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Guideline-concordant endometrial cancer treatment and survival in the Women's Health Initiative Life and Longevity After Cancer study

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Abstract

In the Women's Health Initiative (WHI) Life and Longevity After Cancer (LILAC) cohort we examined predictors of guideline-concordant treatment among endometrial cancer (EC) survivors and associations between receipt of guideline-concordant treatment and survival. Receipt of guideline-concordant EC treatment was defined according to year-specific National Comprehensive Cancer Network (NCCN) guidelines. Multivariable logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for predictors of guideline-concordant treatment receipt. We estimated multivariable-adjusted hazard ratios (HRs) and 95% CIs for relationships between guideline-concordant treatment and overall survival using Cox proportional hazards regression. We included 629 women with EC, of whom 83.6% (n=526) received guideline-concordant treatment. Receipt of guideline-concordant treatment was less common among women with non-endometrioid histology (OR=0.24, 95% CI=0.13-0.45) but was more common among women living in the Midwest (OR=2.09, 95% CI=1.06-4.12) or West (OR=3.02, 95% CI=1.49-6.13) compared to the Northeast. In Cox regression models adjusted for age, histology, and stage, receipt of guideline-concordant EC treatment was borderline associated with improved overall survival (HR=0.80, 95% CI=0.60-1.01) in the overall population. Guideline-concordant treatment was also linked with better overall survival among women with low-grade uterine-confined endometrioid EC or widely metastatic endometrioid EC. Guideline-concordant treatment varies by some patient characteristics and those women in receipt of

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guideline-concordant care had borderline improved survival. Studies evaluating regional differences in treatment along with randomized clinical trials to determine appropriate treatment regimens for women with aggressive tumor characteristics are warranted.

Keywords

Uterus Neoplasm; Radiation Treatment; Chemotherapy; Survival

INTRODUCTION

The National Comprehensive Cancer Network (NCCN) formulates treatment guidelines for a number of cancers, including uterine cancer, the most common gynecological cancer in the United States (U.S.) and the fourth most common cancer overall in women (1). Decades of observational and clinical trials research on uterine cancer treatment paradigms have shaped current treatment strategies, which represent the best information we have for treating women with this malignancy. Women diagnosed with endometrial cancer (EC), which comprises 90% of all uterine cancers, have a generally favorable prognosis, with five-year survival rates of 82% (2). However, survival is adversely affected by several risk factors, including aggressive tumor characteristics (3), older age at diagnosis (4), and presence of comorbidities (5, 6). These factors also influence treatment decisions, which in turn, influence survival.

EC treatment typically begins with hysterectomy with bilateral salpingo-oophorectomy. Approximately 20-25% of EC patients, on the basis of having aggressive tumor characteristics or metastatic disease, will undergo adjuvant treatment to reduce risk of local recurrence and improve overall survival (7). Importantly, patient characteristics, such as morbid obesity, a history of cardiovascular disease, or cardiopulmonary disease, may lead to intolerance, dose/schedule adjustment or deviation from guideline-directed adjuvant therapy. On the other hand, patient preferences, which reflect judgements regarding the harms and benefits of various treatment options, influence treatment decisions (8). The extent to which epidemiological factors (*e.g.* age, race, insurance status) influence receipt of guideline-concordant EC treatment has not been examined, yet this information would be useful for understanding patterns of care, subsequent outcomes, and identification of potential disparities. Moreover, while the effect of various treatments on endometrial cancer survival has been examined in randomized clinical trials (4, 9–12), few studies specifically examined the impact of receiving guideline-recommended EC treatment on survival. Using data from the Women's Health Initiative (WHI) Life and Longevity After Cancer (LILAC) survivorship cohort, we hypothesized that receipt of guideline-concordant EC treatment would vary based on patient characteristics and receipt of guideline-concordant treatment would be associated with favorable survival.

