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Significance of abnormal peritoneal cytology on survival of women with stage I–II endometrioid endometrial cancer☆

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HIGHLIGHTS

- Examined abnormal peritoneal cytology (APC) in early-stage endometrial cancer.
- Incidence of APC was ~10% (malignant cells 7.5%, atypical cells 3.5%).
- Non-obese smoker had the highest incidence of APC (>20%).
- APC was independently associated with decreased survival.
- In low risk stage I disease, APC was associated with distant recurrence.

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ABSTRACT

Objective. To examine survival of women with stage I–II endometrioid endometrial cancer whose peritoneal cytology showed malignant or atypical cells (abnormal peritoneal cytology).

Methods. This is a multi-center retrospective study examining 1668 women with stage I–II endometrioid endometrial cancer who underwent primary hysterectomy with available peritoneal cytology results between 2000 and 2015. Abnormal peritoneal cytology was correlated to clinico-pathological characteristics and oncological outcome.

Results. Malignant and atypical cells were seen in 125 (7.5%) and 58 (3.5%) cases, respectively. On multivariate analysis, non-obesity, non-diabetes mellitus, cigarette use, and lympho-vascular space invasion were independently associated with abnormal peritoneal cytology (all, $P < 0.05$). Abnormal peritoneal cytology was independently associated with decreased disease-free survival (hazard ratio 3.07, $P < 0.001$) and cause-specific survival (hazard ratio 3.42, $P = 0.008$) on multivariate analysis. Abnormal peritoneal cytology was significantly associated with increased risks of distant-recurrence (5-year rates: 8.8% *versus* 3.6%, $P = 0.001$) but not local-recurrence (5.2% *versus* 3.0%, $P = 0.32$) compared to negative cytology. Among women with stage I disease, abnormal peritoneal cytology was significantly associated with an increased risk of distant-recurrence in the low risk group (5-year rates: 5.5% *versus* 1.0%, $P < 0.001$) but not in the high-intermediate risk group (13.3% *versus* 10.8% $P = 0.60$). Among 183 women who had abnormal peritoneal cytology, postoperative chemotherapy significantly reduced the rate of peritoneal recurrence (5-year rates: 1.3% *versus* 9.2%, $P = 0.039$) whereas postoperative radiotherapy did not (7.1% *versus* 5.5%, $P = 0.63$).

Conclusion. Our study suggests that abnormal peritoneal cytology may be a prognostic factor for decreased survival in women with stage I–II endometrioid endometrial cancer, particularly for low-risk group.

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1. Introduction

In 2009 the International Federation of Gynecology and Obstetrics (FIGO) revised the endometrial cancer staging system; abnormal peritoneal cytology was no longer included in the FIGO staging system [1]. The exclusion of abnormal peritoneal cytology from the current staging system is likely due to lack of evidence regarding the prognostic impact of abnormal peritoneal cytology in endometrial cancer [2–7].

Contrary, there has been mounting evidence for decreased survival in women with endometrial cancer who have abnormal peritoneal cytology [8–19]. Because these studies were conducted in heterogeneous populations across various stages and histology types with relatively limited sample size (median, $n = 292$), the exact population in which evaluation of peritoneal cytology would be beneficial in the management of endometrial cancer remains undetermined [2–19].

Theoretically, abnormal peritoneal cytology will be most likely impactful in women with early-stage endometrioid endometrial cancer. This is based on the rationale that women with non-endometrioid endometrial cancer (any stages) and with advanced-stage endometrioid endometrial cancer receive postoperative chemotherapy regardless of peritoneal cytology results per the current treatment guidelines [20].

In early-stage endometrioid endometrial cancer, the vast majority of women usually do not receive adjuvant therapy, or receive radiotherapy if indicated [20,21]. Therefore, if abnormal peritoneal cytology indeed alters recurrence patterns in this population, particularly for distant-recurrence, consideration of adjuvant chemotherapy would be reasonable because chemotherapy as opposed to radiotherapy seems to be a more applicable treatment approach for abnormal peritoneal cytology [14]. The objective of the study was to examine associations of abnormal peritoneal cytology and survival in stage I–II endometrioid endometrial cancer.

2. Materials and methods

2.1. Study population

This is a multicenter retrospective observational study conducted in two United States institutions and four Japanese institutions. Institutional Review Board approval was obtained at each site. Eligibility criteria were consecutive women with stage I–II, grade 1–3 endometrioid adenocarcinoma of the endometrium who underwent primary hysterectomy-based surgical treatment with available peritoneal cytology results between January 1, 2000 and December 31, 2015. Exclusion criteria were absence of hysterectomy, use of neoadjuvant therapy, stage III-IV disease, non-endometrioid histology, synchronous malignancy at endometrial cancer diagnosis, and lack of peritoneal cytology results. Some of the patients were included within the context of our previous study [22–24].

