



Full length article

The impact of lymphadenectomy on survival endpoints in women with early stage uterine endometrioid carcinoma: A matched analysis



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ABSTRACT

Objectives: The role of pelvic lymphadenectomy (LA) in women with stage I endometrial carcinoma (EC) is controversial. The objective of this study is to investigate the prognostic impact of LA on survival endpoints in matched cohorts of women with stage I EC solely of endometrioid histology. Survival endpoints included recurrence-free (RFS), disease-specific (DSS) and overall survival (OS).

Methods and materials: Patients with FIGO stage I EC who underwent hysterectomy with LA as part of their surgical staging between 1/1990 and 6/2015 were matched to a similar group that underwent hysterectomy without lymphadenectomy (NLA), based on stage, grade and adjuvant management. Univariate and multivariate modeling with Cox regression analysis was carried out for predictors of survival endpoints.

Results: 870 women constituted the study cohort (435 in each group). Median number of dissected lymph node in the LA group was 9 (range, 5–75). There was no statistically significant difference between the two groups in regards to 5-year OS (87.2% for LA vs. 91.7% for NLA) ($p=0.36$), DSS 97.7% vs. 98% ($p=0.54$) and RFS (93.7% vs. 90% ($p=0.08$), respectively. Lymphadenectomy was not a predictor of any of the studied survival endpoints. On multivariate analysis for the entire cohort, older age, deep myometrial invasion and higher tumor grade were predictors of worse RFS. For DSS, higher tumor grade, lower uterine segment (LUS) involvement and FIGO stage IB were significant predictors of worse outcome. For OS, older age and LUS involvement were the only two independent predictors for shorter OS.

Conclusions: After matching for FIGO stage, grade and adjuvant management, it appears that lymphadenectomy in women with stage I EC does not impact survival endpoints.

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Introduction

Endometrial cancer (EC) is the most common gynecological malignancy in the United States, with about 54,870 new cases and 10,170 deaths expected in 2015 [1]. More than 70% of the patients present with early International Federation of Gynecology and Obstetrics (FIGO) stage I with an excellent 5-year survival rate of over 90% [2]. Some investigators estimate lymphatics spread in women with stage I EC to range from 7 to 13% [3,4].

Surgical staging with hysterectomy is the cornerstone of the management of women with early stage EC [3]. Approaches for evaluating pelvic and para-aortic lymph nodes (LN) are

controversial and may include palpation and removal of suspicious enlarged LN, LN sampling that entails dissection of few representative LN from multiple pelvic sub sites and systemic lymphadenectomy (LA) with the removal of all LN in the pelvic region, in addition to the evolving role of sentinel LN sampling [5,6]. Nevertheless, exact sites, number and appearance of the so-called suspicious LN are all matters of controversy that contributed to different guidelines for LN evaluation, especially for early stage EC [3,7].

Two prospective randomized studies [8,9] in addition to a multitude of observational studies [10–13] showed no therapeutic impact of LA on overall survival in women with apparent FIGO stage I endometrial carcinoma. On the contrary, many authors have reported survival benefits for FIGO stage I, either for all women with stage I disease [14–16] or only for women with grade 3 tumors and/or more than 50% myometrial involvement [17–20]. In a meta-analysis reported by Kim et al. with 16,995 patients, the authors

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concluded that systemic LA defined as removal of >10 LN has a significant impact on overall survival (OS) only in women with intermediate/high risk features such as high grade, deep myometrial invasion, as well as non-endometrioid histopathological types [21].

While useful, the two important randomized studies were hampered by study design limitations, such as uneven use of adjuvant therapies [8], allowing the dissection of suspicious bulky LN in the no LA arms and inclusion of non-endometrioid histological types [8,9]. In fact, 8% of the patients who were randomized to the LA arm in the ASTEC trial had no LN harvested and 5% of the no LA arm had some LN removed [8]. Other study limitations in some of the observational studies are the inclusion of patients with all FIGO stages [9,11,12,15,20,22,23], non-endometrioid histological types [15,19,22], uneven distribution of stages and grades between study groups [16,20,22] and lack of information and details of adjuvant management, if any [10,17,23].

In light of the ongoing debate in regards to the therapeutic role of lymphadenectomy in women with early stage EC, we sought to investigate the impact of lymphadenectomy on survival endpoints in a well-balanced cohort of patients with 2009 FIGO stage I endometrial carcinoma solely of endometrioid histology. We used a matched pair analysis methodology to control for other prognostic factors: mainly FIGO stage, grade and adjuvant management.

Methods

After obtaining Institutional Review Board approval, we examined our prospectively-maintained database of all patients with uterine cancer at our institution. We identified 1257 women who underwent hysterectomy for 2009 FIGO stage I endometrial carcinoma between January 1990 and June 2015.