MATERIAL AND METHODS

Study population

Details of the WHI have been described previously (13, 14). Briefly, between 1993 and 1998, postmenopausal women between the ages of 50-79 years were recruited from 40 clinical sites across the U.S. into one or more randomized clinical trials (WHI-CT n=68,132) or observational study (WHI-OS n=93,676). Women in the WHI-OS were either unwilling or ineligible to be included in a CT (14). The WHI-CT and WHI-OS were closed in 2004–2005, and participants were invited to continue follow-up in the WHI Extension Study 1 (2005–2010), Extension Study 2 (2010–2015), and Extension 3 (2015–2020). In the WHI, incident cancer diagnoses were self-reported at least annually in the WHI-CT and WHI-OS. Study physicians adjudicated self-reports of malignancy by reviewing medical records and pathology reports (15). In 2013, women who developed one of eight cancers, including EC, during active follow-up and who were alive were invited to participate in the LILAC survivorship cohort (16). Women who were diagnosed with EC in 2000 or later but died before LILAC enrollment began were included in the study under a partial waiver of consent. Women who developed EC prior to 2000 and died before LILAC enrollment in 2013 were not included to reduce costs associated with medical record abstraction.

Of 1,736 women who developed EC in the WHI, 40.7% (n=706) were enrolled in LILAC. Supplemental Table 1 compares baseline characteristics between WHI participants who developed EC and participated in LILAC (n=760) to EC cases who did not enroll in LILAC (N=976). LILAC EC cases were older at EC diagnosis, more likely to be college educated, less likely to have cardiovascular disease, hypertension, or multiple comorbidities at WHI enrollment, and less likely to have low-grade endometrioid tumors compared to WHI participants with an EC diagnosis who did not enroll in LILAC.

We excluded LILAC EC cases with missing data on treatment (n=87), grade (n=12), substage (n=22), and women with low-frequency histology subtypes [e.g. carcinoma not otherwise specified (NOS), undifferentiated carcinoma NOS, pseudosarcomatous carcinoma, papillary carcinoma NOS, and squamous cell carcinoma NOS] (n=10), as stratification by histology is a primary analytic goal, leaving 629 women in our analytic sample. Written informed consent was obtained from all study participants and IRB approval was obtained from institutional review boards at all participating institutions.

Data collection

During the main WHI study, participants completed a self-administered questionnaire detailing demographic characteristics, health behaviors, previous use of postmenopausal hormone therapy, and medical histories at baseline. Participants also underwent a clinic visit where trained staff measured each participant's weight and height using a standardized protocol. Body mass index (BMI) was calculated based on these height and weight measurements and was updated annually until study closeout for CT participants and at Year 3 for OS participants. Information on tumor characteristics, including stage [according to 1988 or 2009 International Federation of Gynecologic Oncology (FIGO) criteria depending on year of diagnosis], histology (endometrioid, serous, carcinosarcoma, clear cell, mixed

epithelial), and grade (1–3) were collected from pathology reports. We also calculated time from EC diagnosis to LILAC enrollment in order to address whether a survival bias existed (i.e. whether longer-term survivors had higher odds of receiving guideline-concordant treatment).

We abstracted information on surgery type, radiation (type, start and stop dates, total dosage received), chemotherapy (regimen name, start, and stop dates), and endocrine-targeted/hormone therapy (agent name, intermittent vs. continuous use, start and stop dates) from medical records.

Definition of guideline-concordant treatment

Receipt of guideline-concordant care was determined using NCCN guidelines (17), which indicate surgery (hysterectomy plus bilateral oophorectomy and salpingectomy), chemotherapy, radiation therapy (vaginal brachytherapy, pelvic radiation, etc.), and hormone therapy as possible treatments for women with EC dependent on cancer stage, grade, and histology. We used year-specific guidelines due to incremental changes in NCCN treatment guidelines. Receipt of guideline-concordant treatment was determined using algorithms that compared the course of treatment predicted by NCCN with the actual treatment received. For example, all women with EC should receive surgery; those who did not were automatically considered non-concordant. As an additional example, a woman diagnosed with EC in 2012, with stage II, grade 1 endometrioid disease, was recommended to have surgical intervention plus vaginal brachytherapy and/or pelvic radiation. Women who underwent surgery and had at least one of the radiation modalities were considered in receipt of guideline-concordant care.