2.2. Clinical information

Among eligible cases, patient demographics, treatment type, pathology results, and survival outcomes were abstracted. Patient demographics included age, race, body mass index (BMI, kg/m^2), pregnancy history, medical comorbidities (hypertension, diabetes mellitus, hypercholesterolemia), cigarette use, and surgical history (tubal sterilization). Treatment type included route of hysterectomy (abdominal *versus* minimally-invasive), use of lymphadenectomy (pelvic and para-aortic), and type of adjuvant therapy (radiotherapy, chemotherapy, or none).

For pathology results, tumor grade (1, 2, or 3), cervical stromal tumor invasion (yes *versus* no), depth of myometrial tumor invasion (<50% *versus* ≥50%), lympho-vascular space invasion (LVSI; yes *versus* no), and peritoneal cytology test results (malignant cells, atypical cells, or negative) were collected from records for hysterectomy-based surgical staging. In our institutions, peritoneal cytology is generally collected at the beginning of surgery.

For survival outcome, disease-free survival (DFS) and cause-specific survival (CSS) were recorded. Among recurrent cases, anatomical locations were collected (local- *versus* distant-recurrence). Data entry into a de-identified data sheet was performed by co-investigators in each participating institution, and the principal investigator reviewed all the data for accuracy and consistency.

2.3. Study definition

Cutoffs for age (<60 *versus* ≥60 years) and BMI (<30 *versus* ≥30 kg/m^2) were based on previous studies [22–24]. Cancer stage was re-classified based on the 2009 FIGO staging system [1]: stage IA refers disease with myometrial tumor invasion of <50% whereas stage IB refers disease with myometrial tumor invasion of ≥50%. Stage II disease refers tumors with cervical stromal invasion. Tumor grade was based on the FIGO classification: ≤5% solid component for grade 1, 6–50% solid component for grade 2, and >50% solid component for grade 3 [25]. Presence of malignant or atypical cells on peritoneal cytology was defined as abnormal peritoneal cytology in this study whereas absence of malignant or atypical cells was defined as negative cytology.

DFS was defined as the time interval between the date of hysterectomy and the date of the first recurrence of endometrial cancer or the last follow-up date if there was no recurrence. CSS was defined as the time interval between the date of hysterectomy and the date of death due to endometrial cancer, and the alive status at last follow-up or death from other causes were censored. Local-recurrence was defined as recurrence in the vaginal cuff or pelvis. Distant-recurrence was defined as recurrence other than local-recurrence, grouped into peritoneal, lymphatic, or hematogenous recurrence.

Among stage I endometrial cancer, the high-intermediate risk group was defined either by the ESMO-ESGO-ESRTO criteria (stage IA grade 3

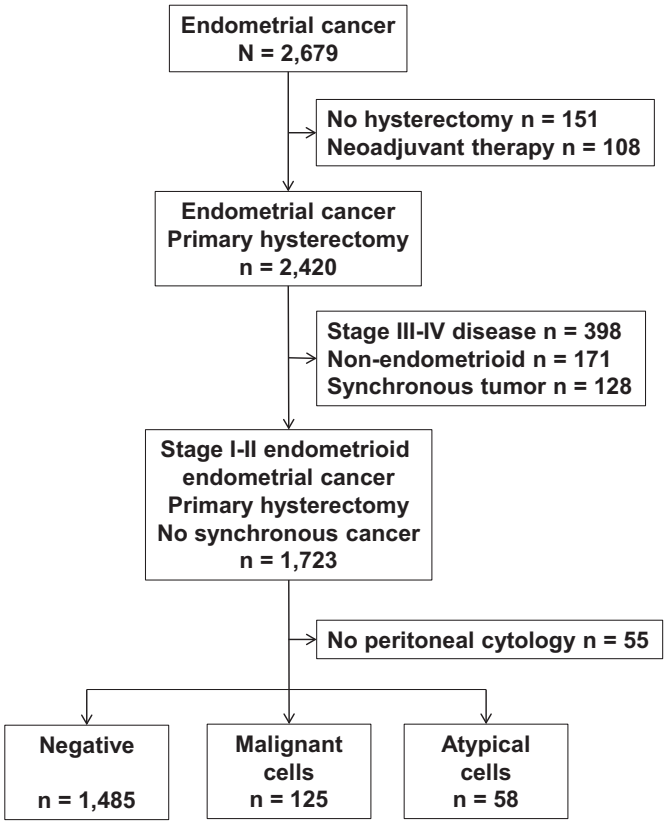

Fig. 1. Study selection schema.

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