Inverse Correlation between Tumoral Indoleamine 2,3-Dioxygenase Expression and Tumor-Infiltrating Lymphocytes in Endometrial Cancer: Its Association with Disease Progression and Survival

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Abstract

Purpose: Tumor escape from host immune systems is a crucial mechanism for disease progression. We recently showed that the immunosuppressive enzyme indoleamine 2,3-dioxygenase (IDO) is a prognostic indicator for endometrial cancer. The purpose of the present study was to investigate the relationship between IDO expression and tumor-infiltrating lymphocytes (TIL) or natural killer (NK) cells and to clarify their prognostic effect in endometrial cancer.

Experimental Design: Immunohistochemical staining for IDO expression in endometrial cancer tissues (n = 65) was done. Tumor-infiltrating CD3+ and CD8+ lymphocytes, as well as CD57+ NK cells, were counted in serial tissue sections.

Results: High IDO expression in tumor cells was found in 32 of 65 cases and was positively correlated with myometrial invasion, nodal metastasis, and lymph-vascular space involvement. We also found a significant correlation between high IDO expression and reduced numbers of CD3+, CD8+, and CD57+ cells infiltrating into both the tumor epithelium and stroma. Patients with high IDO expression, a low number of stromal CD3+ (≤60), low intraepithelial CD8+ (≤25), or low stromal CD8+ (≤40) had significantly impaired progression-free survival. On multivariate analysis, IDO expression and the number of stromal CD3+ TILs were independent prognostic factors for impaired progression-free survival.

Conclusions: Tumoral IDO expression correlated with a reduced number of TILs and NK cells in endometrial cancer, possibly contributing to disease progression and impaired clinical outcome. These findings suggest that targeting IDO to restore host antitumor immunity may be a therapeutic strategy for endometrial cancer.

Tumor escape from host immune surveillance creates a state of “tolerance” and is a crucial mechanism for cancer progression (1). However, its underlying cellular and molecular basis remains poorly understood. Recent studies suggest that one mechanism that may contribute to this tolerance is the immunoregulatory enzyme indoleamine 2,3-dioxygenase (IDO; ref. 2).

IDO is an intracellular enzyme that catalyzes the initial and rate-limiting steps in the metabolism of the essential amino acid tryptophan along the kynurenine pathway (3). Recently, evidence that indicates an immunosuppressive function for IDO has been accumulating. It was first found that IDO is expressed in the mouse placenta during pregnancy and prevents rejection of the allogeneic fetus, thereby suggesting involvement of IDO in fetal-maternal tolerance (4). Subsequent studies clarified the mechanism of IDO immunosuppression to be local depletion of tryptophan and/or production of toxic tryptophan catabolites, causing growth arrest and the apoptosis of alloreactive T cells or natural killer (NK) cells that are extremely sensitive to tryptophan shortage (5). The tryptophan-derived catabolite kynurenine also inhibits the expression of specific triggering receptors on NK cells and regulates NK-cell function (6).

In malignancy, it was firstly shown that IDO is expressed by the tumor cells themselves in various human cancers and that tumors expressing IDO can resist immune rejection by tumor-associated antigen-specific host cytotoxic T cells in mouse models (7). Furthermore, IDO is also expressed by certain subsets of dendritic cells in tumor-draining lymph nodes in mice, and these IDO-expressing dendritic cells potently suppress host antitumor T-cell responses and induce tolerance to tumor-derived antigens (8, 9). More recently, it was shown that IDO inhibitors potentiated the antitumor activity of chemotherapeutic agents in tumor-bearing mice, suggesting the involvement of IDO in chemoresistance (10, 11). Evidence from these animal studies has prompted further examination of the clinical relevance of IDO in human cancers.
Several limited studies showed that expression of IDO is associated with poor clinical outcome in malignant melanoma (9), ovarian cancer (12), lung cancer (13), and colorectal cancer (14). We have recently shown that high IDO expression in endometrial cancer tissues is positively correlated with disease progression and impaired patient survival, suggesting that IDO is a prognostic indicator for endometrial cancer (15). However, the functional significance of IDO in human cancers remains to be clarified.

In the current study, we investigated the relationship between IDO expression and the degree of tumor infiltration of T cells or NK cells in endometrial cancer using immunohistochemical staining. We also attempted to elucidate whether the number of tumor-infiltrating lymphocytes (TIL) and level of IDO expression are related to disease progression and survival in endometrial cancer patients.