Statistical analysis

Multiple imputation and inverse probability weighting methods were used to account for missing data and possible selection bias causing differences in women with EC who did and did not participate in LILAC. Weighting was determined by fitting a logistic regression model to predict inclusion in LILAC with the following independent variables: age, BMI measured closest to the time of diagnosis, WHI study arm, race, education, insurance status, geographic region, marital status, parity, smoking status, alcohol use, physical activity, use of anti-hyperlipidemia drugs, use of oral contraceptives, use of menopausal hormones, diabetes, hypertension, cardiovascular disease, and cancer characteristics (stage, grade, and morphology). The inverse of the predicted probabilities for each woman's inclusion into LILAC were used as the weights for the logistic and Cox regression models. Due to the non-monotone missing data pattern, a fully conditional specification imputation procedure was used, generating 40 imputed datasets. Model parameters from imputed datasets were combined using the MIANALYZE procedure in SAS 9.4.

Frequency distributions or means and standard deviations of baseline characteristics according to receipt of guideline-concordant treatment were evaluated with chi-square tests or t-tests, respectively. We estimated univariable odds ratios (ORs) and 95% confidence intervals (CIs) for relationships between epidemiological and clinical factors with receipt of guideline-concordant treatment (no vs. yes) using logistic regression. We next ran a

multivariable logistic regression model including variables demonstrating a univariable association with receipt of guideline-concordant treatment at $p < 0.20$ or variables identified *a priori* (WHI study arm). Our final logistic regression model predicting receipt of guideline-concordant treatment included age at EC diagnosis, use of anti-hyperlipidemia drugs, region, WHI study arm, histology and stage.

Follow-up time was computed from the date of EC diagnosis to date of death or date of last contact and was used as the underlying time metric. Univariable and multivariable-adjusted Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and 95% CIs for associations between guideline-concordant treatment and overall survival. Given the low number of deaths in the study population, we included age (continuous), histology [low-grade (grades 1-2) endometrioid, high-grade (grade 3) endometrioid, and non-endometrioid (serous, carcinosarcoma, mixed epithelial, and clear cell)], and stage (stages I/II, III/IV) as covariates in the model. We also investigated associations between receipt of guideline-concordant and overall survival in models stratified by tumor subgroup. The tumor subgroup variable was created by combining histology and stage into clinically relevant groups of women for whom NCCN guidelines apply, including: 1.) stage IA, low-grade endometrioid; 2.) stage IA, high-grade endometrioid; 3.) stage IB, low-grade endometrioid; 4.) stage IB, high-grade endometrioid; 5.) stage IC, low-grade endometrioid; 6.) stage IC, high-grade endometrioid; 7.) stage II (any substage), low-grade endometrioid; 8.) stage II, high-grade endometrioid; 9.) stage IIIA/IIIC, endometrioid (any grade); 10.) stages IVA/IVB, endometrioid (any grade); 11.) stages IA/IB/IC, II, non-endometrioid; 12.) stages III/IV, non-endometrioid. No confounder adjustments were made in these exploratory analyses as the number of events within groups was low. Proportional hazards were evaluated by including a multiplicative interaction term between receipt of guideline-concordant treatment and time.

All analyses were conducted using SAS (version 9.4, SAS Institute, Cary, NC, USA). All P values were two-sided with the probability of a Type I error set at $< 5\%$.

Data availability

The data that support the findings of this study are available from the Women's Health Initiative. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the Women's Health Initiative Coordinating Center (www.whi.org) with the permission of the Women's Health Initiative.

