Elmer Press Original Article J Clin Gynecol Obstet. 2014;3(3):85-92

Does Lower Uterine Segment Involvement in Grade 3 Endometrial Cancer Impact Recurrence Patterns and Patient Outcomes?

Leslie H. Clark[a, b, d], Paola A. Gehrig[a, b], Victoria Bae-Jump[a, b], Jason Franasiak[a], Emily M. Ko[c]

Abstract

Background: The aim of the study was to determine the impact of lower uterine segment (LUS) on progression free survival (PFS), recurrence patterns and outcomes in women with high-grade endometrial cancer.

Methods: A single-institution, retrospective cohort study was performed to evaluate the impact of LUS involvement in women with stage I-III high-grade endometrial cancer diagnosed between January 2005 and September 2010. Clinical and pathology data were collected from electronic medical records. Univariate tests and multivariate Cox modeling were applied.

Results: Of 282 cases, 48.6% (137/282) were LUS-positive. Body mass index, age, hypertension and diabetes did not differ by LUS status. LUS involvement was associated with lymphovascular space invasion (LVSI) (52.9% vs. 30.5%, P < 0.001), deep myometrial invasion (48.9% vs. 24.1%, P < 0.001), and nodal metastases (38.7% vs. 11.6%, P < 0.001). Even after adjusting for obesity, deep myometrial invasion, LVSI, nodal status, stage, histology, and adjuvant therapy, LUS-positive cases had significantly worse PFS (HR 1.83, 95% CI 1.11 - 3.02, P = 0.02). LUS-positive cases recurred more frequently despite adjuvant therapy including radiation, chemotherapy or both. Recurrence patterns did not differ by LUS status (P = 0.22).

Conclusions: LUS involvement in high-grade endometrial cancers is associated with worse PFS independent of other poor prognostic factors. Future studies evaluating volume-directed therapy may improve patient outcomes.

Keywords: Lower uterine segment involvement; Endometrial cancer; High grade; Prognosis; Outcomes

Introduction

Endometrial cancer is the fourth most common cancer in women in the US, and the most common gynecologic malignancy. According to the American Cancer Society, approximately 49,560 new cases will be diagnosed in the US in 2013, with an estimated 8,190 cancer-related deaths [1]. Although approximately 68% of endometrial cancers are diagnosed at an early stage, with overall reassuring prognosis, a subset of these cases with high-grade histology, may behave more aggressively [2]. For example, uterine papillary serous carcinoma is diagnosed in advanced stages approximately 40% of the time, and while this uncommon histologic subtype represents only 10% of endometrial cancer cases, it is responsible for a disproportionate 40% of deaths from this disease [3-5].

In addition to high-grade histology, various pathologic features have been associated with worse prognosis. Stage, lymphovascular space invasion (LVSI), deep myometrial invasion, histologic subtypes and nodal involvement have been associated with increased recurrence risk and cancer-related mortality [6, 7]. More recent investigation has suggested that LUS involvement may be associated with other poor prognostic features such as increased myometrial invasion, LVSI [8], nodal metastases [9], and higher-grade histology [10].

In an unadjusted survival analysis evaluating primary tumor location in 88 patients, Hachisuga et al found no significant difference in outcomes between those women with a tumor located higher in the corpus and those women with tumors located in the LUS [11]. Brown et al found that LUS involvement, when adjusted for other risk factors such as deep myometrial invasion or high-risk histologies, was not independently associated with worse progression free sur-

Manuscript accepted for publication July 31, 2014

[a]Department of Obstetrics and Gynecology, University of North Carolina, Chapel Hill, NC, USA
[b]Division of Gynecologic Oncology, University of North Carolina, Chapel Hill, NC, USA
[c]Division of Gynecologic Oncology at Hospital of the University of Pennsylvania, Philadelphia, PA, USA
[d]Corresponding Author: Leslie Clark, Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, University of North Carolina at Chapel Hill, 170 Manning Drive, CB# 7572, Chapel Hill, NC 27599-7572, USA. Email: leslie.clark@unchealth.unc.edu

