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# Lymphovascular space invasion in uterine corpus cancer: What is its prognostic significance in the absence of lymph node metastases?

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## HIGHLIGHTS

- Lymphovascular space invasion (LVSI) is a poor prognostic indicator in uterine cancer.
- In subjects with negative lymph nodes, LVSI is associated with worse survival.
- The inclusion of LVSI does not enhance the predictive ability of a survival model.

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## ABSTRACT

*Objective.* Lymphovascular space invasion (LVSI) is a poor prognostic indicator in uterine cancer, primarily due to its association with lymph node metastases. We sought to determine if LVSI provides any prognostic information for uterine cancer subjects in the absence of nodal disease.

*Methods.* A retrospective review was performed using a database of women treated for uterine cancer at MUSC from 2005 to 2012. Subjects with negative nodes after complete staging were identified. Multiple regression modeling was used to adjust for demographic and histopathologic covariates. The C-index was calculated for models of survival that included LVSI and those that did not. Competing risks analysis was conducted to examine factors associated with time to recurrence.

*Results.* Two hundred and five subjects were completely staged and had negative nodes, 24 with LVSI and 181 without. Factors significantly associated with survival included age, race, stage, grade, histology, and LVSI. Regression models for recurrence-free survival (RFS) and overall survival (OS) had similar C-indices regardless of whether LVSI was included. Competing risks analysis confirmed no significant difference in time to recurrence for subjects with LVSI compared to those without, after adjusting for other prognostic factors ($P = 0.53$).

*Conclusions.* LVSI is associated with shorter recurrence-free and overall survival in uterine cancer subjects with negative lymph nodes. However, after adjusting for other prognostic factors, LVSI status does not provide additional prognostic information. This finding suggests that recurrence-free and overall survival for uterine cancer patients with negative lymph nodes can be estimated without factoring in LVSI.

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## 1. Introduction

Uterine cancer is the most common gynecologic malignancy in the United States, with 54, 870 new cases and 10,170 deaths estimated for 2015 [1]. The standard treatment for uterine corpus cancer is surgery, with adjuvant therapy administered in select cases.

There are a number of well-established prognostic factors in uterine corpus cancer, including stage, grade, histology, and lymph node metastases [2,3]. Lymphovascular space invasion (LVSI) has also been identified as a poor prognostic factor [4–11]. A number of studies have demonstrated an association between LVSI and disease recurrence [4–6]. LVSI is also known to be an independent risk factor for nodal disease

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[4,7–9] and distant metastases [10,11]. Based upon these findings, Cohn et al. suggested that the presence of LVSI on pathologic review indicates the need for lymphadenectomy or adjuvant therapy in patients who did not initially undergo full surgical staging [9]; however, many patients undergo full pelvic and paraaortic lymphadenectomy at the time of surgery. Little data exists regarding the prognostic value of LVSI in the setting of lymph nodes that are known to be negative for disease.

The objective of this study is to determine if LVSI provides any prognostic information for uterine cancer subjects in the setting of negative lymph nodes.

## 2. Materials and methods

Data for this study was obtained from a large Institutional Review Board approved database of uterine corpus cancer patients treated at MUSC from 1987 through 2012. The current study included patients who underwent surgery for uterine corpus cancer in the most recent 8 year time period (2005–2012). This interval was chosen to minimize the impact of cohort effect on our data analysis. Inclusion criteria were all women with uterine corpus cancer who underwent complete surgical staging (both pelvic and paraaortic lymph node dissection) and had negative lymph nodes. Subjects were excluded if they were incompletely staged, had positive nodes, or their pathology reports did not comment on the presence or absence of LVSI. In addition, subjects were excluded if they had Stage IV disease based upon the much lower five-year survival of Stage IV patients (20.1–25.5%) when compared to Stage I–IIIB (49.9–90.8%) [12].

All subjects underwent total hysterectomy, removal of bilateral adnexae, pelvic and paraaortic lymphadenectomy. Specimens were reviewed by experienced gynecologic pathologists. LVSI was defined as the presence of tumor emboli within endothelium-lined channels but outside the tumor mass. Staging was assigned according to the FIGO 1988 staging guidelines [13]. Adjuvant therapy was administered at the discretion of the treating gynecologic oncologist and involved chemotherapy, pelvic radiation, brachytherapy, or a combination of these treatment modalities.