RESULTS

Associations of guideline-concordant treatment, epidemiological, and tumor characteristics

Among 629 with an EC diagnosis in the WHI LILAC cohort, 83.6% ($n=526$) received guideline-concordant treatment. Supplemental Table 2 shows examples of non-concordant care according to tumor subgroup. Distributions of epidemiological and tumor characteristics according to receipt of guideline-concordant treatment along with univariable and multivariable ORs and 95% CIs are shown in Table 1. In univariable models, receipt of

guideline-concordant treatment was inversely related to age at diagnosis (OR = 75 vs. <50 years=0.42, 95% CI=0.20-0.87) and use of anti-hyperlipidemia drugs (OR=0.42, 95% CI=0.22-0.80). Compared with women living in the Northeast, participants residing in the West (OR=2.23, 95% CI=1.19-4.21) or Midwest (OR=1.83, 95% CI=1.00-3.35) had higher odds of receiving guideline-concordant treatment. Stage and histology were also related to receipt of guideline-concordant treatment. Compared to women with low-grade endometrioid EC, women with non-endometrioid EC had lower odds of receiving guideline-concordant treatment (OR=0.24, 95% CI=0.13-0.45) as did women with advanced stage disease: compared to women with stage IA disease, those with stage IIB (OR=0.15, 95% CI=0.04-0.57) or stage IV (OR=0.24, 95% CI=0.09-0.64) had lower odds of guideline-concordant treatment. Associations were similar in the multivariable-adjusted logistic regression model, although some associations were attenuated (i.e. age, anti-hyperlipidemia drug use, and stage) while others became stronger (i.e. region).

Guideline-concordant EC treatment and survival in the overall study population

During follow-up (median: 7.0 years, range: 0.1-17.1 years) 25.1% (132/526) of women who received guideline-concordant treatment died due to any cause, compared to 35.9% (37/103) among those not receiving guideline-concordant treatment. In the unadjusted Cox regression model, women who received guideline-concordant treatment had a 46% (HR=0.54, 95% CI= 0.44-0.68) lower risk of death compared to women who did not receive guideline-concordant treatment. In models adjusted for age, histology, and stage, guideline-concordant treatment was borderline significantly associated with lower risk of death (HR=0.80, 95% CI=0.64-1.01, Table 2).

Guideline-concordant EC treatment and survival according to tumor subgroup

Univariable Cox regression models stratified by tumor subgroup demonstrate significantly improved overall survival associated with receipt of guideline-concordant treatment among women with stage IA, low-grade endometrioid (HR=0.20, 95% CI=0.04-0.94) and stages IVA/IVB, endometrioid any grade (HR=0.31, 95% CI=0.15-0.65) (Figure 1). We observed borderline associations between guideline-concordant treatment and survival among women with stage IB, low-grade endometrioid (HR=0.56, 95% CI=0.29-1.07) or stage IC, low-grade endometrioid (HR=0.54, 95% CI=0.29-1.01) EC.

DISCUSSION

In this cohort of EC survivors, greater than 80% of women received treatment in line with NCCN guidelines. We noted variations in receipt of guideline-defined treatment according to patient and tumor characteristics; namely, use of anti-hyperlipidemia drugs was borderline associated with lower odds of receiving guideline-concordant EC treatment, while living in the Midwest or West was associated with higher odds of receiving guideline-concordant care. Further, women diagnosed with non-endometrioid tumors were less likely to receive treatment in line with NCCN guidelines compared to women with low-grade endometrioid histology. In line with our hypothesis, we observed better survival among those women who received guideline-concordant care in the overall study population, albeit this association

was attenuated after covariate adjustment. This pattern was also evident among women with certain tumor characteristics (i.e. stage I, low-grade endometrioid).

