Published in final edited form as:

Gynecol Oncol. 2016 March ; 140(3): 387–393. doi:10.1016/j.ygyno.2016.01.002.

Magnitude of Risk for Nodal Metastasis Associated with Lymphovascular Space Invasion for Endometrial Cancer

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Abstract

Objectives—While lymphovascular space invasion (LVSI) is a risk factor for nodal metastasis in endometrial cancer, the magnitude of risk is poorly described. We examined the risk of nodal metastasis associated with LVSI for various combinations of tumor grade and depth of invasion and examined the effect of LVSI on survival.

Methods—We identified patients with T1A (<50% myoinvasion) and T1B (>50% myoinvasion) endometrioid adenocarcinomas of the endometrium diagnosed between 2010 to 2012 and recorded in the National Cancer Database. The risk of nodal metastasis associated with LVSI stratified by grade and stage is reported. The association of LVSI and survival was examined using Kaplan-Meier analyses and Cox proportional hazards models.

Results—We identified 25,907 patients, including 3928 (15.2%) with LVSI. Among patients with LVSI, 21.0% had positive lymph nodes, compared to 2.1% in patients without LVSI ($P<0.0001$). In analyses stratified by stage and grade, LVSI was associated with increased risks of LN metastasis by a magnitude of 3 to over 10-fold. In a multivariable model controlling for clinical and demographic characteristics, the risk ratio of nodal disease with LVSI was 9.29 (95%

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The authors declare that there are no conflicts of interest.

CI, 7.29-11.84) for T1A tumors and 4.64 (95% CI 3.99-5.39) for T1B tumors. LVSI was associated with decreased survival even after adjustment for the presence of lymph node metastases (HR=1.92, 95% CI 1.56-2.36).

Conclusions—LVSI is independently associated with lymph node metastases in women with apparent early-stage endometrial cancer and an independent predictor of survival even after adjustment for the presence of lymph node metastases.

Introduction

Endometrial cancer is the most common gynecologic malignancy in the developed world, with an estimated 54,870 new cases and 10,170 deaths in 2015 in the United States.^{1,2} Endometrial cancer is classically thought to spread in a stepwise manner with invasion into the myometrium followed by metastasis to the regional lymph nodes and ultimately systemic spread. The most important prognostic factor for endometrial cancer is disease stage and the detection of metastasis to the lymph nodes.^{3,4} Tumor grade and depth of invasion into the myometrium are important uterine factors that predict the risk of lymph node metastasis and help inform the decision as to whether or not to perform lymphadenectomy.⁵⁻⁸

More recently, lymphovascular space invasion (LVSI), the presence of tumor deposits in the lymphatic and vascular channels of the uterus, has also been recognized as an important prognostic factor for endometrial cancer.⁹⁻¹⁹ LVSI has been described as an independent risk factor for lymph node metastasis and may be associated with survival.⁹⁻¹⁹ Given this association, the Gynecologic Oncology Group includes LVSI as a risk factor for the stratification of intermediate risk endometrial cancers into high and low risk sub-groups.²⁰ As such, LVSI often influences the decisions to perform lymphadenectomy and to administer of adjuvant therapy.

Despite the fact that LVSI is a known prognostic factor for endometrial cancer, less is known about the magnitude by which LVSI increases the risk of lymph node metastasis in the setting of other pathologic risk factors for women with early-stage endometrial cancer. The objectives of our study were therefore twofold. First, to determine the risk of nodal metastasis associated with LVSI for various combinations of tumor grade and depth of invasion for women with T1 endometrial cancer and second, to determine the effect of LVSI on survival in women with apparent early-stage tumors.

Methods

Data source and patient selection

The National Cancer Data Base (NCDB) was used for our analysis. NCDB is a nationwide registry developed and sponsored by the American College of Surgeons and American Cancer Society (ACS).^{21,22} The database records all patients with newly diagnosed invasive cancers from over 1500 Commission on Cancer (CoC) affiliated hospitals located throughout the United States. The NCDB catalogs data on patient demographic factors, tumor characteristics and treatment data, staging, and survival.^{21,22} Data are abstracted by trained registrars and audited regularly to ensure accuracy. It is estimated that 77% of

women with invasive uterine cancer in the U.S. are recorded in NCDB.²³ The Columbia University Institutional Review Board deemed the study exempt.

