Gynecologic Oncology xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Detection of endometrial cancer cells in the fallopian tube lumen is associated with adverse prognostic factors and reduced survival

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HIGHLIGHTS

- Endometrial cancer stage is an important prognostic factor; however; transtubal spread is not captured in current criteria.
- Intraluminal tumor cells (ILTCs) are a putative marker of transtubal spread.
- ILTCs were associated with higher stage, serous histology, and lymphovascular space invasion.
- ILTCs were significantly associated with lower survival among women with serous or stage I disease.
- In our small sample associations were attenuated after adjustment for other prognostic factors.

ARTICLE INFO

Article history:
Received 18 April 2018
Received in revised form 3 May 2018
Accepted 4 May 2018
Available online xxxx

Keywords:
Uterus neoplasm
Fallopian tube
Disease-specific mortality
Patterns of spread

ABSTRACT

Objective. Stage is a critical determinant of prognosis and treatment for endometrial cancer (EC) patients. Women who have had a tubal ligation for sterilization have improved EC survival, secondary to lower stage at presentation, suggesting that transtubal spread may represent an important route of metastasis. We evaluated detection of intraluminal tumor cells (ILTCs) in relation to tumor characteristics and survival.

Methods. One pathologist retrospectively evaluated hematoxylin and eosin sections of routinely collected fallopian tubes for ILTCs from 295 EC patients, masked to outcome. We used logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for associations between demographic (age, race) and clinical [FIGO 2009 stage, lymphovascular space invasion (LVSI), histological subtype] characteristics and ILTCs. Cox regression was used to estimate hazard ratios (HRs) and 95% CIs for associations between ILTCs and recurrence-free survival (RFS) and EC-specific survival, overall and stratified by histological subtype or stage.

Results. In univariable logistic regression models, age (55–64 vs. ≥65: OR = 3.41, 95% CI = 1.48–7.84), stage (stage IV vs. stage I OR = 14.58, 95% CI = 5.27–40.35), LVSI (OR = 2.93, 95% CI = 1.42–6.04), and histological subtype (serous vs. low-grade endometrioid OR = 3.21, 95% CI = 1.08–9.58), were associated with ILTCs. Only age and stage remained significantly associated with ILTCs in adjusted models. ILTCs were significantly associated with lower EC-specific survival among women with serous EC or stage I disease; however, adjustment for age, stage, and histology attenuated these associations.

Conclusion. Our findings suggest that ILTCs are associated with adverse EC prognostic features and reduced survival in cases of early stage or serous histology.

1. Introduction

Endometrial cancer (EC) is the most common gynecological malignancy in the United States. In 2018, 63,230 new cases and 11,350 deaths are expected [1]. EC stage characterizes the extent of disease and is strongly linked with prognosis, independent of histology or grade [2].

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https://doi.org/10.1016/j.ygyno.2018.05.005
0090-8258/

Furthermore, stage is a strong determinant of adjuvant treatment selection and post-diagnosis surveillance [3]. EC staging has evolved over time, reflecting advances in our understanding of the pathogenesis of this disease [4,5]. However, the current staging criteria do not capture the presence of tumor cells in the lumen of the fallopian tube, or transtubal spread, which is distinct from invasion into the stroma of the fallopian tubes and represented by stage IIIA disease.

Transtubal spread is proposed to occur when EC cells are exfoliated through the fallopian tubes into the abdominal cavity. The possibility of transtubal spread was first recognized when malignant EC cells were identified within cytology specimens from fallopian tubes [6]. The presence of intraluminal tumor cells (ILTCs) – a putative histological marker of transtubal spread – is more common among women with aggressive compared to indolent EC histologic subtypes [7], and is associated with extra-uterine spread [8]. Despite the recognition that EC cells have the capacity for cellular detachment and transtubal transportation, and that this mechanism co-occurs with other aggressive tumor characteristics, we lack empirical data on the independent prognostic impact of transtubal spread and whether this relationship is modified by other tumor characteristics. Thus, we cannot make evidence-based decisions as to whether EC stage criteria should be revised to incorporate information on ILTCs for improvement in prognostic accuracy. Therefore, our main objective was to extend prior analyses by evaluating the association between ILTCs and EC survival, overall and stratified by histologic subtype or stage. Secondarily, we examined relationships between ILTCs and tumor characteristics to confirm prior associations.

2. Methods

2.1. Study population

We have previously described our institutional database of 896 consecutive EC patients (carcinoma and carcinosarcoma) treated at The Ohio State University Wexner Medical Center between 2007 and 2012 [9]. All women included in the database underwent standard hysterectomy and bilateral salpingo-oophorectomy, with lymph node staging performed in 86% of cases based on the surgeon's clinical judgment. For the current analysis, which required retrospective pathological review of fallopian tube sections, we sampled a subset of the cohort, chosen based on histological subtype. Based on prior work [7,8,10] we hypothesized that transtubal spread is most clinically relevant for women with aggressive histological subtypes. Therefore, we included all women with diagnoses of grade 3 endometrioid ($n = 64$), serous ($n = 41$), carcinosarcoma ($n = 30$), clear cell ($n = 10$), and mixed epithelial tumors ($n = 59$) and randomly sampled 100 women with grades 1 or 2 endometrioid histology among 686 such patients (all stages). Of the 100 women we randomly selected with grades 1 or 2 endometrioid histology, three did not have evaluable slides.