Consideration of treatment as guideline-concordant vs. not concordant requires an analytic strategy that compares the actual treatment received to the course of treatment predicted by evidence-based guidelines that are based on tumor characteristics (i.e. stage, grade, histology). In this WHI study, our findings that older age at diagnosis and use of anti-hyperlipidemia drugs were related to lower odds of guideline-concordant treatment, suggest that clinicians deviate from treatment guidelines when patient comorbid conditions (age, intercurrent illnesses) could indicate increased risks with treatment according to NCCN guidelines. Although age did not remain an independent predictor of lower guideline-concordant in our multivariable analysis, others have reported important age-related disparities in the treatment of older EC patients. In a retrospective, single-institution cohort study of 1,064 EC patients, the greatest gap between actual and recommended adjuvant radiotherapy or chemotherapy occurred among patients older than 70 years of age, despite these patients having the highest frequency of advanced stage and aggressive histology (18). Our findings of higher odds of guideline concordant care in certain regions are novel and worthy of additional investigations. Whether these findings reflect regional differences in physician practices or other characteristics of EC patients that we did not assess in this study is unknown. Although it is reassuring to note that we did not observe differences in receipt of guideline-concordant treatment according to race or insurance status, these analyses were likely underpowered due to low numbers of non-White women (n=47) and uninsured women (n=20). Therefore, future studies addressing relationships of social determinants of health and receipt of guideline-concordant treatment are warranted.

Similar to a Netherlands-based cohort study (19), we observed higher EC treatment concordance among women with low-grade endometrioid vs. non-endometrioid histology. NCCN guidelines for early-stage, low-grade endometrioid disease include surgery; in our study, 95.8% of women in this category received guideline concordant EC treatment, which is likely the result of high-quality evidence from the Post-Operative Radiation Therapy in Endometrial Carcinoma (PORTEC)-1 and -2 studies, Gynecologic Oncology Group (GOG)-99, and the UK Medical Research Council (MRC) A study in the Treatment of Endometrial Cancer (ASTEC), all of which support surgery-alone for this subgroup (4, 9). Among the few in this subgroup who received adjuvant radiotherapy or chemotherapy (i.e. non-concordant), it is possible that other aggressive tumor features (e.g. presence of lymphovascular space invasion), for which we could not directly observe in our data, were present and influenced the clinical decision to treat with more aggressive therapy. On the other hand, we observed a lower proportion of guideline-concordant treatment among women with non-endometrioid EC, which may reflect a lower level of evidence for these subtypes. In general, randomized clinical trials of ECs have included limited numbers of women with non-endometrioid histology types; therefore, conclusive evidence on treatment regimens for women with these subtypes are lacking, prompting variable treatment regimens. Recently published results from GOG 249 (20) and GOG 258 (21), which included larger numbers of women with non-endometrioid and advanced stage disease, may help clarify treatment patterns among women with aggressive EC.

The few studies of the relationship between guideline-concordant EC treatment and survival are conflicting, with two studies showing no survival association (22, 23), and two recent studies showing higher risk of death associated with non-concordant EC treatment (19, 24). In a study of 335 clinical stage I and 24 clinical stage II patients diagnosed between 1995 and 1999, Van Lankveld et al. (22) observed no relationship between receipt of guideline surgery or guideline radiation and 5-year overall survival. During this time, Dutch guidelines recommended total abdominal hysterectomy with bilateral salpingo oophorectomy for clinical stage 1 patients and radical hysterectomy with pelvic lymph node dissection for patients with clinical stage 2 cancers. Likewise, Boll et al. (23) did not observe overall or EC-specific survival differences associated with concordant treatment receipt. Conversely, Eggink and colleagues (19) observed that patients not treated according to adjuvant therapy guidelines had a 32% higher risk of dying compared with those receiving guideline-compliant treatment in models adjusted for age, histology, grade, stage, and socioeconomic status. Similarly, in a Surveillance, Epidemiology, End Results database analysis, patient decline of recommended treatment was an independent predictor of worse cause-specific mortality (24). Our results are in line with the latter group of studies that demonstrate a survival benefit for those women who receive care in line with NCCN guidelines. Moreover, among women with stages IA-IC, low-grade endometrioid EC or those diagnosed with stage IV endometrioid EC, improved survival was evident among those receiving guideline-concordant care. These findings might indicate subgroups of tumors that are more responsive to treatment. However, we cannot rule out that low numbers within the other subgroups underlie the null associations.