The primary exposure of interest was lymphovascular space invasion. Each patient was classified based on whether LVSI was reported in the primary tumor. We selected women with T stage I endometrioid adenocarcinomas of the endometrium. Tumors were classified as stage T1A (tumor confined to the endometrium or invading < 50% of the myometrium) or T1B (tumor with ≥ 50% myoinvasion). The cohort was limited to women who underwent hysterectomy between 2010 and 2012 with exclusion of patients who received preoperative radiotherapy or had unknown tumor grade. The cohort was also limited to only those women who underwent lymph node assessment.

Clinical and demographic characteristics

Demographic data analyzed included age (<40, 40–49, 50–59, 60–69, ≥ 70 years), race (white, black, Hispanic, other or unknown), and insurance status (commercial, Medicare, Medicaid, uninsured and unknown). Comorbidity was measured using the Deyo classification of the Charlson comorbidity score (0, 1, ≥ 2).^{24,25} Primary tumor stage (stages T1A, T1B) and grade (1, 2, 3, and unknown) were recorded for each patient. Hospital characteristics analyzed included region (Northeast, Midwest, South, or West) and location (metropolitan, urban, rural). Based on the ACS CoC criteria, hospitals are also classified as academic/research cancer centers or community cancer centers.²¹ NCDB does not release data on tumor recurrence.

Statistical analysis

Frequency distributions between categorical variables were compared using χ^2 tests. The rates with 95% confidence intervals of lymph node metastases stratified by tumor stage and grade and the presence of LVSI are reported. The associations between LVSI and regional nodes metastasis were examined using multivariable log-binomial regression models with Poisson estimation to account for hospital-level clustering of patients and other covariates (including facility location, facility type, age, race, insurance status, urban/rural, comorbidity, year of diagnosis, and tumor grade). Results are reported as adjusted risk ratios (RR) with 95% confidence intervals (CI).

Cox proportional hazards were used to estimate the association between LVSI and survival, accounting for hospital-level clustering. Models are reported with and without inclusion of lymph node metastasis. The primary outcome of these models is overall survival, estimated as the number of months from diagnosis until death from any cause. The models only included patients diagnosed in 2010 and 2011 due to the availability of survival data in NCDB. Patients who were alive at the last follow-up were censored. The models were tested for the assumption of proportional hazards by a visual inspection of the scaled Schoenfeld residuals. Stage and grade specific Kaplan-Meier curves were developed to compare survival between women with and without LVSI. The log-rank test was used to compare the curves. All hypothesis tests were two-sided. A P-value of 0.05 was considered statistically significant. All analyses were conducted using SAS version 9.4 (SAS Institute Inc, Cary, North Carolina).

Results

A total of 25,907 patients with endometrial cancer from 1086 facilities were identified (Table 1). The median age at diagnosis was 62 years (range 18-90 years). All patients underwent lymphadenectomy with a median of 13 and mean of 15.2 regional lymph nodes removed. There were 18,713 (72.2%) patients with T1A tumors and 7194 (27.8%) women with T1B tumors. There were 3928 (15.2%) women with LVSI and 21,979 (84.8%) without LVSI. Overall, lymph node metastases were present in 1290 (5.0%) women.

LVSI was more common in more recent years of diagnosis, in older women, in uninsured women, in patients with grade 2 and 3 neoplasms, and in patients with T1B tumors. Compared to women with grade 1 tumors, the risk ratio for LVSI for those with grade 3 tumors was 3.04 (95% CI, 2.79-3.32). Similarly, the risk ratio for LVSI was 3.31 (95% CI, 3.10-3.54) for T1B vs. T1A cancers. Women with LVSI had a higher number of nodes removed and were more likely to receive adjuvant therapy (both radiation and chemotherapy).

