GYNECOLOGY

All-cause mortality in young women with endometrial cancer receiving progesterone therapy

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BACKGROUND: Uterine-preserving therapy with progesterone may be used in young women with endometrial cancer who desire fertility preservation. Such therapy delays definitive treatment with hysterectomy.

OBJECTIVE: We examined the use and safety of progestational therapy in young women with endometrial cancer. The primary outcome of the analysis was overall survival.

STUDY DESIGN: We identified women ≤49 years of age with stage I endometrial cancer in the National Cancer Database from 2004 through 2014. Women treated with hormonal therapy with or without hysterectomy were compared to women treated with hysterectomy. After propensity score weighting, overall survival was examined using proportional hazards models.

RESULTS: A total of 23,231 patients, including 872 (3.8%) women treated with hormonal therapy were identified. Use of hormonal therapy was 2.4% (95% confidence interval, 1.8—3.3%) in 2004 and increased over time to 5.9% (95% confidence interval, 5.0—6.9%) by 2014 ($P < .0001$). Use of hormonal therapy decreased with older age, higher substage, and increasing grade. Black women were more likely to receive hormonal therapy while Medicaid recipients were less likely to receive hormonal therapy. The 5-year survival for patients treated with hormonal therapy was 96.4% (95% confidence interval, 94.3—98.0%) compared to 97.2% (95% confidence interval, 96.9—97.4%) for hysterectomy. In a multivariable model, women treated with hormonal therapy were 92% (hazard ratio, 1.92; 95% confidence interval, 1.15—3.19) more likely to die compared to women who underwent primary hysterectomy. When stratified by stage, hormonal therapy was associated with increased mortality in women with stage IB and I-not otherwise specified tumors but not for stage IA neoplasms.

CONCLUSION: Use of progestational therapy is increasing. Its use was associated with decreased survival, particularly in women with stage IB tumors.

Introduction

Hysterectomy in combination with bilateral salpingo-oophorectomy remains the standard of care for endometrial cancer.[1] Hysterectomy results in excellent oncologic outcomes, particularly for women with low-grade, early-stage neoplasms. However, despite the success of surgical treatment for cancer control, removal of the reproductive organs has a number of long-term consequences including loss of fertility.[2]

As an alternative to hysterectomy, medical management of endometrial cancer with progestational agents has been described for young women.[3,4] Endometrioid tumors typically express progesterone receptors; thus, there is a strong rationale for this type of hormonal therapy. Data describing the efficacy of progestin therapy are largely based on small studies with a wide range of response rates reported.[3,5-11] A meta-analysis of 45 studies that included 391 subjects reported an overall response rate of 75% with a complete response rate of 48%. Among women with a complete response, over one third ultimately recurred.[6] Progestational therapy is administered either orally, or delivered locally to the uterus through an intrauterine device (IUD).

Progestational therapy is typically administered for several months until patients either have regression of the cancer or have persistence of endometrial cancer and undergo hysterectomy. While small studies suggested that progestin therapy is safe, such therapy delays definitive treatment with hysterectomy for several months in women who do not respond. Further, the optimal duration of therapy, follow-up schedule, and most appropriate formulation of progesterone are uncertain.[3,4] Even more importantly, little is known about the frequency of use of progestin therapy in young women, and the comparative effectiveness of hormonal therapy in real-world populations is unknown. We performed a population-based study to examine the trends in use of progestational therapy in young women with endometrial cancer and examined the comparative effectiveness of hormonal therapy compared to hysterectomy.

Materials and Methods

Data source and cohort selection

The National Cancer Database (NCDB) was used for analysis. NCDB is a nationwide oncology outcomes database developed by the American College of Surgeons and the American Cancer Society.[12] The database includes >1500 hospitals affiliated with the Commission on Cancer in the United States, registering approximately 70% of newly diagnosed cancers in the nation.[13] The database includes information on patient demographics, hospital factors, tumor characteristics, first course of therapy, follow-up, and survival data. Information is abstracted by trained cancer

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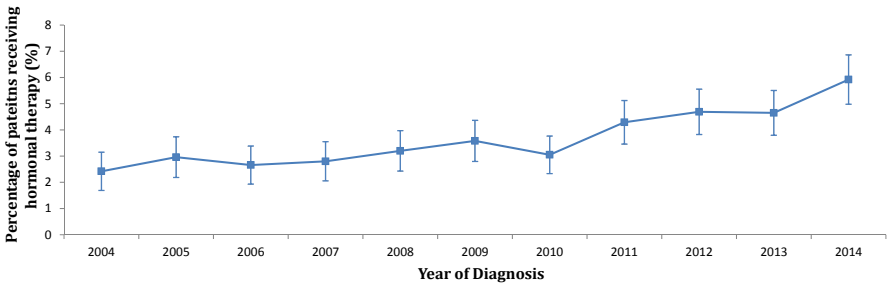
FIGURE



Trends in use of progesterone therapy over time in young women with endometrial cancer.

