ONCOLOGY

Comparison of the prognostic significance of uterine factors and nodal status for endometrial cancer

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OBJECTIVE: We examined the prognostic significance of uterine risk factors (RF) compared to nodal metastases in endometrial cancer.

STUDY DESIGN: Women with stage I–IIIC endometrioid cancer were stratified based on the presence of positive or negative lymph nodes. Each patient was characterized by the number of RF present: myoinvasion ≥50%, cervical stromal involvement, and grade 3 histology.

RESULTS: A total of 26,967 women were identified. In a multivariable model, uterine RF strongly influenced survival but nodal disease was a more important negative prognostic factor. Five-year overall survival was 68% (95% confidence interval [CI], 63–72%) for group 1 (node positive/no RF) vs 69% (95% CI, 66–72%) for group 5 (node negative/multiple RF). Five–year survival was lower for node–positive patients with RF (58%; 95% CI, 54–61%) than node–positive patients without RF (68%; 95% CI, 63–72%).

CONCLUSION: Uterine RF strongly influenced survival both in the presence and absence of nodal metastasis.

Key words: endometrial cancer, lymph nodes, lymphadenectomy, myometrial invasion, uterine cancer

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Endometrial cancer is the most common gynecologic malignancy. In 2010, it is estimated that 42,160 women in the United States were diagnosed with the disease.[1] While the vast majority of women with endometrial cancer are diagnosed with early-stage tumors that are associated with an excellent prognosis, a subgroup of women have more aggressive neoplasms and are at increased risk of relapse and death. A number of local uterine risk factors (RF) including poor tumor differentiation, deep myometrial invasion, lymphvascular space invasion (LVSI), and cervical stromal involvement have been linked with decreased survival.[2-9]

Metastasis to the regional lymph nodes (LN) is one of the most important predictors of survival for endometrial cancer.[10-13] In 1 series, 5-year disease-specific survival in women with nodal metastases was 42%.[12] The association between uterine RF and LN metastasis has been well established. The Gynecologic Oncology Group's surgical pathology study of endometrial cancer found that uterine RF were strong predictors of nodal metastasis. The risk of nodal metastases was 25% in women with deep myometrial invasion compared to 5% in women with superficially invasive tumor. Likewise, patients with poorly differentiated tumors were 6 times more likely to have nodal disease than well-differentiated tumors, while the presence of LVSI increased the risk of nodal disease nearly 4-fold.[3] In light of the patterns of spread of endometrial cancer and the importance of nodal disease on survival, it has been hypothesized that the poor prognosis for women with early-stage tumors with uterine RF is most likely due to occult nodal disease at the time of presentation.[2]

However, a growing body of evidence suggests that uterine RF may negatively impact survival independently of nodal metastasis.[4,5,14] The independent effect of uterine RF has been shown in women with early-stage disease with pathologically negative nodes as well as in women with advanced-stage disease in which uterine RF continue to negatively influence survival even after controlling for extrauterine disease.[13] The objective of our study was to estimate the influence of uterine RF on survival for women with endometrial cancer. Specifically, we compared the prognostic significance of uterine RF and nodal metastases and determined the independent effects of each on outcome.

Materials and Methods

The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database was utilized. SEER is a population-based cancer registry that includes approximately 26% of the US population.[15] SEER is composed of a

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TABLE 1
Classification schema for analysis

Risk factors	Risk factor absent	Risk factor present
Grade	1, 2	3
Cervical stromal invasion	No	Yes
Depth of invasion	<50%	≥0%
Risk groups	**Lymph nodes**	**Risk factors present**
Group 1	Positive	0
Group 2	Positive	≥1
Group 3	Negative	0
Group 4	Negative	1
Group 5	Negative	≥2

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number of geographically distinct tumor registries. The demographic characteristics of the SEER registries have been previously characterized.[16,17] Data from SEER 17 registries were used. Exemption from the Columbia University Institutional Review Board was obtained.