When stratified by tumor grade and depth of invasion, LVSI was associated with a 3-fold to 16-fold increased risk of nodal metastases (Table 2). Among women with T1A tumors, LVSI was associated with an increased risk of nodal metastases from 0.7% (95% CI, 0.5-0.9%) to 11.4% (95% CI, 8.9-14.4%) for grade 1 tumors, 1.3% (95% CI, 1.0-1.6%) to 13.2% (95% CI, 10.8-16.0%) for grade 2 tumors, and 3.6% (2.8-4.6%) to 13.9% (10.9-17.6%) for grade 3 neoplasms ($P<0.0001$ for all). Similarly, for T1B tumors, LVSI was associated with an increased risk of nodal disease from 4.0% (95% CI, 3.2-4.9%) to 25.4% (95% CI, 21.7-29.3%) for grade 1 tumors, 6.0% (95% CI, 5.9-7.1%) to 28.8% (95% CI, 26.1-31.6%) for grade 2 malignancies and 8.2% (95% CI, 6.4-10.4%) to 24.0% (95% CI, 21.1-27.0%) for grade 3 cancers ($P<0.0001$).

In a multivariable analysis, LVSI was independently associated with lymph node metastasis for both T1A tumors (RR=9.29; 95% CI, 7.29-11.84) and T1B tumors (RR=4.64; 95% CI, 3.99-5.39) (Table 3). For women with T1A tumors, age, insurance status, facility type, region, and grade were associated with lymph node metastases ($P<0.05$ for all). For those with T1B cancers, grade, region and facility type were associated with nodal metastases.

The presence of LVSI was associated with decreased survival. The association between LVSI and survival was noted in models without adjusting for the status of the regional lymph nodes (HR=2.09, 95% CI 1.71-2.55), as well as in a model adjusted for the presence of lymph node metastases (HR=1.94, 95% CI 1.58-2.39) (Table 4). Other variables significantly associated with mortality included lymph node metastasis, advanced age, Medicare or Medicaid insurance coverage, comorbidity, tumor grade, and tumor stage ($P<0.05$ for all).

When stratified based on the presence or absence of nodal metastases, LVSI remained associated with survival in node negative patients (HR=2.06; 95% CI, 1.65-2.58), but was not associated with survival in women with lymph node metastases (HR=1.19; 95% CI, 0.70-2.00) (Supplemental Table 1). In a series of Kaplan-Meier analyses stratified by tumor stage and grade, LVSI was associated with decreased survival at 45 months for stage T1A/

grade 2 tumors ($P=0.006$), stage T1A/grade 3 ($P=0.01$), stage T1B/grade 1 ($P=0.03$), stage T1B/grade 2 ($P<0.0001$) and stage T1B/grade III ($P<0.001$) tumors (Figure 1).

Discussion

We noted that LVSI is an independent predictor of lymph node metastases for women with stage T1 endometrial cancer. For women with $<50\%$ myoinvasion as well as those with deep myoinvasion, LVSI substantially increased the rate of nodal metastasis regardless of tumor grade. Further, LVSI is an independent predictor of survival even after adjustment for the presence or absence of lymph node metastases.

Our findings are in concordance with previous investigations that have identified LVSI as a significant factor in predicting the risk of retroperitoneal lymph node metastases, disease recurrence, and death.⁹⁻¹⁹ Another study by Briet and colleagues¹⁸ reviewed 609 cases from their institution and also found that LVSI was an independent predictor of lymph node metastases, as well as a risk factor for relapse at all stages by a factor of 2.6. Even in patients with proven negative nodes, LVSI remained a significant predictor of disease recurrence.