All patients underwent simple hysterectomy, salpingo-oophorectomy, with or without lymphadenectomy (LA) and peritoneal

cytology examination. To ensure a uniform study cohort, only patients with endometrioid histology were included. Patients were followed up every 2–6 months in the first 2–3 years post hysterectomy and then yearly thereafter, or as clinically indicated.

Two groups were created; the first consisted of 435 women who had no lymphadenectomy (NLA) and the second consisted of 822 women who had lymphadenectomy (LA). The 435 women in the NLA group were then matched with 435 women in the LA group based on 2009 FIGO stage (IA or IB), tumor grade and the type of adjuvant management received (observation, vaginal brachytherapy (VB) and/or pelvic external beam radiation treatment (EBRT) (1:1 match). Once a patient in the lymphadenectomy arm was matched, she was removed from the potential match pool for consideration for future patients with no lymphadenectomy, thereby ensuring that each patient is unique. All matching was done blind to patient's outcome. This resulted in two balanced groups, each with 435 patients.

The two matched groups were then compared with regard to the patients' demographics, tumor characteristics, risk category, treatments, recurrence pattern and survival endpoints. Survival endpoints included recurrence-free (RFS), disease-specific (DSS) and overall survival (OS). In addition to patient demographics, the following prognostic factors were assessed: tumor grade, FIGO stage, lymphovascular space invasion (LVSI), lower uterine segment involvement (LUS), total number of lymph nodes resected, number of dissected pelvic and para-aortic lymph nodes, and status of peritoneal cytology, if assessed.

Kaplan–Meier plots were generated for each group for RFS, DSS and OS. The survival probabilities were calculated at 5 years from the date of hysterectomy and compared using log-rank *p*-values. Univariate comparisons were performed using Wilcoxon rank-sum and Fisher's exact tests. Cox regression model was used for multivariate analysis. Manual stepwise selection was used to arrive at each multivariable model with entry criteria of *p* < 0.1 and stay criteria of *p* < 0.05. A two-sided *p*-value < 0.05 was considered

Table 1
Patient characteristics of the study cohort of 870 patients with 2009 FIGO stage I uterine endometrioid carcinoma.

Variable	Category	Lymphadenectomy (N = 435)	No lymphadenectomy (N = 435)	<i>p</i> -value
Median age in years		60 (range, 32–91)	60 (range, 31–91)	0.67
Median follow-up in months		54 (range, 11–302)	47 (range, 11–220)	0.07
Race	Caucasian	330 (76%)	335 (77%)	0.76
	African American	88 (20%)	87 (20%)	
	Other	17 (4%)	13 (3%)	
Median body mass index (BMI)		34.5 (range 17.8–68.6)	35.4 (range 18.4–71.3)	0.45
Tumor FIGO ^a Grade	Grade 1	371 (85%)	371 (85%)	>.99
	Grade 2	55 (13%)	55 (13%)	
	Grade 3	9 (2%)	9 (2%)	
Median percentage of Myometrial invasion (%)		20% (range 0–100%)	10% (range 0–100%)	0.20
2009 FIGO Stage	IA	394 (91%)	394 (91%)	>.99
	IB	41 (9%)	41 (9%)	
Lymphovascular space invasion	Yes	21 (5%)	28 (6%)	0.30
Lower Uterine Segment involvement	Yes	63 (14%)	33 (8%)	0.01
Peritoneal Cytology	Negative	411 (94%)	345 (79%)	<0.001
	Positive	5 (1%)	9 (2%)	
	Not performed	19 (4%)	81 (19%)	
Median number of LNs ^b dissected		9 (range, 5–75)	N/A	<0.001
Median number of Pelvic LNs ^b dissected		9 (range, 5–43)	N/A	<0.001
Median number of para-aortic LNs dissected		2 (range 0–32)	N/A	<0.001
Type of adjuvant management	Observation	389 (89%)	389 (89%)	>0.99
	VB ^d	29 (7%)	29 (7%)	
	Pelvic EBRT ^c	17 (4%)	17 (4%)	
Tumor recurrence	Yes	23 (5%)	23 (7%)	0.32
- Vaginal only		14 (61%)	19 (63%)	0.73
- Pelvic only		1 (4%)	2 (7%)	0.56
- Extra pelvic		8 (35%)	9 (30%)	0.78
Uterine cancer deaths		9 (2%)	9 (2%)	>0.99

^aInternational Federation of Gynecology and Obstetrics. ^bLymph nodes. ^cvaginal brachytherapy. ^dexternal beam radiation treatment.

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