doi: http://dx.doi.org/10.14740/jcgo264w

Table 1. Demographic Data for Lower Uterine Segment Positive and Negative Tumors

	LUS-positive (n = 137) (% or SD)	LUS-negative (n = 145) (% or SD)	P value
Age (mean)	65.5 (10.9)	66.8 (10.8)	0.3267
Race			0.099
Caucasian	81 (59.1)	100 (69.0)	
African American	49 (35.8)	35 (24.1)	
Other	7 (5.1)	10 (6.9)	
BMI (mean)	32.5 (8.3)	31.1 (8.2)	0.1905
Overweight-obese	108 (78.8)	109 (75.2)	0.527
Diabetes	34 (24.8)	33 (22.8)	0.685
Hypertension	78 (57.8)	86 (59.7)	0.742
Adjuvant therapy	106 (77.4)	90 (62.1)	0.005
Radiation	90 (65.7)	73 (50.3)	0.021
Chemotherapy	83 (60.6)	68 (46.9)	0.066
Recurrence	53 (38.7)	30 (20.7)	0.001

vival (PFS) or overall survival (OS) in surgically staged node negative patients [12]. In contrast, Lavie et al found a trend for worse PFS (HR 2.4, 95% CI 0.7 - 8.2, P = 0.16) and OS with LUS involvement (HR 1.54, 95% CI 0.82 - 2.91, P = 0.18) in clinical stage I endometrial cancer patients who underwent primary surgical management [13]. In a larger multi-institutional retrospective study where adjustments were made for age, tumor grade, deep invasion, LVSI, lymph node sampling, and post-operative adjuvant radiotherapy, worse OS (HR 2.3, 95% CI 1.3 - 3.9, P = 0.003) was associated with LUS involvement [14]. Additionally, Kizer et al found that LUS involvement increased recurrence (HR 2.27, 95% CI 1.1 - 4.7, P = 0.03) and worsened OS (HR 1.76, 95% CI 1.12 - 2.87, P = 0.01) in women with surgical stage I/II disease [15].

To date, the majority of studies evaluating LUS involvement have focused on the low-grade, endometrioid histology. Simpkins et al evaluated stage I endometrioid adenocarcinomas with LVSI and found recurrence and OS to be significantly associated with LUS involvement [16]. Few studies have focused on high-grade histologies. In a small series of 79 patients with stage I/II serous and clear cell endometrial cancer, LUS involvement, LVSI, and adjuvant radiation were associated with recurrence-free survival and disease-specific survival [17].

The results of the studies performed to date have been conflicting and failed to focus upon those cases with the highest risk histologies. This study sought to determine the relationship of LUS involvement to other clinical-pathologic factors in a large cohort of women with high-grade endometrial cancers limited to pelvic and retroperitoneal disease (i.e. stage I-III), and to evaluate the impact of LUS involvement on endometrial cancer outcomes and patterns of recurrence.

Materials and Methods

Following IRB approval, a single-institution, retrospective cohort analysis was performed, comparing LUS-positive to LUS-negative cases in women with stage I-III, grade 3 endometrial cancer diagnosed between January 1, 2005 and September 30, 2010. Surgeries were performed by gynecologic oncologists via open, laparoscopic or robotic modalities, and retroperitoneal lymph node dissection was performed in all cases where surgically feasible. Thirty-four (12%) patients did not undergo lymph node dissection. Clinical and pathologic data were abstracted from electronic medical records. Pathology reports with a histologic diagnosis of grade 3 endometrioid, papillary serous, clear cell, and carcinosarcoma were included. All pathology diagnoses were reviewed by gynecologic pathologists and at a weekly multidisciplinary tumor board conference. FIGO 2008 staging criteria were

Table 2. Stage and Uterine Characteristics Associated With Lower Uterine Segment Positive and Negative Tumors

	LUS-positive (%)	LUS-negative (%)	P value
Primary stage			< 0.001
I	67 (48.9)	121 (83.5)	
II	20 (14.6)	3 (2.1)	
III	50 (36.5)	21 (14.5)	
Histology			0.148
Endometrioid	42 (30.7)	60 (41.4)	
Serous/clear cell	68 (49.6)	64 (44.1)	
Carcinosarcoma	27 (19.7)	21 (14.5)	
LVSI[a]	72 (52.9)	43 (30.5)	< 0.001
Myometrial invasion > 50%	67 (48.9)	35 (24.1)	< 0.001
Nodal metastases	46 (38.7)	15 (11.6)	< 0.001
Pelvic node +	42 (37.2)	14 (11.2)	
Para-aortic node +	23 (23.5)	7 (6.0)	