The presence of lymphovascular space invasion is strongly associated with tumor dissemination to the regional lymph nodes.⁹⁻¹⁹ An analysis of 366 women treated at two institutions reported positive lymph nodes in 18-48% of tumors with LVSI compared to 0-13% of cases without LVSI when stratified for tumor grade and depth of invasion. The relative risk of lymph node metastases in the setting of lymphovascular space invasion was 2.1.¹⁷ One report of women with early endometrial cancer noted that the risk of pelvic lymph node metastases was 44% in those with LVSI compared to 14% in women without LVSI.¹⁸

Our data including over 25,000 women help to quantify the risk of nodal metastases associated with LVSI for women with apparent early-stage endometrial cancer. When stratified by grade and depth of invasion, we noted that LVSI increased the risk of lymph node metastasis by 3 to 16 fold. For patients with low-risk, T1A, grade 1 tumors LVSI increased the risk of lymph node metastasis from 0.7 to 11.4%. Similarly, the increased risk conferred by LVSI was noted in patients with deeply invasive, high-grade tumors; for women with stage T1B, grade 3 tumors the risk of nodal disease rose from 8.2% to 24%. These findings suggest that the presence of LVSI is an even more important factor in predicting lymph node metastases than previously recognized.

Traditionally, endometrial cancer is thought to spread to the regional lymphatics followed by systemic spread. The impact of LVSI on survival has been hypothesized to result from the association between LVSI and nodal disease. More recently, LVSI and local tumor factors have been shown to independently predict prognosis regardless of the status of the regional lymph nodes.^{26,27} A population-based analysis from Canada noted that five-year survival was 20% lower in women with negative lymph nodes with 2 or 3 high-risk uterine factors compared to women with positive lymph nodes and none or only 1 adverse uterine risk factor.²⁶ Similarly, LVSI appears to be independently associated with survival. One report noted that LVSI increased the risk of both loco-regional and distant relapse.¹⁸ In patients

with apparent stage I endometrial cancer, the presence of LVSI was independently associated with lower recurrence free survival and decreased disease specific and overall survival.¹⁹

Our data which demonstrates that LVSI is not only associated with nodal metastases, but it also predicts survival independent of nodal disease, is in accord with what has previously been reported in the literature. In a series of models we noted that the risk of death was 2-fold higher in women with LVSI. This was attenuated somewhat (hazard ratio 1.92) after adjusting for the presence of lymph node metastases, but remained significant. Notably, in this model, the risk of death associated with positive lymph nodes was not as great as the risk associated with LVSI. These data confirm prior work that LVSI is an independent predictor of survival. The effect of LVSI on survival may be due in part to hematogenous dissemination of tumor.

Our findings have a number of important clinical implications. First, LVSI should be included as a standard uterine factor to help guide management. Second, for those women who have not undergone lymphadenectomy, the presence of LVSI carries a significant risk for occult nodal disease. While the role of adjuvant therapy for early-stage endometrial cancer remains controversial, similar to GOG 99, the presence of LVSI should be considered as a factor in classifying women as high intermediate risk.²⁸ Finally, if feasible, intraoperative determination of LVSI could be used to help inform the decision to perform lymphadenectomy. While not standard, one report noted a discrepancy of 32% between identification of LVSI intraoperatively on frozen section and final pathology, similar to the discrepancies for both grade and depth of invasion.²⁹

While our study benefits from the inclusion of a large sample of women, we recognize a number of important limitations. First, central pathology review is not available and therefore we cannot verify the findings of LVSI. However, LVSI has long been recognized as a prognostic factor for endometrial cancer and is frequently reported. Although this reflects treatment patterns of women with endometrial cancer, we cannot exclude the possibility that a small number of women were misclassified. Within NCDB reporting of LVSI only began in 2010 and we lack long-term follow-up on the cohort. While we noted that even within 3 years of follow-up there was a difference in survival associated with LVSI, examination of longer term outcomes will be of great interest. By definition our study is limited to only those women who underwent lymphadenectomy. Although we stratified our analysis by grade and depth of invasion, there were likely unmeasured factors that contributed to the decision to perform lymphadenectomy. Additionally, the lack of availability of data on the rates and sites of tumor recurrence is a shortcoming of NCDB and this would be worthwhile to evaluate in future studies. Lastly, a priori we chose to limit our analysis to women with endometrioid adenocarcinomas. Evaluation of the association between LVSI and outcomes for other histologies would be of value.

