ONCOLOGY

Prognostic factors and risk of extrauterine metastases in 3867 women with grade 1 endometrioid corpus cancer

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OBJECTIVE: The purpose of this study was to evaluate the role of surgical staging in patients with grade 1 endometrioid uterine cancer.

STUDY DESIGN: Data were extracted from Surveillance, Epidemiology, and End Results Program from 1988 to 2001. Kaplan-Meier and Cox proportional hazards analyses were used to determine predictors for disease-specific survival.

RESULTS: Twelve thousand seven hundred and twelve women were reported with endometrioid carcinoma, including 3867 with grade 1 disease, of which 25.5% had stage IC or more advanced disease, 15.4% with disease extending beyond the uterine corpus, 7.3% with extrauterine metastases, and 3.3% with lymph node metastases. On multivariate analysis, younger age and earlier stage remained as significant prognostic factors for improved survival.

CONCLUSION: Since grade 1 endometrioid uterine cancers have a 15.4% risk of extrauterine spread, a complete surgical staging procedure is recommended when clinically feasible. Younger age and earlier stage are significant prognostic factors for improved survival.

Key words: endometrioid, grade 1, surgical staging, uterine cancer

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Endometrial cancer is the most common gynecologic malignancy and the fourth most common cancer in women, with more than 40,000 newly diagnosed cases in 2006 and 7350 deaths reported in the United States.[1] Histologic grade is one of the important factors associated with extrauterine spread and survival. In a Gynecologic Oncology Group staging study of patients with clinical stage I disease, Creasman et al showed that the risk of pelvic nodal metastases is 2.8%, 8.7%, and 18.3% in those with grade 1, 2, and 3 disease, respectively.[2] Furthermore, a review of 1566 patients with endometrioid cancer showed that the 5-year crude survival for patients with grade 1, 2, and 3 tumors is 87%, 75%, and 58%, respectively, across all stages.[3]

Most surgeons will perform full surgical staging procedures including a lymph node dissection on women with grade 1 or 2 tumors with greater than 50% myometrial invasion, grade 3 disease, and high-risk cell types such as papillary serous, clear cell, or sarcomas. However, the role of full surgical staging in those with grade 1 endometrioid cancers remains controversial.[4] Some studies indicated that patients with grade 1 histopathology are at low risk for lymph node metastases and probably do not benefit from routine pelvic and periaortic lymphadenectomy.[5] However, others have suggested that at least 30% of tumors with preoperative grade 1 histology will demonstrate postoperative pathologic features suggesting a significant risk for metastatic disease and thus could benefit from the information obtained from a surgical staging procedure.[6]

Prior reports on surgically staged grade 1 endometrial cancers have been limited by small numbers of patients who were entered into clinical trials or received treatment from academic tertiary care centers.[2,7,8] Because these studies may comprise a disproportionate number of patients with poor prognostic factors, the reported extent of extrauterine spread of grade 1 tumors may be higher than for the general population. In contrast, previously reported population-based studies have included a large proportion of patients who did not undergo surgical staging with lymphadenectomy. For example, only 30% of the endometrial cancer patients received a lymph node staging in a study from the

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US National Cancer Database.[9] Thus, given that the majority of the patients with preoperative diagnoses of grade 1 cancers do not undergo full staging procedures, it is difficult to determine the true risk of metastatic spread.

In this population-based study, we propose to analyze the risk of local regional and metastatic spread in patients with grade 1 endometrioid uterine cancers on final pathologic analysis after a thorough staging procedure. In this manner, one can determine the potential value of comprehensive staging in patients with grade 1 endometrioid corpus cancers.

Materials and Methods

Demographic, clinicopathologic, and survival information from women diagnosed with endometrioid uterus cancer from January 1, 1988 to December 31, 2001 were extracted from the Surveillance, Epidemiology and End Results (SEER) database of the United States National Cancer Institute. Data are reported from 12 population-based registries that represent approximately 14% of the US population: San Francisco-Oakland, Connecticut, metropolitan Detroit, Hawaii, Iowa, New Mexico, Seattle (Puget Sound), Utah, metropolitan Atlanta, Alaska, San Jose-Monterey, and Los Angeles.