[a]Lypmhovascular invasion.

used. LUS involvement was determined based on permanent-section paraffin embedded hematoxilin and eosin histology and captured in the pathology report. Cases without LUS status documented were excluded. The gynecologic pathologists at our institution defined LUS as gross visualization of tumor involvement of the narrowest portion of the uterine canal between the cervical os and uterine fundus. LUS is further defined by confirmation by histologic examination, where tumor involvement is present at the junctional mucosa between endocervical mucinous glands and endometrial glands.

For clinical factors, race was obtained from self-reported information at the time of patient registration. Body mass index (BMI) was obtained from intake height and weight at the preoperative visit. Information on medical comorbidities was collected by the physician at the preoperative consultation. Recurrence data were captured from electronic medical chart review. Recurrence location was defined as vaginal only, pelvic only (excluding the vagina), or distant (beyond the pelvis). OS data were captured from electronic medical records and the social security death index (http://www.genealogybank.com/gbnk/ssdi/?kbid).

Statistical analyses were performed with STATA v.11 using univariate and bivariate analyses with *t*-tests, X2, and log-rank tests. Multivariate regressions were performed by Cox modeling. Interaction terms were tested for covariates deemed significant based on bivariate analysis. Two-sided P values < 0.05 were considered statistically significant.

Results

Two hundred eighty-two cases were identified. This sample population had a mean age of 66.2 years (SD 10.9) and a mean BMI of 31.8 (SD 8.3). Sixty-four percent of the patients were white, 29.8% black, and 6.1% other. More than half of the patients had hypertension (58.2%) and nearly one-quarter (23.8%) had diabetes. Staging distribution included the following: 49.7% stage Ia, 17.0% stage Ib, 8.2% stage II, 3.6% stage IIIa, 0.7% stage IIIb, 10.3% stage IIIc1, and 10.6% stage IIIc2. Uterine serous carcinoma and clear cell carcinomas consisted of the largest proportion of cases (46.8%), followed by endometrioid (36.2%), and carcinosarcoma (17.0%). Uterine factors revealed that 36.2% of cases had deep myometrial invasion, and 40.8% had positive LVSI. One-fifth (21.5%) of cases were positive for nodal disease. The overall recurrence rate was 29.4%.

Of the 282 patients described above, 48.6% (137/282) were LUS-positive. Age and BMI did not differ by LUS status (Table 1). African-Americans consisted of a greater pro-