The Gynecologic Oncology Group initially recognized the importance of LVSI for early-stage endometrial cancer and it is now an accepted prognostic factor.²⁸ LVSI is used not only to guide intraoperative decision making, including performance of lymphadenectomy, but also for adjuvant treatment planning.²⁸ Our data not only support the importance of

lymphovascular space invasion, but also provide estimates of the magnitude of risk for lymph node metastasis associated with LVSI. Importantly, this work adds to a growing body of literature demonstrating that the impact of LVSI on survival is only partially dependent on nodal status.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

Dr. Wright (NCI R01CA169121-01A1 and Dr. Hershman (NCI R01CA134964) are recipients of grants from the National Cancer Institute.

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Research Highlights

- LVSI is associated with a 3 to 16-fold increased risk of nodal metastases.
- LVSI is independently associated with lymph node metastases.
- LVSI is an independent predictor of survival.

Figure 1.
Kaplan-Meier analysis of survival stratified by grade, depth of myometrial invasion and LVSI.

Table 1

Clinical and demographic variables associated with lymphovascular space invasion.

	No LVSI		LVSI			
	N	(%)	N	(%)	Univariate P-value	Multivariable Model of LVSI Risk Ratio (95% CI)
	21,979	(84.8)	3928	(15.2)		
<i>Year of diagnosis</i>					0.08	
2010	7,148	(32.5)	1,218	(31.0)		Referent
2011	7,575	(34.5)	1,348	(34.3)		1.06 (0.99-1.14)
2012	7,256	(33.0)	1,362	(34.7)		1.12 (1.04-1.21)*
<i>Age</i>					<0.0001	
<40	617	(2.8)	52	(1.3)		Referent
40-49	1,816	(8.3)	198	(5.0)		1.24 (0.93-1.66)
50-59	6,837	(31.1)	1,110	(28.3)		1.48 (1.14-1.94)*
60-69	8,126	(37.0)	1,506	(38.3)		1.44 (1.10-1.87)*
70-79	3,560	(16.2)	773	(19.7)		1.38 (1.04-1.84)*
80	1,023	(4.7)	289	(7.4)		1.44 (1.08-1.92)*
<i>Race/Ethnicity</i>					0.74	
White	18,246	(83.7)	3,289	(83.7)		Referent
Black	1,524	(6.9)	249	(6.3)		0.92 (0.82-1.03)
Hispanic	1,120	(5.1)	198	(5.0)		1.01 (0.89-1.16)
Other	845	(3.8)	148	(3.8)		1.03 (0.89-1.19)
Unknown	244	(1.1)	44	(1.1)		0.98 (0.76-1.26)
<i>Insurance Status</i>					<0.0001	
Private Insurance	12,071	(54.9)	1,880	(47.9)		Referent
Medicaid	974	(4.4)	163	(4.1)		1.01 (0.88-1.15)
Medicare	7,577	(34.5)	1,617	(41.2)		1.01 (0.94-1.09)
Uninsured	811	(3.7)	179	(4.6)		1.23 (1.07-1.42)*
Other Government	273	(1.2)	41	(1.0)		0.97 (0.72-1.31)
Unknown	273	(1.2)	48	(1.2)		0.88 (0.66-1.16)
<i>Comorbidity</i>					0.52	
0	16,380	(74.5)	2,959	(75.3)		Referent
1	4,634	(21.1)	797	(20.3)		0.99 (0.92-1.06)
2	965	(4.4)	172	(4.4)		0.98 (0.86-1.12)
<i>Grade</i>					<0.0001	
1	11,448	(52.1)	1,023	(26.0)		Referent
2	8,122	(37.0)	1,698	(43.2)		1.80 (1.67-1.94)**
3	2,409	(11.0)	1,207	(30.7)		3.04 (2.79-3.32)**