Women with stage I (IA, IB, IC), II (IIA, IIB), and IIIC tumors of the uterine corpus classified as endometrioid carcinoma (8380/3) and adenocarcinoma not otherwise specified (8140/3) treated from 1998 through 2006 were analyzed. Only those patients who underwent lymphadenectomy and had tumor grade recorded were included. Clinical and pathologic data including age at diagnosis (<40, 40-65, >65 years), race (white, black, other), marital status, and receipt of radiation were examined. Year of diagnosis was stratified as 1988 through 1994, 1995 through 2000, and 2001 through 2006 for analysis. Patients were categorized based on the geographic area of residence within the United States at the time of diagnosis as: central (Detroit, MI; Iowa; Kentucky; Louisiana; Utah), eastern (Connecticut; New Jersey; Atlanta, GA; rural Georgia), and western (Alaska; Hawaii; Los Angeles, CA; New Mexico; San Francisco, CA; San Jose, CA; Seattle, WA). Staging information was derived from the American Joint Cancer Committee staging information and recorded extent of disease codes.

The overall goal of the analysis was to determine the independent effects of uterine RF and nodal disease on survival. Based on prior data we examined the following RF: grade (1, 2, or 3), depth of invasion (<50% or ≥50%), and cervical stromal invasion (present or absent).[3,18,19] Each patient was assigned a risk score based on the number of RF present. The risk score was used in combination with the presence or absence of nodal involvement to classify each patient into 1 of 5 groups: group 1 (node positive, 0 RF), group 2 (node positive, ≥1 RF), group 3 (node negative, 0 RF), group 4 (node negative, 1 RF), and group 5 (node negative, ≥2 RF). The classification schema is displayed in Table 1. We then examined survival for the 5 groups.

The vital status of each patient was recorded. Survival was calculated as the number of months from cancer diagnosis to date of death. Patients who were alive at last follow-up were censored. Both overall and cancer-specific survivals were calculated. Frequency distributions between categorical variables were compared using χ^2 test. Cox proportional hazards models were developed to examine survival. In Cox proportional hazards analyses, we modeled the cancer-specific and overall mortality hazard ratios (HRs) including risk group assignment. All of the predictor variables, including the risk group, were added to the models simultaneously. Kaplan-Meier curves were generated and overall and cancer-specific survivals were examined using the log rank test. All analyses were performed with software (SAS, version 9.2; SAS Institute Inc, Cary, NC).

RESULTS

A total of 26,967 women met the inclusion criteria and were included in the analysis. The distribution of patients by risk group was: group 1, 683 (3%); group 2, 1486 (6%); group 3, 15,754 (58%); group 4, 7470 (23%); and group 5, 1574 (6%). The demographic and clinical variables of the cohort stratified by risk group are displayed in Table 2. The majority of women in the analysis were white and diagnosed >1995. In general, patients with uterine RF, either with positive or negative LN, tended to be older ($P < .0001$). Adjuvant radiotherapy was more frequently given to node-positive women and those with uterine factors. Radiotherapy was given to 67 (67%) women in group 1, 69% of group, 12% of group 3, 45% of group 4, and 66% of group 5.

In Cox proportional hazards models risk group, age, race, and marital status were all associated with both cancer–specific and overall survival (Table 3). Among the risk groups, the highest risk of death was noted in patients with positive LN and uterine RF. Compared to node–positive patients without RF, node–positive patients with RF were 24% (HR, 1.24; 95% confidence interval [CI], 1.02–1.52) more likely to die from their tumors. All of the node–negative groups, whether RF were present or not, fared better than the node–positive groups. Women with pathologically negative nodes and ≥2 uterine RF were 36% (HR, 0.64; 95% CI, 0.52–0.79) less likely to die from their tumors than node–positive women without RF.

Five-year survival is shown in Table 4. Survival was lowest for patients with positive nodes and uterine RF (group 2, 58%; 95% CI, 54–61%) and best for node-negative women without uterine RF (group 3, 92%; 95% CI, 91–92%) Five-year survival was 68% (95% CI, 63–72%) for group 1 (LN positive, 0 RF) vs 69% (95% CI, 66–72%) for group 5 (LN negative, ≥2 RF). For each group survival was lower for older women. Five-year survival for women >65 years of age for group 1 was 55% (95% CI, 48–62%) vs 60% (95% CI, 56–64%) for group 5.