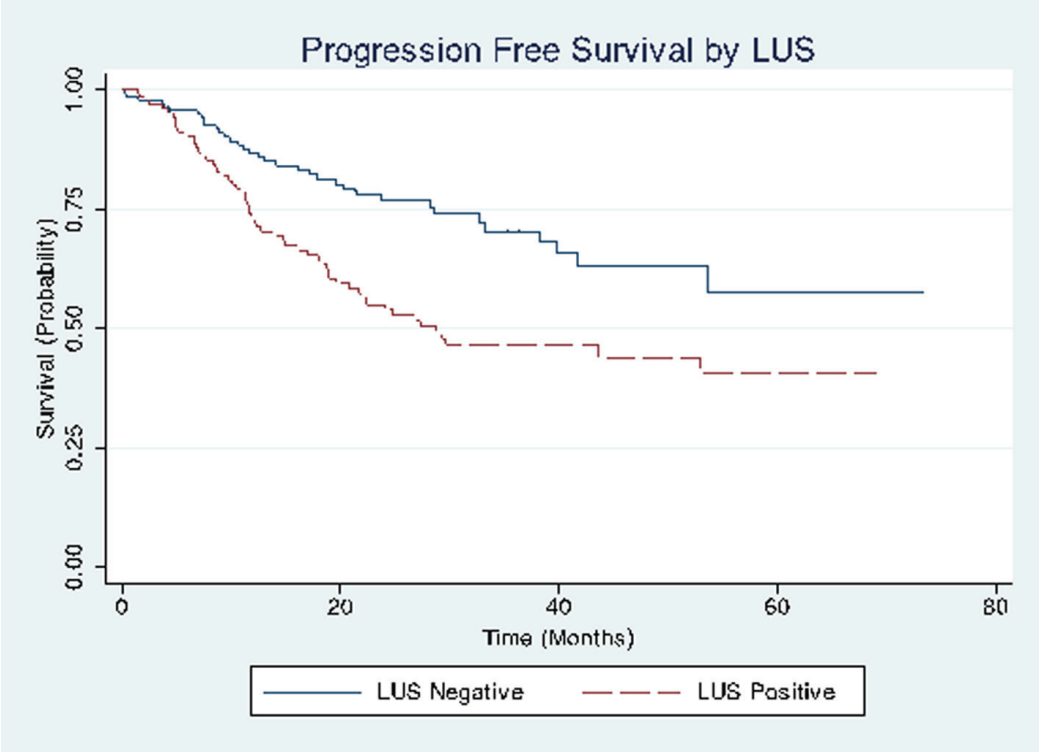

Figure 1. Progression free survival by LUS.

portion of LUS-positive than LUS-negative groups (35.8% vs. 24.1%, P = 0.10). LUS-positive tumors were more likely to be associated with advanced stage (36.5% vs. 14.5% stage III cases, P < 0.001), LVSI (52.9% vs. 30.5%, P < 0.001), deep myometrial invasion (48.9% vs. 24.1%, P < 0.001), and positive lymph nodes (38.7% vs. 11.6%, P < 0.001), as summarized in Table 2. Both pelvic lymph nodes (37.2% vs. 11.2%, P < 0.001) and periaortic lymph nodes (23.5% vs. 6.0%, P < 0.001) were more likely to be positive in LUS-positive tumors. Similar histology was seen in both LUS-positive (endometrioid 41.4%, papillary serous and clear cell 44.1% and carcinosarcoma 14.5%) and LUS-negative tumors (endometrioid 30.7%, papillary serous and clear cell 49.6% and carcinosarcoma 19.7%, P = 0.15), with a higher percentage of endometrioid tumors in LUS-negative group. Due to more advanced stages and an increased risk of nodal disease, LUS-positive group received more adjuvant treatment (77.4% vs. 62.1%, P = 0.005). Specifically they received more adjuvant chemotherapy (60.6% vs. 46.9%, P = 0.07) and more radiation therapy (65.7% vs. 50.3%, P = 0.02).

Despite receiving more adjuvant therapy, women with LUS-positive group had more recurrences (38.7% vs. 20.7%, P = 0.001) and worse PFS than the LUS-negative group, with a median of 16.3 months compared to 21.4 months. As seen in Figure 1, worse PFS was observed in LUS-positive tumors even after adjusting for race, BMI, LVSI, myometrial invasion, stage, and adjuvant treatment (HR 1.83, 95% CI 1.11 - 3.02, P = 0.02). The LUS-positive group also had worse OS (HR 2.18, 95% CI 1.25 - 3.80, P = 0.006) in the unadjusted analysis, with a median of 24.0 versus 25.5 months (Fig. 2). However, this effect was diminished after adjusting for race, BMI, LVSI, myometrial invasion, stage and adjuvant treatment (HR 1.74, 95% CI 0.89 - 3.40, P = 0.10). Within the subset of serous and clear cell histologies, LUS involvement had worse median PFS (18.6 vs. 22.9 months), with three times the likelihood of progression (HR 3.10, 95% CI 1.51 - 6.38, P = 0.002), although the effect was diminished in the adjusted model (HR 1.52, 95% CI 0.63 - 3.70, P = 0.35). Patients with LUS involvement also exhibited worse OS (24.4 vs. 28.7 median months) (HR 2.69, 95% CI 1.31 - 5.52, P = 0.07), although the effect was diminished in the adjusted model (HR 1.25, 95% CI 0.48 - 3.24, P = 0.65).