	No LVSI		LVSI			
	N	(%)	N	(%)	Univariate P-value	Multivariable Model of LVSI Risk Ratio (95% CI)
Depth of invasion					<0.0001	
T1A	17,141	(78.0)	1,572	(40.0)		Referent
T1B	4,838	(22.0)	2,356	(60.0)		3.31 (3.10-3.54) **
Area of residence					0.04	
Metropolitan	17,491	(79.6)	3,119	(79.4)		Referent
Urban	3,412	(15.5)	586	(14.9)		0.96 (0.88-1.05)
Rural	418	(1.9)	73	(1.9)		0.94 (0.76-1.15)
Unknown	658	(3.0)	150	(3.8)		1.19 (1.04-1.36) *
Region					<0.0001	
Eastern	4,899	(22.3)	1,017	(25.9)		Referent
South	6,269	(28.5)	1,017	(25.9)		0.81 (0.70-0.94) *
Midwest	7,571	(34.4)	1,293	(32.9)		0.86 (0.75-0.99) *
West	3,240	(14.7)	601	(15.3)		0.88 (0.76-1.03)
Facility type¹					0.25	
Academic/research program	9,151	(41.6)	1,611	(41.0)		Referent
Community cancer program	758	(3.4)	143	(3.6)		0.97 (0.82-1.15)
Comprehensive community cancer	11,999	(54.6)	2,168	(55.2)		1.01 (0.91-1.12)
Lymph nodes removed					<0.0001	
<10	7,619	(34.7)	1,092	(27.8)		-
10	14,120	(64.2)	2,785	(70.9)		-
Unknown number	240	(1.1)	51	(1.3)		-
Lymph node metastases					<0.0001	
Negative	21,512	(97.9)	3,105	(79.0)		-
Positive	467	(2.1)	823	(21.0)		-
Adjuvant radiation					<0.0001	
None	18,309	(83.3)	1,884	(48.0)		-
External beam	522	(2.4)	576	(14.7)		-
Brachytherapy	2,891	(13.2)	1,180	(30.0)		-
Combination	244	(1.1)	269	(6.8)		-
Other/Unknown	13	(0.1)	19	(0.5)		-
Adjuvant chemotherapy					<0.0001	
No	20,991	(95.5)	2,893	(73.7)		-
Yes	826	(3.8)	996	(25.4)		-
Unknown	162	(0.7)	39	(1.0)		-
Vital status					<0.0001	
Dead	374	(1.7)	215	(5.5)		-

	No LVSI		LVSI			
	N	(%)	N	(%)	<i>Univariate P-value</i>	Multivariable Model of LVSI Risk Ratio (95% CI)
Alive	14,349	(65.3)	2,351	(59.9)		-
Unknown	7,256	(33.0)	1,362	(34.7)		-

*
P<0.05

**
P<0.0001

Table 2

Rates of nodal metastasis in women with lymphovascular space invasion stratified by tumor grade and depth of myometrial invasion.

	Grade	LVSI	Regional Node Status				<i>P-value</i>
			Negative		Positive		
			N	% (95% CI)	N	% (95% CI)	
T1A	1	Not present	9,307	99.3 (99.1-99.5)	65	0.7 (0.5-0.9)	<0.0001
T1A	1	Present	459	88.6 (85.6-91.1)	59	11.4 (8.9-14.4)	
T1A	2	Not present	6,004	98.7 (98.4-99.0)	78	1.3 (1.0-1.6)	<0.0001
T1A	2	Present	559	86.8 (84.0-89.2)	85	13.2 (10.8-16.0)	
T1A	3	Not present	1,627	96.4 (95.4-97.2)	60	3.6 (2.8-4.6)	<0.0001
T1A	3	Present	353	86.1 (82.4-89.1)	57	13.9 (10.9-17.6)	
T1B	1	Not present	1,993	96.0 (95.1-96.8)	83	4.0 (3.2-4.9)	<0.0001
T1B	1	Present	377	74.7 (70.7-78.3)	128	25.4 (21.7-29.3)	
T1B	2	Not present	1,918	94.0 (92.9-95.0)	122	6.0 (5.0-7.1)	<0.0001
T1B	2	Present	751	71.3 (68.4-73.9)	303	28.8 (26.1-31.6)	
T1B	3	Not present	663	91.8 (89.6-93.6)	59	8.2 (6.4-10.4)	<0.0001
T1B	3	Present	606	76.0 (73.0-78.9)	191	24.0 (21.1-27.0)	

Table 3

Multivariable model of regional lymph node metastasis for women with stage I endometrial cancer.