Clinical and histopathologic data obtained from the charts included the following: age, race, BMI, parity, co-morbidities, histology, stage, grade, lesion size, depth of invasion, presence or absence of LVSI, number of nodes removed, and adjuvant therapy. Uterine cancer type was assigned based upon histology and grade. Date of recurrence, date of death, and cause of death were noted as applicable for each subject.

Simple Cox regression analysis was used to evaluate the associations between the above-mentioned covariates and survival, with recurrence-free survival defined as date of surgery until date of recurrence, and overall survival defined as date of surgery until date of death. Subjects were censored at the date of last contact. A multivariable regression model was then constructed taking into consideration those covariates that were significantly associated with survival by $P$ value $< 0.10$. A similar multivariable regression model which excluded LVSI was created. A C-index was calculated for each model to describe the predictive value of the model [14]. This was done for the model the included LVSI as well as the one that excluded LVSI, for both recurrence-free and overall survival. To obtain a 95% confidence interval for the difference in the C-indices comparing models including and excluding LVSI, a bootstrap approach was used.

Lastly, competing risks analysis was conducted to model time to recurrence [15]. The competing risk was defined as death due to causes other than cancer. Because lesion size was significantly associated with time to recurrence, only subjects who had a documented lesion size in their pathology reports were included in this analysis. The contribution of each covariate to the model was expressed as a hazard ratio with a 95% confidence interval. A $P$ value of $< 0.05$ was considered statistically significant. All data analysis was performed using R version 3.0.2 software [16].

## 3. Results

A total of 489 subjects were diagnosed with uterine cancer during the study period. Of these, 209 were excluded because they did not undergo surgery or because they had incomplete surgical staging (reasons included morbid obesity, advanced disease that was clinically apparent, and/or technical inability to obtain lymph nodes such as in the case of vaginal hysterectomy). Forty-six patients were excluded due to one or more positive lymph nodes. Of the 234 subjects who underwent complete surgical staging and had negative lymph nodes, 15 were excluded due to Stage IV disease and 14 were excluded due to the absence of information regarding LVSI in their surgical pathology reports. This left a total of 205 subjects for evaluation: 24 with LVSI and 181 without LVSI (Fig. 1).

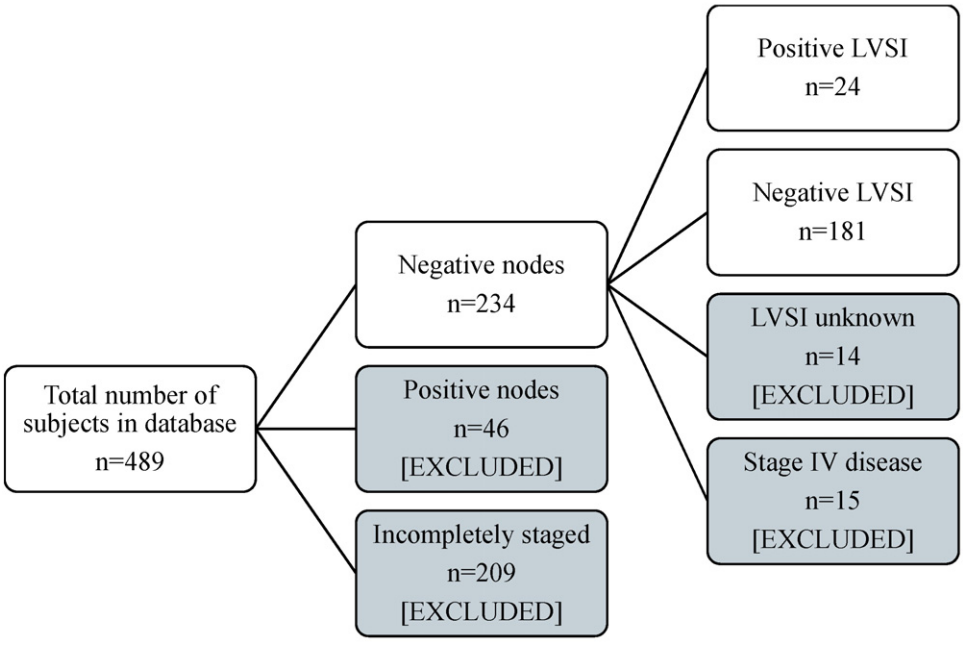


**Fig. 1.** Selection of subjects (N = 205).

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