Materials and Methods

Patients and case selection. Sixty-five patients with endometrial endometrioid adenocarcinoma who underwent surgical treatment at Nagoya University Hospital between 1992 and 2001 were included in this study. Surgical treatment consisted of total abdominal hysterectomy and bilateral salpingo-oophorectomy and followed by surgical staging, including peritoneal washing cytology and lymphadenectomy. Patients with histologic cell types other than endometrioid adenocarcinoma, such as papillary serous or clear cell, were not included in this study. The mean age of the patients was 57.7 y. All patients were staged according to the 1988 International Federation of Gynecology and Obstetrics (FIGO) criteria: 44 were stage I (4 were IA, 27 were IB, 13 were IC), 6 were stage II, 9 were stage III, and 6 were stage IV. Histologic grade was assigned according to the criteria of WHO classification: 31 were G1, 23 were G2, and 11 were G3. In this study, all patients with FIGO stage IC and higher received postoperative chemotherapy with six cycles of either cisplatin/doxorubicin/cyclophosphamide or cisplatin/etoposide in 1992 to 1999 and paclitaxel/carboplatin after 2000. Patients receiving postoperative radiation therapy or any preoperative treatment were excluded from this study because their number was very small. Patients with tumor recurrence were treated with chemotherapy, local radiotherapy, or surgical resection, if possible.

Antibodies. Antihuman IDO monoclonal antibody was prepared as described previously (16). The reactivity and specificity of this monoclonal antibody was confirmed via Western blot analysis of tumor tissue samples, where IDO protein was detected as a 42-kDa protein (single band (15)). A rabbit polyclonal antibody against human CD3, a marker of T cells, was purchased from Dako, and a mouse monoclonal antibody against human CD8, a marker of cytotoxic T cells, was purchased from Nichirei. In addition, a mouse monoclonal antibody against human CD57 was purchased from Becton Dickinson. The CD57 antigen is one of the markers for a subset of NK cells and has been used for immunohistochemical evaluation of tumor-infiltrating NK cells in many previous reports (17–20).

Immunohistochemistry. Informed consent was obtained from individual patients for the use of their tissue samples. Surgical specimens were fixed in 10% formalin and embedded in paraffin. Paraffin specimens were cut at a thickness of 4 μm. For heat-induced epitope retrieval, deparaffinized sections were soaked in Target Retrieval Solution (Dako) and incubated at 95°C for 15 min in a microwave oven. Immunohistochemical staining was done using the avidin-biotin immunoperoxidase technique. Endogenous peroxidase activity was blocked by incubation with 0.3% H2O2 in methanol for 15 min, and nonspecific immunoglobulin binding was blocked by incubation with 10% normal goat serum for 10 min. Sections were incubated at room temperature for 2 h with primary antibodies against IDO, CD3, CD8, and CD57. The sections were rinsed and incubated for 30 min with the biotinylated second antibody. After washing, the sections were incubated for 30 min with horseradish peroxidase–conjugated streptavidin and finally treated with 3,3′-diaminobenzidine tetrahydrochloride in 0.01% H2O2 for 10 min. The slides were counterstained with Meyer’s hematoxylin. As a negative control, the primary antibody was replaced with normal mouse or rabbit IgG at an appropriate dilution. As a positive control for IDO immunostaining, tissue sections of normal placenta were used as previously reported (21).

Scoring of IDO expression in tumor cells. IDO expression levels were classified semiquantitatively based on the percentage of tumor cells with IDO staining and the staining intensity. The percentage positivity was scored as 0 if ≤5% of cells were stained (negative), 1 if 5% to 30% (sporadic), 2 if 30% to 70% (focal), and 3 if >70% (diffuse), whereas the staining intensity was scored as 0 if there was no staining, 1 if cells were weakly stained, and 2 if strongly stained (equal to the positive control level). The final IDO expression score was defined as follows: IDO− if the sum of the percentage positivity score and the staining intensity score was 0 to 1, IDO1+ if the sum was 2 to 3, and IDO2+ if the sum was 4 to 5. In this scoring system, IDO expression in the tumor stromal cells was not considered because IDO immunostaining in nontumor cells was not remarkable or absent in all cases examined. In each case, three different areas were evaluated, and the mean of the results was considered to be the final IDO expression score. The scoring procedure was carried out by two independent observers (each blinded to the other’s score) without any knowledge of the clinical data. The concordance rate was over 95% between the observers.