	T1A Risk Ratio (95% CI)	T1B Risk Ratio (95% CI)
<i>LVSI</i>		
No	Referent	Referent
Yes	9.29 (7.29-11.84) **	4.64 (3.99-5.39) **
<i>Year of Diagnosis</i>		
2010	Referent	Referent
2011	1.00(0.79,1.28)	1.04 (0.89-1.20)
2012	1.11(0.88-1.38)	0.97 (0.84-1.13)
<i>Age</i>		
<40	Referent	Referent
40-49	0.95 (0.54-1.65)	1.44 (0.83-2.51)
50-59	0.73 (0.44-1.23)	1.12 (0.67-1.89)
60-69	0.58 (0.34-1.00) *	0.83 (0.49-1.40)
70-79	0.39 (0.22-0.70) *	0.71 (0.41-1.22)
>=80	0.35 (0.15-0.79) *	0.69 (0.39-1.24)
<i>Race/Ethnicity</i>		
White	Referent	Referent
Black	1.04 (0.76-1.42)	1.02 (0.78, 1.33)
Hispanic	1.00 (0.68-1.45)	0.95 (0.75, 1.22)
Other	1.23 (0.81-1.86)	0.88 (0.63, 1.21)
Unknown	0.84 (0.38-1.86)	0.76 (0.43, 1.35)
<i>Insurance Status</i>		
Private Insurance	Referent	Referent
Medicaid	1.51 (1.03-2.20) *	1.12 (0.84-1.49)
Medicare	1.23 (0.92-1.64)	1.02 (0.87-1.18)
Uninsured	1.19 (0.78-1.83)	0.97 (0.74-1.28)
Other Government	1.09 (0.49-2.41)	0.76 (0.37-1.55)
Unknown	3.04 (1.76-5.24) **	0.90 (0.53-1.55)
<i>Comorbidity (Charlson Score)</i>		
0	Referent	Referent
1	0.80 (0.62-1.04)	1.02 (0.87-1.19)
2	0.99 (0.61-1.61)	1.08 (0.83-1.41)
<i>Grade</i>		
1	Referent	Referent
2	1.63 (1.27-2.08) **	1.30 (1.12-1.51) *

	T1A Risk Ratio (95% CI)	T1B Risk Ratio (95% CI)
3	2.60 (1.95-3.47) **	1.20 (1.01-1.43) *
<i>Area of residence</i>		
Metropolitan	Referent	Referent
Urban	0.99 (0.75-1.30)	0.99 (0.83-1.17)
Rural	0.89 (0.44-1.84)	0.79 (0.48-1.27)
Unknown	0.94 (0.48-1.81)	1.17 (0.88-1.55)
<i>Region</i>		
Eastern	Referent	Referent
South	1.43 (1.05-1.97) *	1.14 (0.94-1.38)
Midwest	1.06 (0.77-1.45)	1.30 (1.09-1.54) *
West	1.38 (0.98-1.96)	1.49 (1.23-1.81) **
<i>Facility Type</i>		
Academic/Research program	Referent	Referent
Community Cancer Program	1.65 (1.10-2.47) *	1.24 (0.95-1.61)
Comprehensive Community Cancer Program	0.93 (0.74-1.17)	0.99 (0.87-1.13)
Other specified types of cancer programs	1.81 (1.39-2.37) **	1.34 (1.16-1.55) **

* P<0.05

** P<0.0001

Table 4

Factors associated with survival for women with stage I endometrial cancer.