2.2. Assessment of clinical characteristics and outcomes

Information on age at diagnosis (<55, 55–64, ≥65), self-reported race (white vs. non-white), body mass index (BMI) (<25, 25–30, ≥30 kg/m^2), history of tubal ligation (no vs. yes), use of an intrauterine manipulator (no vs. yes), lymphovascular space invasion (LVSI) (no vs. yes), percent myometrial invasion (<25, 25–50, 50–74, ≥75%), stage [I, II, III, IV, according to the 2009 International Federation of Gynecologic Oncology (FIGO)] [5], histology (endometrioid, serous, carcinosarcoma, clear cell, mixed epithelial), and grade (1–3) were collected from electronic medical records and pathology reports. We further classified women with endometrioid tumors according to grade: low-grade endometrioid (grades 1 or 2) or high-grade endometrioid (grade 3). By definition, serous, carcinosarcoma, clear cell, and mixed epithelial are considered high grade tumors [11]. We also examined EC type according to the traditional Type I/II dichotomy, with Type I including endometrioid histology (all grades) and Type II including serous, carcinosarcoma, clear cell, and mixed epithelial. Dates of diagnosis and death were also available from electronic medical records. Data registrars collect information on the cause and date of death through periodic follow-up assessments of patients remaining in care in the OSU Wexner Medical Center system.

2.3. Determination of ILTC status

At the time of EC surgery, hematoxylin-eosin (H&E) stained slides from salpingectomy specimens were processed. The number of sections per woman varied based on availability, but at least one cross-section of the diameter of each fallopian tube was reviewed for each woman. For this study, one gynecologic pathologist (AAS) retrospectively reviewed all fallopian tube archival glass slides and recorded ILTCs without knowledge of clinical characteristics. ILTCs were defined histologically as unequivocally malignant viable cells, whether individually distributed or forming groups in the lumen of the tubes.

2.4. Statistical analysis

We compared characteristics of women with and without ILTCs using chi-square tests. Univariable logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for associations between ILTCs and clinical/tumor characteristics. Variables significantly associated with ILTC detection in the univariable models ($p < 0.05$) were included in a multivariable logistic regression model. Days between EC surgery and recurrence or EC-related death were computed and defined as recurrence-free survival (RFS) and EC-specific survival, respectively. Kaplan–Meier estimates and log-rank tests were used to compare survival distributions according to ILTCs. Patients who did not experience a recurrence or EC death were censored at the date of last contact or end of follow-up (December 31, 2014) in the respective analyses. Women who died of other causes were censored on their date of death. We used Cox proportional hazards regression to estimate hazard ratios (HRs) and 95% CIs for associations between ILTCs with RFS and EC-specific survival in models unadjusted and adjusted for age, histological subtype, and stage. We repeated these analyses stratified by histological subtype or stage. For analyses of RFS, only patients that were known to be disease-free following the primary surgery were included (e.g. stages I-III).

We also conducted a subgroup analysis comparing survival between women with stage I or II tumors with ILTCs and women with stage IIIA tumors to evaluate whether ILTCs in otherwise stage I or II disease led to reduced EC-specific survival.

The proportional hazards assumption, which was evaluated by modeling interaction terms of ILTCs with follow-up time in each model, was confirmed for all analyses. Statistical analyses were performed using SAS/STAT software (version 9.4 of the SAS System for Windows, SAS Institute, Cary, NC, USA). The Institutional Review Board at the Ohio State University approved this study.

3. Results

3.1. Associations of ILTCs and clinical/tumor characteristics

ILTCs were detected in 35 (11.9%) of 295 EC patients studied. Distributions of tumor characteristics according to ILTCs along with univariable and multivariable-adjusted ORs are shown in Table 1. Higher odds of ILTCs were related to age (55–64 vs. ≥65: OR = 3.41, 95% CI = 1.48–7.84), stage (stage IV vs. stage I OR: 14.58, 95% CI = 5.27–40.35), LVSI (OR: 2.93, 95% CI = 1.42–6.04), EC type (Type II vs. Type I, OR: 2.13, 95% CI = 1.03–4.42, p = 0.04) and histological subtype (serous vs. low-grade endometrioid OR: 3.21, 95% CI = 1.08–9.58). In a multivariable model including age, histological subtype, LVSI, and stage, only age and stage remained significantly associated with ILTCs.

Please cite this article as: A.S. Felix, et al., Detection of endometrial cancer cells in the fallopian tube lumen is associated with adverse prognostic factors and reduced survival, Gynecol Oncol (2018), https://doi.org/10.1016/j.ygyno.2018.05.005