Quantification of TILs and NK cells within tumors. Tumor-infiltrating CD3+ and CD8+ T cells were classified into two groups by their localization: (a) intraepithelial, cells infiltrating into the tumor epithelium, and (b) stromal, cells infiltrating the tumor stroma adjacent to cancer epithelia or the stroma along the invasive margin of the cancer epithelia. Three independent areas with the most abundant lymphocyte infiltration were selected, and the intraepithelial TILs and stromal TILs were independently counted in each microscopic field at 200× (0.0625 mm2). The average count for three areas was accepted as the number of TILs in each case. CD57+ NK cells were similarly counted at 200× in the three areas with the most abundant infiltration. Because the number of tumor-infiltrating CD57+ cells was very low, the total count of both intraepithelial and stromal cells was taken.

Statistical analysis. Pearson χ2 test was used to analyze the correlation of IDO expression with clinicopathologic variables or the number of TILs. Comparison of the numbers of TILs between IDO1−/IDO1+ and IDO2+ groups was done using the Mann-Whitney U test. Overall survival and progression-free survival (PFS) were calculated from the date of surgery to the date of death and the date of progression/recurrence, respectively, or date of last follow-up. Survival analyses were done according to the Kaplan-Meier method. Comparison of survival between groups was done with the log-rank test. Cox proportional hazard model and stepwise analysis were used for univariate and multivariate analyses. SAS software (SAS Institute, Inc.) was used for all statistical analyses, and a P value of <0.05 was considered significant.

Results

Immunohistochemical expression of IDO in endometrial cancer tissues. As shown in Fig. 1A–D, IDO immunoreactivity was detected at variable levels and was localized to the cytoplasm of tumor cells. In contrast, IDO immunoreactivity in the tumor stroma was very faint or absent. Based on the IDO expression score in tumor cells, all cases were classified into two groups: high IDO expression (IDO2+) and no or low IDO expression (IDO− or IDO1+). Of the 65 specimens examined, high IDO
expression was found in 32 cases (49%), whereas IDO- and IDO1+ tumors were found in 13 (20%) and 20 (31%) cases, respectively.

The correlations of high IDO expression with clinicopathologic variables is summarized in Table 1. High IDO expression was positively correlated with FIGO stage ($P = 0.001$), depth of myometrial invasion ($P = 0.004$), lymph node metastasis ($P = 0.035$), and lymph-vascular space involvement ($P = 0.001$), but not with histologic grade ($P = 0.741$). These results suggest that high IDO expression is strongly associated with disease progression in endometrial cancer.

Association of IDO expression with the infiltration of TILs. Next, we evaluated the number of T cells and NK cells infiltrating into the tumor epithelium or tumor stroma (Fig. 1E-H) to investigate the relationship between IDO expression and TILs. The number of intraepithelial CD3+ cells in IDO2+ tumors (range, 3-55; median, 28) was significantly lower ($P = 0.0094$) than in IDO-/IDO1+ tumors (range, 7-78; median, 41; Fig. 2A), whereas the number of stromal CD3+ cells in IDO2+ tumors (range, 14-95; median, 48) was significantly lower ($P < 0.0001$) than in IDO-/IDO1+ tumors (range, 30-142; median, 75; Fig. 2B). Similarly, the number of intraepithelial CD8+ cells in IDO2+ tumors (range, 1-48; median, 18) was significantly lower ($P = 0.0013$) than in IDO-/IDO1+ tumors (range, 3-58; median, 29; Fig. 2C) and the number of stromal CD8+ cells in IDO2+ tumors (range, 8-68; median, 24) was also significantly lower ($P < 0.0001$) than in IDO-/IDO1+ tumors (range, 14-118; median, 55; Fig. 2D). Furthermore, the number of CD57+ cells in IDO2+ tumors (range, 0-16; median, 2) was significantly lower ($P = 0.0139$) than in IDO-/IDO1+ tumors (range, 0-20; median, 4; Fig. 2E).

The correlation of IDO expression and TIL counts is summarized in Table 1. High IDO expression was significantly correlated with low numbers of intraepithelial CD3+ cells ($P = 0.018$), stromal CD3+ cells ($P = 0.001$), intraepithelial CD8+ cells ($P = 0.001$), stromal CD8+ cells ($P = 0.001$), and total CD57+ cells ($P = 0.025$).