	Model adjusted for LVSI Hazard Ratio (95% CI)	Model adjusted for LVSI and lymph node metastases Hazard Ratio (95% CI)
LVSI		
No	Referent	Referent
Yes	2.09 (1.71-2.55) **	1.94 (1.58-2.39) **
Lymph node metastases		
Negative	-	Referent
Positive	-	1.96 (1.38-2.79) *
Lymph nodes removed		
<10	-	Referent
10	-	0.90 (0.76-1.07)
Unknown number	-	1.08 (0.50-2.32)
Year of Diagnosis		
2010	Referent	Referent
2011	1.00 (0.84-1.20)	1.00 (0.84-1.20)
Age		
<40	Referent	Referent
40-49	1.63 (0.48-5.58)	1.61 (0.47-5.53)
50-59	2.11 (0.66-6.78)	2.17 (0.67-7.01)
60-69	2.38 (0.74-7.70)	2.46 (0.76-7.98)
70-79	4.60 (1.42-14.93) *	4.75 (1.46-15.47) *
80	8.22 (2.52-26.82) *	8.28 (2.53-27.14) *
Race/Ethnicity		
White	Referent	Referent
Black	1.34 (1.00-1.79) *	1.35 (1.01-1.81) *
Hispanic	0.91 (0.59-1.38)	0.91 (0.59-1.39)
Other	0.46 (0.24-0.89) *	0.47 (0.24-0.90) *
Unknown	0.90 (0.42-1.95)	0.94 (0.44-2.03)
Insurance Status		
Private Insurance	Referent	Referent
Medicaid	1.93 (1.29-2.87) *	1.87 (1.25-2.80) *
Medicare	1.43 (1.11-1.83) *	1.41 (1.09-1.81) *
Uninsured	0.98 (0.55-1.73)	0.98 (0.55-1.74)
Other Government	1.19 (0.52-2.74)	1.20 (0.52-2.76)
Unknown	0.62 (0.24-1.61)	0.55 (0.20-1.49)
Comorbidity (Charlson score)		

	Model adjusted for LVSI Hazard Ratio (95% CI)	Model adjusted for LVSI and lymph node metastases Hazard Ratio (95% CI)
0	Referent	Referent
1	1.32 (1.10-1.60) *	1.32 (1.09-1.59) *
2	2.65 (2.02-3.48) **	2.69 (2.05-3.53) **
Area of residence		
Metropolitan	Referent	Referent
Urban	1.21 (0.97-1.51)	1.19 (0.95-1.48)
Rural	0.92 (0.55-1.56)	0.91 (0.53-1.55)
Unknown	1.19 (0.74-1.91)	1.20 (0.75-1.92)
Region		
Eastern	Referent	Referent
South	1.14 (0.87-1.50)	1.14 (0.87-1.49)
Midwest	1.09 (0.84-1.41)	1.09 (0.85-1.41)
West	1.18 (0.86-1.60)	1.17 (0.86-1.60)
Facility Type		
Academic/Research program	Referent	Referent
Community Cancer Program	1.20 (0.81-1.78)	1.15 (0.78-1.71)
Comprehensive Community Cancer Program	1.00 (0.83-1.20)	0.99 (0.82-1.20)
Other	-	-
Grade		
1	Referent	Referent
2	1.60 (1.29-1.98) **	1.59 (1.29-1.97) **
3	2.95 (2.35-3.69) **	3.01 (2.40-3.77) **
Stage		
T1A	Referent	Referent
T1B	1.23 (1.03-1.46) *	1.18 (0.99-1.41)
Adjuvant radiation		
None	Referent	Referent
External beam	1.14 (0.83-1.55)	1.05 (0.78-1.43)
Brachytherapy	1.01 (0.80-1.27)	1.08 (0.85-1.36)
Combination	1.07 (0.69-1.67)	1.00 (0.66-1.52)
Other/Unknown	0.75 (0.09-5.94)	0.80 (0.10-6.34)
Adjuvant chemotherapy		
No	Referent	Referent
Yes	0.94 (0.72-1.24)	0.71 (0.51-0.99) *
Unknown	1.71 (0.88-3.32)	1.41 (0.71-2.81)

* P<0.05

** P<0.0001