When further examined by stage and type of adjuvant therapy, stage I patients treated only with chemotherapy (n = 18) had a 50% (6/12) recurrence rate in the LUS-negative group as compared to 33% (2/6) in the LUS-positive group (P = 0.44). For stage I patients who received only radiation (n = 34), the LUS-positive group had slightly more recurrences at 29% (4/14) versus 15% (3/20), P = 0.30. Those who received both chemotherapy and radiation (n = 57) also showed a trend towards higher rates of recurrence in the LUS-positive group at 29% (6/21) as compared to 14% in the LUS-negative group (5/36), P = 0.16. Stage II had the smallest number of patients in general (n = 23), and there

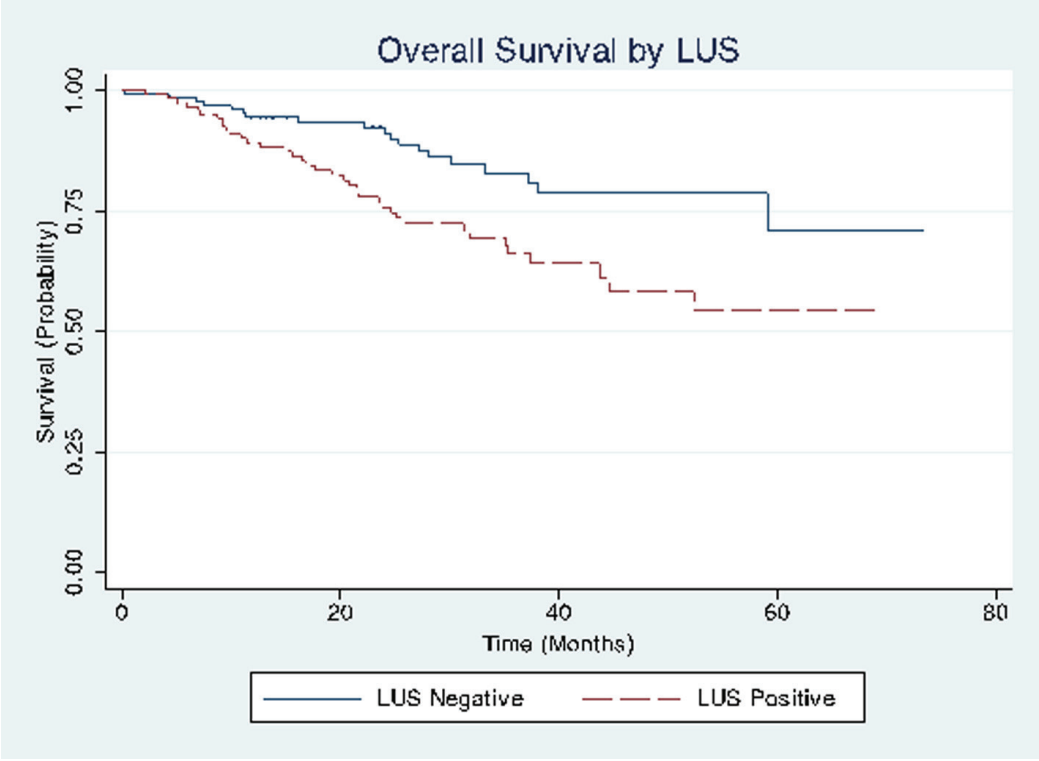

Figure 2. Overall survival by LUS.

were no recurrences seen in the LUS-negative group. Within the LUS-positive stage II tumors, one patient who received only chemotherapy recurred, one patient who received no adjuvant treatment recurred, 25% (2/8) who received only radiation recurred, and 40% (4/10) treated with both chemotherapy and XRT recurred for an overall recurrence rate of 34% (8/23). Evaluation of stage III patients treated with chemotherapy alone (n= 13) revealed that the LUS-positive group had more recurrences at 75% (6/8) than the LUS-negative group with 20% (1/5), P = 0.09. Only two patients received radiation alone, and no recurrence was noted at the time of analysis. Of those that received chemotherapy and radiation (n = 49), the LUS-positive group had more recurrences at 53% (19/36) versus the LUS-negative group with 23% (3/13), P = 0.06.