EC treatment paradigms have evolved over the last few decades and represent an accumulation of information from randomized clinical trials and observational studies. The randomized clinical trials that inform the existing NCCN guidelines include the PORTEC 1-2 studies (9, 10), GOG-99 (4), and MRC ASTEC (12). Together, these trials provide consistently strong evidence that among women with early-stage, low-grade endometrioid disease with minimal risk factors, surgery alone is sufficient. On the other hand, these studies identified a group of women with high-intermediate risk features for whom adjuvant radiation improves loco-regional control but not overall survival. Although data for patients with non-endometrioid disease are sparse, recently published results from GOG-249 and PORTEC-3, which enrolled women with high-risk, early-stage disease, suggest that pelvic radiotherapy as opposed to vaginal brachytherapy and chemotherapy is the most appropriate treatment for these women.

Our study has several limitations, including the low overall sample size, coupled with a low number of events among women receiving guideline-concordant care, which potentially limited our ability to observe associations between guideline-concordant care and survival in models stratified by clinically relevant tumor characteristics. Given the smaller sample size, we chose to examine guideline-concordant treatment overall as opposed to considering receipt of guideline-concordant surgery, radiation, chemotherapy, etc. in order to reduce the number of comparisons we made in this analysis. As noted in Supplementary Table 2, there are a number of reasons why a case was not coded as being guideline-concordant. Due to the nuances in direct patient care, lack of guideline-concordant care does not always imply poor quality or inappropriate care and we lacked physician and patient perspectives on treatment

choices in this study. Finally, our results may be influenced, to a certain extent, by survivorship bias. All women who developed EC during WHI follow-up and who were alive at the time of LILAC initiation were invited to participate. We also included the subset of women who developed EC in 2000 or later but died prior to LILAC enrollment; missing from our study population are those EC patients diagnosed prior to 2000 who died prior to LILAC enrollment. We used inverse probability weighting to account for the probability of inclusion in LILAC, somewhat mitigating selection bias. Further, our analysis demonstrated no difference in receipt of guideline-concordant treatment receipt according to amount of survivorship time, suggesting that exclusion of long-term EC cases (i.e. diagnosis before 2000) did not materially influence our findings. Although our study is smaller than the registry-based studies conducted in the Netherlands, our analysis has several strengths including availability of information on patient-level factors that are typically missing from cancer registry studies as well as centralized adjudicated outcomes.

In conclusion, despite the finding that a large proportion of women received guideline-concordant EC treatment, receipt varied by epidemiological and tumor characteristics. Moreover, the extent to which guideline-concordant treatment impacted survival varied according to tumor subgroup. Future studies with larger numbers of EC cases, thorough treatment data, and contextual information regarding reasons for treatment decisions are needed to understand the full spectrum of EC treatment patterns. In addition, randomized clinical trials of EC patients are needed to clearly define the treatment paradigms that will control local disease and improve survival outcomes, particularly for women with aggressive endometrial tumor characteristics.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

ASTE^C

A study in the Treatment of Endometrial Cancer

BMI	body mass index
CIs	confidence intervals
EC	Endometrial cancer
FIGO	International Federation of Gynecologic Oncology
GOG	Gynecologic Oncology Group
HRs	hazard ratios
LILAC	Life and Longevity After Cancer
MRC	UK Medical Research Council
NCCN	National Comprehensive Cancer Network
ORs	odds ratios
PORTEC	Post-Operative Radiation Therapy in Endometrial Carcinoma
WHI	Women's Health Initiative

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NOVELTY AND IMPACT STATEMENT

Endometrial cancer (EC) treatment recommendations are based on randomized clinical trials and observational studies. The extent to which U.S. women with endometrial cancer receive treatment in line with recommendations is unknown. Moreover, predictors of guideline-concordant treatment and associations with survival are understudied. In this cohort of 629 endometrial cancer patients, receipt of guideline-concordant treatment varied by histology and region. In addition, receipt of guideline-concordant EC treatment was borderline associated with improved overall survival.