All patients who did not undergo a lymph node staging or had a diagnosis of non-endometrioid histologies were excluded from the analysis. Data recorded include age at diagnosis, race, surgery, stage, grade, lymph node involvement, radiation treatment, and disease-specific survival. Race was classified into 4 groups, including whites, blacks, Asians, and others. Surgery information included hysterectomy with pelvic and/or peri-aortic lymphadenectomy.

Statistical evaluation was performed using SPSS 14.[10] (SPSS, Inc, Chicago, IL). Survival probability data were computed using the Kaplan-Meier method and differences between groups were calculated using the log-rank test. Time to death was censored in women who died from causes other than endometrial cancer and who were alive at last follow-up. Two-tailed tests at P values less than .05 were considered significant. Cox regression analysis was used to investigate for factors independently associated with disease-specific survival. Data analysis was exempt from Institutional Review Board approval.

Results

From 1988 to 2001, 46,804 patients were diagnosed with endometrial cancer, including 39,775 (85.0%) with endometrioid cell type. Of these 39,775 patients, 12,712 (32%) patients underwent surgical staging with pelvic and/or periaortic lymphadenectomy. There were 3867 (30.4%) patients with grade 1 disease, 5285 (41.6%) grade 2 disease, and 3560 (28.0%) with grade 3 disease. Of the 12,712 patients who underwent a lymph node dissection, positive nodes were found in 3% of patients with grade 1 tumors, 9% grade 2 tumors, and 18% of grade 3 tumors. Overall, 1280 (10%) of the 12,712 surgically staged patients were found to have nodal metastases. Of the 1280 women with node-positive disease, 10% had grade 1, 39.1% grade 2, and 50.9% had grade 3 disease. The 5-year disease-specific survivals of patients with grade 1, 2, and 3 endometrioid tumors were 97.8%, 92.1%, and 78.0%, respectively ($P < .001$).

The demographic and clinical features of the 3867 patients with grade 1 disease who had surgical staging are shown in Table 1. The mean age of the patients was 61.2 years (range 22-96). The majority (87.9%) were white. Of the 3867 patients with grade 1 disease, 3270 (84.5%) had stage I, 317 (8.2%) stage II, 177 (4.6%) stage III, and 103 (2.7%) had stage IV disease with corresponding 5-year disease-specific survivals of 98.6%, 96.5%, 93.1%, and 84.0%, respectively ($P < .001$). Of those with stage I disease, 390 (11.9%) had greater than 50% myoinvasion. Three hundred seventeen patients had stage II disease, which consisted of 67 (21.1%) with endocervical glandular involvement and 58 (18.3%) had stromal invasion. Of the 177 stage III patients, 96 (54.2%) had adnexal disease and/or positive cytology, 3 (1.7%) had vaginal metastases, 75 (42.4%) had pelvic and/or periaortic lymph nodes involvement. In the 103 women with stage IV cancers, 10 (9.7%) had bladder and/or bowel involvement, and 93 (90.3%) had distant metastases. In sum-

TABLE 1
Demographic and clinical features of patients with grade 1 disease (n = 3867)

Characteristics	No. (%)
Age of diagnosis	
Mean (range)	61.2 (22-96)
Race	
White	3399 (87.9%)
Asian	232 (6.0%)
Black	142 (3.7%)
Other/unknown	94 (2.4%)
Stage at diagnosis	
Stage I	3270 (84.5%)[a]
IA	994 (30.4%)[b]
IB	1654 (50.6%)[b]
IC	390 (11.9%)[b]
Not specified	232 (7.1%)[b]
Stage II	317 (8.2%)[a]
IIA	67 (21.1%)
IIB	58 (18.3%)
Not specified	192 (60.6%)[b]
Stage III	177 (4.6%)[a]
IIIA	96 (54.2%)[b]
IIIB	3 (1.7%)[b]
IIIC	75 (42.4%)[b]
Not specified	3 (1.7%)[b]
Stage IV	103 (2.7%)[a]
IVA	10 (9.7%)[b]
IVB	93 (90.3%)[b]
Lymph node status	
Negative	3739 (96.7%)
Positive	128 (3.3%)
Radiation	
No	3095 (80.0%)
Yes	772 (20.0%)

[a] Percent represents number of patients with stage of disease of overall study group.

[b] Percent represents number of patients with substage disease of specified stage only.

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