GYNECOLOGY

Prognosis and treatment of positive peritoneal cytology in early endometrial cancer: matched cohort analyses from the National Cancer Database

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BACKGROUND: While positive peritoneal cytology is no longer included among the endometrial cancer staging criteria, Federation International de Gynecologie et Obstetrique recommends continued collection of pelvic washings for cytology to produce additional data that may be used to determine the significance of positive cytology for prognosis and treatment of endometrial cancer.

OBJECTIVES: The objectives of the study was to validate that positive cytology is a predictor of decreased survival in early endometrial cancer and to test whether adjuvant chemotherapy for positive cytology is associated with increased survival.

STUDY DESIGN: We performed an observational retrospective cohort analysis of the 2010–2013 National Cancer Database including women with cytology status and Federation International de Gynecologie et Obstetrique stage IA–II endometrial cancer. Overall cohort and matched cohort survival analyses were performed with and without imputation of missing data. We also performed survival analyses of women with positive cytology grouped by chemotherapy exposure. Multivariable Cox proportional-hazards regressions were performed to adjust for possible confounders. A variety of sensitivity analyses, including robustness of results to possible unmeasured confounding, were reported.

RESULTS: A total of 16,851 women including 953 with positive cytology were included. Four-year overall survival was 79.5% (range, 76.2–83.0%) for women with stage I/II with positive cytology vs 92.2% (range, 91.5–92.9%), 83.3% (range, 81.6–84.9%), and 86.8% (range, 85.1–88.5%) for stage IA, IB, and II with negative cytology, respectively ($P \leq .001$). Positive cytology was associated with decreased survival (hazard ratio [95% confidence interval], 1.85 [range, 1.54–2.21], $P < .001$). For women with Federation International de Gynecologie et Obstetrique grade 1/2 endometrioid adenocarcinoma, the hazard of death associated with positive cytology was similar (hazard ratio [95% confidence interval], 1.85 [1.28–2.67], $P < .001$). Use of adjuvant chemotherapy by women with positive cytology was associated with increased survival (hazard ratio [95% confidence interval], 0.62 [0.40–0.95], $P = .03$).

CONCLUSION: Positive peritoneal cytology was associated with decreased overall survival of women with Federation International de Gynecologie et Obstetrique stage I/II endometrial cancer, including low-grade endometrioid endometrial cancer. Treatment of women with stage I/II endometrial cancer and positive cytology with adjuvant chemotherapy was associated with increased survival.

Key words: cytology, endometrial cancer, prognosis, survival

Microscopic peritoneal metastasis is suspected when cytopathologic examination of pelvic washings demonstrate malignant cells. Positive cytology is highly predictive of survival in multiple gynecological malignancies.[1] However, in 2009, the Federation International de Gynecologie et Obstetrique (FIGO) removed cytology as a staging criteria from the endometrial cancer staging system.[2]

Previously, positive cytology assigned a woman with otherwise uterus-confined disease a stage of IIIA. Citing the revised FIGO staging system, anecdotally we know that some surgeons have stopped performing pelvic washings for endometrial cancer. This practice may lead to under treatment of early advanced disease if positive cytology is associated with decreased survival. Additionally, FIGO recommends continued collection of washings to provide data to clarify the prognostic significance of positive peritoneal cytology.[2]

A 2013 report of 14,704 women (485 with positive cytology) with stage I/II endometrial cancer from the Surveillance, Epidemiology, and End Results (SEER) database showed that positive cytology predicted decreased survival ($P < .001$).[3] An ancillary analysis of 753 women with type II endometrial cancers from the LAP2 trial reported that positive cytology was a negative prognostic factor in these high-risk histologies.[4] Authors who compared the performance of the 2009 and 1988 FIGO staging systems for predicting overall and disease-free survival in a 351-patient retrospective cohort concluded: "To withdraw the positive cytology from staging may mislead the prognosis estimation in these patients and lead to undertreatment."[5]

Additional small retrospective cohort studies published in 2013–2014 added evidence that positive cytology is a negative prognostic factor for recurrence and survival in endometrial cancer.[6,7] It remained unclear whether positive cytology is a negative prognostic factor in low-grade, early-stage endometrioid adenocarcinoma, the most common uterine malignancy.

Detecting positive cytology in early endometrioid endometrial cancer raises immediate clinical dilemmas for patient counseling and treatment. Evidence is lacking to guide management of positive cytology in otherwise low-risk endometrial cancers.[8] Consequently, many gynecologic oncologists may not treat

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positive cytology in early endometrial cancer. Some (albeit likely fewer) experts may routinely offer adjuvant hormonal therapy or chemotherapy to women with positive cytology. The outcomes of these practices are unknown, and relevant experience on these practices is anecdotal.