There was no difference in patterns of recurrence between LUS-positive and LUS-negative tumors (Table 3). Within the LUS-positive group, 22.6% of recurrences occurred in the vagina, 9.4% in the pelvis, and 67.9% in the abdomen or distantly. Tumors without LUS involvement had 20% vaginal cuff recurrences, 23.3% pelvic recurrences, and 56.7% distant recurrences (P = 0.22).

Discussion

LUS involvement in endometrial cancer appears to be an independent risk factor for increased risk of recurrence and worse PFS in grade 3 endometrial cancers, even after controlling for high-risk factors such as race, myometrial invasion, LVSI and histology [18]. Despite receiving more adjuvant treatment (77.4% vs. 62.1%), LUS-positive patients had worse PFS (HR 1.83, P = 0.02). In contrast to earlier studies that did not find a significant association between LUS involvement possibly due to limited sample size, our study shows that LUS may be an independent prognostic factor associated with worse prognosis.

Our study confirms that LUS involvement is associated with other poor prognostic factors including deep myometrial invasion (48.9% vs. 24.1%, P < 0.001), LVSI (52.9% vs. 30.5%, P < 0.001), and nodal metastases (38.7% vs. 11.6%, P < 0.001) similar to previously published studies [9, 13, 15]. In their analysis, which was limited to stage I and II tumors, Kizer et al found that 30% of LUS-positive cases had LVSI compared to only 16.3% in LUS-negative cases (P = 0.01). However, they did not evaluate myometrial invasion or nodal status [15]. Madom et al found that LUS-positive cases had substantially more LVSI (39% vs. 4.3%, P < 0.01), positive nodes (25% vs. 8%, P < 0.01), and deep myometrial invasion (33.6% vs. 7.4%, P < 0.01) [9] and Lavie et al also reported more deep myometrial invasion in LUS-positive cases (34% vs. 14%, P = 0.003) [13].

LUS involvement has also been shown to be more frequently associated with type II histologies [12]. Sixty-nine

Table 3. Location of Recurrence in Lower Uterine Segment Positive and Negative Tumors

	LUS-positive (%)	LUS-negative (%)	P value
Vaginal recurrence	12 (22.6)	6 (20.0)	0.223
Pelvic recurrence	5 (9.4)	7 (23.3)	
Extrapelvic recurrence	36 (67.9)	17 (56.7)	

percent of LUS-positive tumors consisted of high-risk histologies including serous, clear cell and carcinosarcoma compared to 59% in LUS-negative tumors. Interestingly, when limiting our analysis of grade 3 tumors to type II histologies (clear cell and papillary serous, n = 132), there also appeared to be worse PFS and OS in LUS-positive patients. However, after controlling for stage, myometrial invasion, nodal status and adjuvant treatment, LUS-positive tumors were associated with a smaller effect on PFS (HR 1.52, 95% CI 0.63 - 3.70, P = 0.35) and OS (HR 1.25, 95% CI 0.48 - 3.24, P = 0.65). In both cases, the smaller sample size likely precluded finding statistical significance. In light of the association of LUS involvement with not only grade 3 endometrioid cancers, but also the more aggressive histologic subtypes, it appears that tumors with LUS involvement may behave more aggressively than those with the same risk factors and no LUS involvement.

Furthermore, exploration of recurrence frequency by treatment modality in patients of the same stage, revealed more recurrences in those that were LUS-positive. Within the subset of patients with stage I disease, recurrence was seen more frequently in LUS-positive patients who had radiation alone (29% vs. 15%) or combination therapy (29% vs. 14%). Interestingly, those who had only chemotherapy alone fared worse in the LUS-negative group (50% vs. 33%) than the LUS-positive group; of course, it is difficult to draw conclusions based on this subset of only 18 patients. Within stage III patients, recurrences were also more common in LUS-positive patients, whether they received only adjuvant chemotherapy (75% vs. 20%) or both radiation and chemotherapy (53% vs. 23%). Small sample size precluded finding statistical significance in these comparisons; however, further analyses are warranted to understand these interesting trends associated with LUS involvement, particularly in those of similar stage who received systemic therapy.