Correlation of IDO expression and TIL counts with patient survival. The median follow-up period was 72 months (range, 5-148). During the follow-up period, disease progression/recurrence was observed in 14 cases (21.5%) in which
nine patients (13.8%) died of the disease. The overall survival rates of patients with IDO-/IDO1+ tumors and IDO2+ tumors were 95.7% and 73.1%, respectively, whereas the PFS rates for IDO-/IDO1+ and IDO2+ were 97.0% and 56.5%, respectively (Fig. 3A). Patients with high IDO expression (IDO2+) had significantly impaired PFS ($P = 0.0001$) when compared with patients with weak or no expression of IDO (IDO-/IDO1+; Fig. 3A).

Next, we analyzed the effect of the TIL count on patient survival. As shown in Fig. 3B and C, the PFS rates for high ($>35$) and low ($<35$) intraepithelial CD3 groups were 87.1% and 68.8%, respectively, whereas the PFS rates for high ($>60$) and low ($<60$) stromal CD3 groups were 93.9% and 59.4%, respectively. Patients with low ($<60$) stromal CD3+ cell counts had significantly impaired PFS ($P = 0.0001$) when compared with patients with high ($>60$) stromal CD3+ cell counts (Fig. 3C). Similarly, the PFS rates for high ($>25$) and low ($<25$) intraepithelial CD8 groups were 89.3% and 68.7%, respectively, whereas the PFS rates for high ($>40$) and low ($<40$) stromal CD8 groups were 96.6% and 61.4%, respectively (Fig. 3D and E). There was a significant difference in the PFS between high and low intraepithelial CD8 groups ($P = 0.0493$) and between high and low stromal CD8 groups ($P = 0.0011$; Fig. 3D and E).

**Multivariate analysis of prognostic variables in endometrial cancer patients.** Univariate analysis showed that FIGO stage ($P = 0.002$), nodal status ($P = 0.001$), lymph-vascular space involvement ($P = 0.020$), IDO expression ($P = 0.024$), and stromal CD8 count ($P = 0.041$) were significant prognostic factors for overall survival (Table 2). Among these variables, only FIGO stage [hazard ratio (HR) = 2.456, $P = 0.032$] and nodal status (HR = 4.904, $P = 0.026$) were independent prognostic factors with respect to overall survival on multivariate analysis. In contrast, FIGO stage ($P = 0.001$), nodal status ($P = 0.010$), lymph-vascular space involvement ($P = 0.031$), IDO expression ($P = 0.005$), stromal CD3 count ($P = 0.006$), intraepithelial CD8 count ($P = 0.044$), and stromal CD8 count ($P = 0.012$) were significant prognostic factors for PFS on univariate analysis. Among these variables, FIGO stage (HR = 3.878, $P = 0.019$), IDO expression (HR = 6.317, $P = 0.025$), and stromal CD3 count (HR = 3.693, $P = 0.047$) were