Figure 1.

Univariable hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between guideline-concordant treatment and overall survival stratified by tumor subgroup. Figure 1 shows significantly improved overall survival associated with receipt of guideline-concordant treatment among women with stage IA, low-grade endometrioid; stage IB, low-grade endometrioid; and stage IC, low-grade endometrioid disease.

Table 1.

Odds ratios and 95% confidence intervals (CIs) for associations between patient and tumor characteristics with receipt of guideline-concordant treatment (n=629)

Patient characteristic	Guideline-concordant treatment, n (%) ¹					
	No (n=103)	Yes (n=526)	OR (95% CI) ²	P	OR (95% CI) ³	P
Age at diagnosis				0.008		0.15
50-64	11 (12.5)	77 (87.5)	1.00		1.00	
65-74	42 (13.6)	266 (86.4)	0.80 (0.68-1.66)		0.97 (0.45-2.07)	
75	50 (21.5)	183 (78.5)	0.42 (0.20-0.87)		0.61 (0.28-1.32)	
Marital status				0.19		
Unmarried/Divorced	39 (17.8)	180 (82.2)	1.00		---	
Married	64 (15.7)	345 (84.4)	1.36 (0.86-2.16)		---	
Race				0.18		
White	92 (15.8)	489 (84.2)	1.00		---	
Black	8 (30.8)	18 (69.2)	0.46 (0.19-1.12)		---	
Other	3 (14.3)	18 (85.7)	1.47 (0.42-5.19)		---	
Education				0.81		
Less than high school diploma/GED	3 (18.8)	13 (81.3)	1.00		---	
High school diploma/GED	14 (20.9)	53 (79.1)	1.15 (0.27-4.85)		---	
Some college	30 (15.0)	170 (85.0)	1.49 (0.38-5.81)		---	
College graduate	54 (15.8)	288 (84.2)	1.53 (0.40-5.79)		---	
Any insurance				0.82		
None	3 (15.0)	17 (85.0)	1.00		---	
Any	99 (16.5)	503 (83.6)	0.86 (0.24-3.13)		---	
Geographic region				0.03		0.01
Northeast	35 (21.5)	128 (78.5)	1.00		1.00	
South	27 (19.0)	115 (81.0)	1.05 (0.58-1.91)		1.50 (0.81-2.77)	
Midwest	22 (13.8)	138 (86.3)	1.83 (1.00-3.35)		2.09 (1.06-4.12)	
West	19 (11.6)	145 (88.4)	2.23 (1.19-4.21)		3.02 (1.49-6.13)	
Study arm				0.60		0.31
Clinical trial	42 (15.3)	233 (84.7)	1.00		1.00	
Observational study	61 (17.2)	293 (82.8)	0.89 (0.56-1.39)		0.78 (0.48-1.27)	
Time from EC diagnosis to LILAC enrollment⁴				0.92		
Less than 1 year	3 (18.8)	13 (81.3)	1.00		---	
1 to 5 years	40 (17.2)	192 (82.8)	1.27 (0.34-4.81)		---	
5 years or more	60 (15.8)	321 (84.3)	1.30 (0.35-4.86)		---	
BMI (kg/m²)				0.76		
<25	32 (18.3)	143 (81.7)	1.00		---	

