or chemotherapy before surgery.

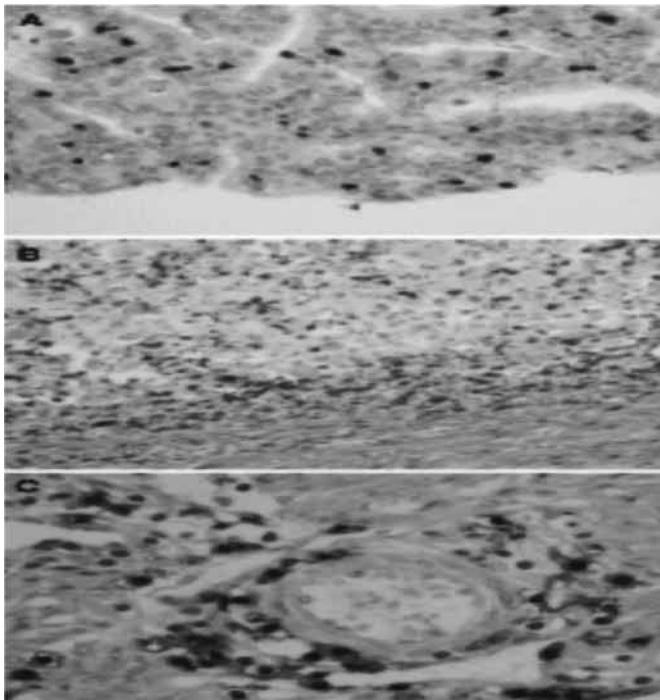
According to results of Kondratiev et al. the relationship between the number of CD8+ lym-

**Table 1.** Clinicopathological characteristics of the patients with endometrial carcinoma (Taken from ref. 10)

	No. of patients (%)
Type	
Endometrioid	75 (83)
Papillary serous	15 (17)
FIGO <sup>a</sup> grade (endometrioid)	
G1	45 (56)
G2	25 (33)
G3	8 (11)
FIGO stage (endometrioid)	
I	50 (66)
II	17 (23)
III	8 (11)
FIGO stage (papillary serous)	
I	3 (20)
II	5 (33)
III	6 (40)
IV	1 (7)

<sup>a</sup>FIGO, Fédération Internationale des Gynaecologistes et Obstétristes

phocytes and other clinicopathological variables was assessed by univariate analysis. Tumor grade and stage were not significantly associated with the number of CD8+ lymphocytes present in the compartments evaluated. The four compartments were evaluated: intraepithelial lymphocytes within superficial tumor epithelium, within the tumor epithelium at the invasive border, within the underlying stroma, and in the perivascular areas of the myometrium (Figure 1).



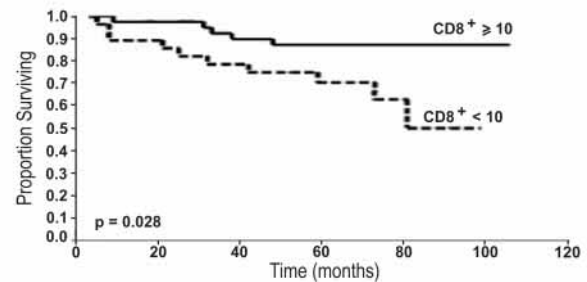
**Figure 1.** Immunohistochemistry for cytotoxic markers. Distribution of CD8+ lymphocytes in superficial tumor epithelium (A), tumor epithelium at the invasive border (B; upper) and underlying stroma (B; lower), and perivascular areas in the myometrium (C) (Taken from ref. 10)

The number of CD8+ lymphocytes in the underlying tumor stroma significantly correlated with the presence of vascular invasion. The number of perivascular CD8+ lymphocytes was significantly associated with vascular invasion. Tumors with >20 perivascular CD8+ lymphocytes showed an increased risk for vascular invasion. Also they found by univariate analysis stage, grade, and vascular invasion all correlated significantly with patient survival in the endometrioid carcinoma group (stage,  $P < 0.0054$  for I versus II; grade,  $P < 0.042$  for I versus II and 0.022 for I versus III; vascular invasion,  $P < 0.0001$ ).

A significant correlation between the number of intraepithelial CD8+ T lymphocytes at the invasive border and patient outcome in the endometrioid carcinoma group was found (Figure 2). Greater overall survival was seen in patients with tumors exhibiting >10 intraepithelial lymphocytes/field (x 200) at the invasive border ( $P = 0.027$ ). At the end of the study, 87% of the patients with >10 lymphocytes/field were alive compared with 50% of patients with <10 lymphocytes/field. The number of lymphocytes present within the underlying stroma and in the superficial tumor epithelium did not show a significant correlation with prognosis. The number of perivascular lymphocytes (total number or CD8+ subsets) also did not correlate with survival.

Kondratiev et al. demonstrated for the first time that infiltration of CD8+ T cells in the tumor epithelium at the invasive border is a favorable prognostic factor in endometrial carcinoma patients. The mechanism of TIL activation and distribution of activated TILs in endometrial carcinoma is not clear. Lymphocyte activation and proliferation may occur after presentation of a tumor-specific antigen by professional antigen-presenting cells or by tumor cells themselves in a HLA-restricted fashion (11).

Ferguson et al. reported that MHC class I antigens were detected in four of eight endometrial carcinomas compared with their normal tissue counterparts (9). Failure to express MHC class I antigens by malignant cells arises from their ability to transform and be selected during tumor progression and is thought to be an advantage of tumor resistance to attack by cytotoxic T cells (9). Interestingly, some endometrial carcinomas express MHC



**Figure 2.** Kaplan-Meier survival curves for endometrioid endometrial carcinoma patients, with 10 CD8+ lymphocytes/computerized x200 field used as the cutoff point ( Taken from ref. 10)

class II DR antigen on the epithelial cells, suggesting that other antitumor mechanisms also play a role in the immune response (9). Alternatively, the CTLs in endometrial carcinoma may be nonspecifically activated by a mechanism of a general inflammatory reaction, such as the release of activating cytokines (12).

In conclusion, Kondratiev's results indicate that increased numbers of TILs at the invasive border of endometrial carcinomas may be a reliable independent prognostic factor of improved patient survival. TILs in endometrial carcinoma express immunohistochemical markers of cytotoxic activity, suggesting that CTL-mediated cytotoxicity may be a key mechanism active in host versus tumor immune response.

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