As much as LUS involvement appears to be an independent risk factor for recurrence, it does not appear to be associated with the location of recurrence. Previous studies have not commented on recurrence location. In our study of women with high-grade endometrial cancer, the distribution of recurrences did not differ between LUS-positive and LUS-negative groups. The majority of recurrences occurred in extra pelvic locations (67.9% of LUS-positive and 56.7% of LUS-negative). In both groups, one-fifth of the patients recurred at the vaginal cuff; these cases did not appear to differ by histology, stage, or radiation received. Limited numbers in these subgroups of patients precluded further statistical analysis. However, given that the LUS lies in close proximity to the vaginal apex and uterine vessels and lymphatics, the question remains whether patients with tumors located in the LUS would benefit from adjuvant radiation in addition to chemotherapy, or whether omission of radiation would result in similar local-regional vaginal and pelvic recurrence rates. While it would likely be inefficient to design a trial specifically to answer this question, one may be able to derive this information based on secondary analysis of the GOG 249 which is a phase III randomized controlled trial comparing adjuvant chemoradiation versus chemotherapy alone for women with early stage, high-risk endometrial cancer. In either case, since the majority of recurrences in the LUS involvement were distant, adjuvant chemotherapy should be considered, particularly in patients with high-grade histology who otherwise would not have received adjuvant treatment given lack of meeting criteria for other high-risk prognostic features [5, 17, 19, 20].

There are several strengths to our study. All patients were treated by a gynecologic oncologist from a single institution, which provided uniformity of care. All cases were read by dedicated gynecologic pathologists and reviewed at a weekly tumor board conference. Limitations of this study included the risk of bias related to all retrospective studies, including the inability to draw conclusions regarding inherent patient differences and physician preferences that may have affected surgical and medical treatment decisions. It may be difficult to generalize these findings to other populations. Additionally, limited follow-up time as well as loss to follow-up could lead to missing recurrence data.

Conclusion

Our study contributes to understanding the impact of LUS involvement in high-grade endometrial tumors, which has

been infrequently reported upon in previously published studies. LUS involvement appears to have a significant prognostic role both in early endometrial cancers as seen in previous studies, as well as in more advanced high-grade cancers, as confirmed by our analysis. The shorter PFS seen in patients receiving adjuvant treatment is worrisome. Further consideration should be given towards use of systemic adjuvant therapy in high-grade endometrial cancer patients with LUS involvement in situations where they may not otherwise have received such treatment. Additionally, strategies for improving adjuvant therapy are needed particularly given the worse outcomes seen in those with LUS involvement who already have received adjuvant therapy. The results from GOG 249 may assist us in evaluating the role of radiation therapy in women with early stage, high-risk histologies and could be stratified for uterine tumor location. Similarly, GOG 258, which is a randomized prospective trial of chemotherapy versus chemoradiation followed by chemotherapy, may assist us in evaluating the role of multimodality therapy in women with advanced stage, optimally cytoreduced endometrial cancer. After stratification for tumor location, the risk of recurrence, patterns of recurrence and OS could be further evaluated to better determine the predictive value of LUS on disease outcomes.

Conflicts of Interest

The author(s) declare that they have no conflicts of interest to disclose.