Patient characteristic	Guideline-concordant treatment, n (%) ¹					
	No (n=103)	Yes (n=526)	OR (95% CI) ²	P	OR (95% CI) ³	P
25-29	28 (14.5)	165 (85.5)	1.24 (0.69-2.23)		---	
30	43 (16.5)	217 (83.5)	1.10 (0.64-1.86)		---	
Anti-hyperlipidemia drug use				0.009		0.08
No	79 (15.1)	446 (85.0)	1.00		1.00	
Yes	17 (27.9)	44 (72.1)	0.42 (0.22-0.80)		0.53 (0.26-1.08)	
CVD				0.35		
No	84 (16.0)	442 (84.0)	1.00		---	
Yes	13 (20.0)	52 (80.0)	0.72 (0.37-1.43)		---	
Diabetes				0.91		
No	98 (16.3)	504 (83.7)	1.00		---	
Yes	5 (18.5)	22 (81.5)	1.06 (0.39-2.92)		---	
Hypertension				0.55		
No	73 (16.2)	379 (83.9)	1.00		---	
Yes	30 (17.0)	147 (83.1)	0.86 (0.53-1.41)		---	
Cardiovascular disease-related comorbidities				0.27		
None	36 (14.0)	221 (86.0)	1.00		---	
One	41 (19.2)	173 (80.8)	0.71 (0.43-1.18)		---	
Two	15 (13.8)	94 (86.2)	1.01 (0.51-2.02)		---	
Three or more	11 (22.4)	38 (77.6)	0.52 (0.24-1.14)		---	
Stage				0.007		0.32
IA	19 (13.6)	121 (86.4)	1.00		1.00	
IB	36 (13.4)	233 (86.6)	0.96 (0.52-1.78)		0.93 (0.50-1.73)	
IC	18 (15.9)	95 (84.1)	0.73 (0.35-1.52)		0.75 (0.35-1.60)	
II	7 (29.2)	17 (70.8)	0.38 (0.13-1.12)		0.62 (0.16-2.41)	
IIA	4 (36.4)	7 (63.6)	0.27 (0.06-1.10)		0.23 (0.06-0.96)	
IIB	4 (50.0)	4 (50.0)	0.15 (0.04-0.57)		0.22 (0.03-1.51)	
IIIA	3 (15.8)	16 (84.2)	0.82 (0.21-3.26)		1.56 (0.29-8.33)	
IIIC	2 (14.3)	12 (85.7)	1.04 (0.20-4.69)		1.11 (0.21-5.90)	
IV	10 (32.3)	21 (67.7)	0.24 (0.09-0.64)		0.44 (0.15-1.27)	
Histology				<0.0001		<0.0001
Low-grade endometrioid	38 (10.7)	317 (89.3)	1.00		1.00	
High-grade endometrioid	19 (11.8)	142 (88.2)	0.82 (0.44-1.52)		0.94 (0.50-1.76)	
Non-endometrioid	47 (38.5)	75 (61.5)	0.21 (0.13-0.36)		0.24 (0.13-0.45)	

¹Frequencies may not sum up the column total due to variables with missing data

²Unadjusted ORs and 95% CIs after inverse probability weighting and multiple imputation

³ORs and 95% CIs adjusted for age at diagnosis, geographic region, study arm, anti-hyperlipidemia drug use, stage, histology and accounting for inverse probability weighting and multiple imputation

⁴For women who died before LILAC began, the day that baseline questionnaires started to be sent (Sept. 1, 2013) was used for their day of enrollment into LILAC

Non-endometrioid includes serous (n=73), carcinosarcoma (n=23), mixed epithelial (n=14), and clear cell (n=12)

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Table 2.

Hazard ratios (HRs) and 95% confidence intervals (CIs) for associations between guideline concordant treatment and overall survival among women with EC in the overall study population (n=629)

	Deaths, n (%)	HR (95% CI) ¹	P	HR (95% CI) ²	P
Guideline-concordant treatment			<0.0001		0.06
No	37/103 (35.9)	1.00		1.00	
Yes	132/526 (25.1)	0.54 (0.44-0.68)		0.80 (0.64-1.01)	

¹Unadjusted HRs and 95% CIs after inverse probability weighting

²HRs and 95% CIs adjusted for age at diagnosis (continuous), histology (low-grade endometrioid, high-grade endometrioid, non-endometrioid), and stage (IA/IB/IC, II/III/IV) and accounting for inverse probability weighting