### Table 1. Correlation of IDO expression with clinicopathologic factors and the number of TILs

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients, n (%)</th>
<th>High IDO expression, n (%)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All cases</strong></td>
<td>65 (100)</td>
<td>32 (49.2)</td>
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</tr>
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<td><strong>Clinicopathologic factors</strong></td>
<td></td>
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<tr>
<td>Age (y)</td>
<td></td>
<td></td>
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<tr>
<td>&lt;60</td>
<td>41 (63.1)</td>
<td>21 (51.2)</td>
<td></td>
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<tr>
<td>≥60</td>
<td>24 (36.9)</td>
<td>11 (45.8)</td>
<td>0.675</td>
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<td>FIGO stage</td>
<td></td>
<td></td>
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<tr>
<td>I/II</td>
<td>50 (76.9)</td>
<td>19 (38.0)</td>
<td></td>
</tr>
<tr>
<td>III/IV</td>
<td>15 (23.1)</td>
<td>13 (86.7)</td>
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</tr>
<tr>
<td>Grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G1-G2</td>
<td>54 (83.1)</td>
<td>26 (48.1)</td>
<td></td>
</tr>
<tr>
<td>G3</td>
<td>11 (16.9)</td>
<td>6 (54.5)</td>
<td>0.741</td>
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<tr>
<td>Myometrial invasion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤50%</td>
<td>39 (60.0)</td>
<td>13 (33.3)</td>
<td></td>
</tr>
<tr>
<td>&gt;50%</td>
<td>26 (40.0)</td>
<td>19 (73.1)</td>
<td>0.004</td>
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<tr>
<td>Nodal status</td>
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<tr>
<td>Negative</td>
<td>59 (90.8)</td>
<td>26 (44.1)</td>
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<td>Positive</td>
<td>6 (9.2)</td>
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<tr>
<td>Absent</td>
<td>40 (61.5)</td>
<td>13 (32.5)</td>
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<tr>
<td>Present</td>
<td>25 (38.5)</td>
<td>19 (76.0)</td>
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</tr>
<tr>
<td><strong>No. TILs</strong></td>
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<td></td>
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<tr>
<td>Intraepithelial CD3+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High (≥35)</td>
<td>32 (49.2)</td>
<td>11 (34.4)</td>
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<tr>
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<td>33 (50.8)</td>
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<td>33 (50.8)</td>
<td>8 (24.2)</td>
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<tr>
<td>Low (&lt;60)</td>
<td>32 (49.2)</td>
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<td>Intraepithelial CD8+</td>
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<td>29 (44.6)</td>
<td>8 (27.6)</td>
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<tr>
<td>Low (&lt;25)</td>
<td>36 (55.4)</td>
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<tr>
<td>High (≥40)</td>
<td>29 (44.6)</td>
<td>4 (13.8)</td>
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<tr>
<td>Low (&lt;40)</td>
<td>36 (55.4)</td>
<td>28 (77.8)</td>
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<tr>
<td>Total CD57+</td>
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<tr>
<td>High (&lt;5)</td>
<td>23 (35.4)</td>
<td>7 (30.4)</td>
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<tr>
<td>Low (&lt;5)</td>
<td>42 (64.6)</td>
<td>25 (59.5)</td>
<td>0.025</td>
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</table>

*Abbreviation: LVSI, lymph-vascular space involvement.*

*TILs were counted with a microscopic field at 200× (0.0625 mm²).*
significantly independent prognostic factors with respect to PFS on multivariate analysis.

**Discussion**

Recent reports showed that the immunoregulatory enzyme IDO is associated with poor clinical outcome in various human cancers (12–14). We also reported that high IDO expression is associated with the impaired patient survival in endometrial cancer (15), although its functional mechanism has not yet been identified. Thus, in the present study, to clarify the relationship between IDO expression and the local immunologic status in endometrial cancer, we immunohistochemically analyzed the tumoral IDO expression, as well as the numbers of TILs and NK cells.
tumor-infiltrating T cells and NK cells using serial tissue sections from 65 patients, and also analyzed the prognostic effect of both IDO and the TIL count.

There have been many reports indicating that the presence of CD3+ or CD8+ TILs correlates with favorable clinical outcome (22–25). In addition to TILs, recent studies have shown that the presence of tumor-infiltrating CD57+ NK cells also correlates with better prognosis in patients with various cancers (17–20). These studies suggest that both cytotoxic T cells and NK cells may play an important role in immune surveillance in cancer patients and have significant antitumor activity. In the present study, we analyzed the infiltration of TILs by separating them into two groups (intraepithelial and stromal) and then evaluating the relationship between tumoral IDO expression and TIL counts in each area. Interestingly, tumors with high IDO expression had significantly reduced numbers of both intraepithelial and stromal CD3+ or CD8+ cells. This is consistent with a recent report showing the association of IDO expression with a reduction of CD3+ lymphocytes in colorectal cancer (14). Furthermore, our data showed that tumors with high IDO expression had a significantly reduced number of CD57+ cells. These findings suggest that tumoral

Fig. 3. PFS curves in endometrial cancer patients according to IDO expression (A), intraepithelial CD3+ cell count (B), stromal CD3+ cell count (C), intraepithelial CD8+ cell count (D), stromal CD8+ cell count (E), and total CD57+ NK-cell count (F). Significant differences in the PFS were found for IDO expression (P = 0.0001), stromal CD3 (P = 0.0011), intraepithelial CD8 (P = 0.0493), and stromal CD8 (P = 0.0011).
IDO expression is associated with the suppressed infiltration of both cytotoxic T cells and NK cells into the tumor epithelium and adjacent stroma, which may contribute to the progression of endometrial cancer.