To validate that positive cytology is a negative prognostic factor, we performed a matched cohort analysis of survival by cytology status among women with FIGO stage IA-II endometrial cancer from the National Cancer Database. Given the body of recent literature supporting the belief that positive cytology is a negative prognostic factor, we considered that an association of positive cytology with decreased survival from this study should be considered a supporting external validation of findings of the prior smaller studies. We specifically sought to confirm that positive cytology is a negative prognostic factor in low-grade, early-stage endometrioid endometrial cancer. In addition, we tested whether treatment with adjuvant chemotherapy was associated with an increased survival among the women with positive cytology.

Materials and Methods

We performed an observational retrospective cohort analysis of women with FIGO stage I/II endometrial cancer from the 2010−2013 National Cancer Database (NCDB). The NCDB, established jointly by the American Cancer Society and the Commission on Cancer of the American College of Surgeons in 1989, is a nationwide, facility-based, comprehensive clinical surveillance resource oncology data set that captures 70% of all newly diagnosed malignancies in the United States.[9]

Individual-level data are prospectively collected by professional registrars and are audited.[9] The NCDB established a Business Associate agreement for research use of data sets at certified facilities, and the Northwestern University Institutional Review Board considered research use of deidentified NCDB data sets exempt from review.

Women with FIGO stage IA, IB, or II endometrial cancer diagnosed from 2010 through 2013 were included. Women with inconsistent coding as having nodal or distant metastasis were excluded. Surgical staging including pathologically negative lymphadenectomy was required to ensure adequate staging of the cohort. Cytology status and FIGO staging were consistently recorded beginning in 2010.

To be included, cases required a cytology status coded as negative or positive. Overall survival was the outcome of interest. Radiotherapy, chemotherapy, and hormonal treatment variables were analyzed as dichotomous yes or no variables. Additional covariates were included to adjust for potential confounding. These covariates were age at diagnosis, Charlson/Deyo composite comorbidity score, history of prior malignancy, race, Hispanic ethnicity, community median household annual income quartile by ZIP code, insurance status, cancer center type, histological type, grade of disease, tumor size, lymphovascular space invasion (LVSI), and pathological surgical margin status.

Histology was classified by ICD-O-3 codes as endometrioid (8380−8383), serous (8441/8450/8460/8461), carcinosarcoma (8950/8951/8980/8981), clear cell (8310/8313), mixed (8323), or other (all remaining codes). Government insurance was combined with Medicaid. Race was categorized as white, black, other or not reported. The other group includes Asians and Pacific Islanders, persons coded as other by NCDB, and a small number of South Asians and Native Americans with counts too small for regression.

Tumor size was truncated at 35 cm because larger tumor sizes were few, are less believable, and may represent coding error. Surgical margin status was coded as negative, positive, or not reported. Standard NCDB variable definitions and sources of data are publicly available online at the American College of Surgeons.

Baseline patient, disease, and treatment characteristics were compared using standardized differences (<0.10 considered acceptable balance). Unadjusted restricted mean survival times and 4 year survival rates were estimated using the Kaplan-Meier method and compared with the log-rank test. A multivariable Cox proportional-hazards model of overall survival was built by backward selection with Akaike information criterion minimization to evaluate survival by the cytology status.

Initial covariates included age at diagnosis, Charlson/Deyo composite comorbidity score, a history of prior malignancy, race, Hispanic ethnicity, median household annual income by ZIP code, insurance status, cancer center type, FIGO stage, histological type, tumor size categories, grade of disease, LVSI, surgical margin status and treatment variables for adjuvant radiotherapy, chemotherapy, or hormonal therapy. The proportional-hazards assumption was checked. The model was stratified by histological type to avoid violation of the proportional-hazards assumption. Goodness of fit of the final model was confirmed with deviance residuals.

In the initial analysis, missing data were coded as not reported to retain the sample size in multivariable regression models (missing-data indicator method). As a sensitivity analysis of uncertainty of estimates related to missing data, we performed multiple imputation using chained equations to create 10 data sets with all missing data imputed.[10] Survival analyses were repeated for each imputed data set, and resulting estimates were pooled using Rubin's rules.[10]

As additional sensitivity analyses and to decrease potential biases, we performed matched cohort analyses. Propensity score methods are effective at reducing bias because of measured confounding in observational studies by simulating the performance of a randomized trial by creation of matched cohorts consisting of exposed vs unexposed cohorts that are matched by a variety of potential confounders prior to analysis.[11]

Two-to-one nearest neighbor matching was performed using the following variables: age, tumor size, income quartile, insurance status, cancer center type, race, FIGO stage, grade, histological type, comorbidity scores, prior malignancy, surgical margin status, LVSI, lymph node count, chemotherapy,