References

1. American Cancer Society. Cancer Facts and Figures 2013. Atlanta, Ga: American Cancer Society; 2013.
2. Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2009 (Vintage 2009 Populations), National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2009_pops09/, based on November 2011 SEER data submission, posted to the SEER web site, 2012.
3. Fader AN, Drake RD, O'Malley DM, Gibbons HE, Huh WK, Havrilesky LJ, Gehrig PA, et al. Platinum/taxane-based chemotherapy with or without radiation therapy favorably impacts survival outcomes in stage I uterine papillary serous carcinoma. Cancer. 2009;115(10):2119-2127.
4. Thomas MB, Mariani A, Cliby WA, Keeney GA, Podratz KC, Dowdy SC. Role of systematic lymphadenectomy and adjuvant therapy in stage I uterine papillary serous carcinoma. Gynecol Oncol. 2007;107(2):186-189.
5. Havrilesky LJ, Secord AA, Bae-Jump V, Ayeni T, Calingaert B, Clarke-Pearson DL, Berchuck A, et al. Outcomes in surgical stage I uterine papillary serous carcinoma. Gynecol Oncol. 2007;105(3):677-682.
6. Guntupalli SR, Zighelboim I, Kizer NT, Zhang Q, Powell MA, Thaker PH, Goodfellow PJ, et al. Lymphovascular space invasion is an independent risk factor for nodal disease and poor outcomes in endometrioid endometrial cancer. Gynecol Oncol. 2012;124(1):31-35.
7. Creasman WT, Odicino F, Maisonneuve P, Quinn MA, Beller U, Benedet JL, Heintz AP, et al. Carcinoma of the corpus uteri. FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer. Int J Gynaecol Obstet. 2006;95(Suppl 1):S105-143.
8. Dilek S, Dede M, Gezginc K, Yenen MC, Goktolga U, Ulutin HC, Deveci MS, et al. Does the localisation of tumour at stage I endometrial endometrioid adenocarcinoma have an impact on invasion of the tumour and individualisation of the surgical procedure? Eur J Gynaecol Oncol. 2008;29(2):138-140.
9. Madom LM, Brown AK, Lui F, Moore RG, Granai CO, Disilvestro PA. Lower uterine segment involvement as a predictor for lymph node spread in endometrial carcinoma. Gynecol Oncol. 2007;107(1):75-78.
10. Hachisuga T, Kaku T, Enjoji M. Carcinoma of the lower uterine segment. Clinicopathologic analysis of 12 cases. Int J Gynecol Pathol. 1989;8(1):26-35.
11. Hachisuga T, Fukuda K, Iwasaka T, Hirakawa T, Kawarabayashi T, Tsuneyoshi M. Endometrioid adenocarcinomas of the uterine corpus in women younger than 50 years of age can be divided into two distinct clinical and pathologic entities based on anatomic location. Cancer. 2001;92(10):2578-2584.
12. Brown AK, Madom L, Moore R, Granai CO, DiSilvestro P. The prognostic significance of lower uterine segment involvement in surgically staged endometrial cancer patients with negative nodes. Gynecol Oncol. 2007;105(1):55-58.
13. Lavie O, Uriev L, Gdalevich M, Barak F, Peer G, Auslender R, Anteby E, et al. The outcome of patients with stage I endometrial cancer involving the lower uterine segment. Int J Gynecol Cancer. 2008;18(5):1079-1083.
14. Gemer O, Gdalevich M, Voldarsky M, Barak F, Ben Arie A, Schneider D, Levy T, et al. Lower uterine segment involvement is associated with adverse outcome in patients with stage I endometroid endometrial cancer: results of a multicenter study. Eur J Surg Oncol. 2009;35(8):865-869.
15. Kizer NT, Gao F, Guntupalli S, Thaker PH, Powell MA, Goodfellow PJ, Mutch DG, et al. Lower uterine segment involvement is associated with poor outcomes in early-stage endometrioid endometrial carcinoma. Ann Surg Oncol. 2011;18(5):1419-1424.
16. Simpkins F, Papadia A, Kunos C, Michener C, Frasure

H, AbuShahin F, Mariani A, et al. Patterns of recurrence in stage I endometrioid endometrial adenocarcinoma with lymphovascular space invasion. Int J Gynecol Cancer. 2013;23(1):98-104.
17. Yechieli R, Rasool N, Robbins JR, Cogan CM, Elshaikh MA. Adjuvant radiation therapy for patients with type II endometrial carcinoma: impact on tumor recurrence and survival. Int J Gynecol Cancer. 2013;23(4):763-768.
18. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin. 2013;63(1):11-30.
19. Cantrell LA, Havrilesky L, Moore DT, O'Malley D, Liotta M, Secord AA, Nagel CI, et al. A multi-institutional cohort study of adjuvant therapy in stage I-II uterine carcinosarcoma. Gynecol Oncol. 2012;127(1):22-26.
20. Robbins JR, Siddiqui MS, Al-Wahab Z, Laser B, Lu M, Ali-Fehmi R, Munkarah A, et al. Clinical outcomes of adjuvant chemotherapy and vaginal brachytherapy with or without pelvic radiation for surgical stage I-II uterine serous carcinoma. Eur J Gynaecol Oncol. 2012;33(5):449-454.