Recently, two possible mechanisms for the immunosuppressive action of IDO in tumor-bearing hosts have been proposed (2); it is thought that IDO expressed by tumor cells can create a localized immunosuppressive status within the tumor microenvironment (effector phase) either by suppressing proliferation and function of TILs via tryptophan depletion or by directly killing them using toxic catabolites of tryptophan, such as kynurenine. Alternatively, host antigen-presenting cells expressing IDO may pick up tumor-derived antigens and migrate into tumor-draining lymph nodes (priming phase) where they cannot effectively prime naive T cells, resulting in the failure of clonal expansion of effector T cells. Our present study showed that IDO was dominantly localized to tumor cells in endometrial cancer tissues, suggesting that tumor-derived IDO rather than IDO-positive antigen-presenting cells may primarily regulate local immune function at the effector phase, where IDO might induce the surrounding effector T cells or NK cells into apoptosis and delete them by creating a tryptophan-depleted, tryptophan catabolite–rich environment (5, 26). This hypothesis may be supported by Uyttenhove et al. (7) showing that IDO-expressing tumors induce a lack of specific T-cell accumulation at the tumor site in mice and can block T-cell proliferation locally. However, further studies are needed to clarify the mechanism for the involvement of tumoral IDO in suppression of TILs in human cancer.

The present study showed that patients with high IDO expression, as well as low numbers of stromal CD3+, intraepithelial CD8+, and stromal CD8+ TILs, had significantly impaired PFS. These data are consistent with a previous report showing the prognostic significance of CD8+ TILs in endometrial carcinoma (24). Furthermore, our multivariate analyses showed that both IDO expression and the number of stromal CD3+ TILs were independent prognostic factors for impaired PFS. These findings indicate that patients having tumors with high IDO expression and less TIL infiltration are more likely to experience recurrence and have poor prognosis. Because over 70% of endometrial cancer patients present the early-stage of the disease and most of them are curable with surgery alone (27), it would be of substantial benefit to define the minority of patients who are likely to experience recurrence and also to give adjuvant therapy to these patients alone. Our data suggest that the expression level of IDO in combination with the TIL count

### Table 2. Univariate and multivariate analyses of overall survival and PFS

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<td>Univariate</td>
<td>Multivariate</td>
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<td></td>
<td>Overall survival</td>
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<tr>
<td>≥40</td>
<td>0.041</td>
<td>3.594</td>
</tr>
<tr>
<td>&lt;40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total CD57+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥5</td>
<td>0.116</td>
<td></td>
</tr>
<tr>
<td>&lt;5</td>
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</tr>
</tbody>
</table>
not only reflects the local immunologic status within tumors, but also can become a reliable prognostic indicator for endometrial cancer. Moreover, it may contribute to the individualization of adjuvant therapy.

Immune escape is a crucial feature of cancer progression, and recent work has identified several important molecules/factors that are involved in tumor-induced immunosuppressive mechanisms, including IDO, programmed cell death 1 ligand 1 (28), and CD4+CD25+FOXP3+ regulatory T cells (29). Furthermore, a close relationship between IDO expression and the occurrence of regulatory T cells in tumors was shown (30, 31). Thus, much attention has been paid to overcoming the immune tolerance created by these factors as a novel strategy for cancer therapy (32). The evidence shown in this paper that high IDO expression is associated with a reduced TIL count and also with a poor clinical outcome could make IDO an attractive new target for the treatment of endometrial cancer. Recent studies in mice showed that combinations of IDO inhibitors with chemotherapeutic agents or irradiation synergistically enhanced antitumor activity by reversing the suppression of T cells, suggesting that IDO inhibitors might have utility as anticancer agents (10, 11). Future preclinical and clinical studies are needed for therapeutic application of IDO inhibitors in human cancer.

In conclusion, we showed here that tumor IDO expression correlated with suppressed infiltration of T cells and NK cells in endometrial cancer tissues, which is associated with disease progression and impaired clinical outcome. Although the precise function of tumoral IDO in human cancer remains to be elucidated, our findings suggest that targeting IDO to restore host antitumor immunity may be a novel therapeutic strategy for endometrial cancer.

References
Inverse Correlation between Tumoral Indoleamine 2,3-Dioxygenase Expression and Tumor-Infiltrating Lymphocytes in Endometrial Cancer: Its Association with Disease Progression and Survival

Kazuhiko Ino, Eiko Yamamoto, Kiyosumi Shibata, et al.


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