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registrars. Data do not contain patient identifiers and the Columbia University Institutional Review Board deemed this study exempt.

Patients and treatments

We included women <50 years of age diagnosed with stage I endometrioid endometrial cancer from 2004 through 2014. Patients who received preoperative radiotherapy were excluded. The cohort was divided into those who received hormonal therapy (with or without hysterectomy) and those who underwent hysterectomy only. Women not treated with hysterectomy or hormonal therapy were excluded.

Demographic data analyzed include age (<35, 35-39, 40-44, 45-49 years), race and ethnicity (white, black, Hispanic, other, unknown), insurance status (private insurance, Medicaid, Medicare, uninsured, unknown), median household income for patient's area of residence (<$30,000, $30,000-35,999, $36,000-45,999, ≥$46,000, and unknown), and urban/rural area of residence (metropolitan, urban, rural, unknown). Comorbidity was estimated using the Deyo classification of the Charlson comorbidity score (0, 1, 2, unknown).[14,15] Tumors were classified as stage IA (tumor confined to the endometrium or <50% of the myometrium), IB (tumor with >50% myoinvasion), and stage I-not otherwise specified (INOS) if the depth of myoinvasion was not available. Tumor grade was categorized as 1 (well), 2 (moderate), 3 (poor), or unknown.

Statistical analysis

The trends in use of hormonal therapy over time are reported as rates with 95% confidence intervals (CI). Univariate analyses of factors associated with use of hormonal therapy were performed by χ^2 tests. A marginal log-linear Poisson regression model based on generalized estimating equations methodology was developed to explore predictors of hormonal therapy while accounting for hospital-level clustering. Results are reported as adjusted rate ratios (RR) with 95% CI. The model included all clinical and demographic factors in the study.

To account for imbalances in the treatment groups, we performed a propensity score analysis. The propensity score is the predicted probability of treatment, use of progesterone in the current analysis.[16-18] The propensity score was estimated using a logistic regression model that included all clinical and demographic characteristics. The predicted probability (the propensity score) was estimated for each patient and ranged from 0-1.

The primary analytic approach using the propensity score relied on an inverse probability of treatment weighting (IPTW) approach.[16,19] With an IPTW approach, each patient is assigned a differential weight based on their treatment group and calculated propensity score. The weighting assumptions of the IPTW approach assigned patients treated with progesterone a weight of 1/propensity score and those who underwent primary hysterectomy a weight of 1/(1-propensity score).[16,19] To reduce the variability of IPTW weights and give individuals with extreme weights less influence, a stabilization technique that multiplies the treatment and comparison weights by a constant and a trimming technique that trims the stabilized weights within a specified range (≤10) were applied.[20] After IPTW, we assessed the balance of measured confounders between treatments via a weighted regression approach, in which each covariate was regressed on the treatment variable. The clinically unimportant differences between treatment groups were determined by a threshold value of <0.2 for all coefficients in the weighted regression model.[21]

The primary outcome of the analysis was overall survival. Marginal Cox proportional hazards models were developed to examine the association between hormonal therapy and overall survival while accounting for hospital-level clustering and all clinical and demographic characteristics. The assumption of proportionality was assessed visually by plotting scaled Schoenfeld residuals. The linear function of year of diagnosis was also checked via the distribution of the simulated cumulative martingale residual curves.[22] Women diagnosed from 2004 through 2013 were included in the survival analyses. Results from Cox proportional hazards models are reported as hazard ratios (HR) with 95% CI. Observed 5-year survival rates with 95% CI were calculated using Kaplan-Meier curves stratified by stage.

We performed a number of sensitivity analyses to examine the robustness of our findings. Separate models were developed for each substage of women in the cohort and for women with each grade of tumor. Similarly, separate models were developed for each comorbidity class. All hypothesis tests were 2-sided. A P value of .05 was considered statistically significant. All analyses were conducted using software

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