



Prognostic impact of lymphadenectomy in uterine clear cell carcinoma

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Objective: The aim of this study was to estimate the survival impact of lymphadenectomy in patients diagnosed with uterine clear cell cancer (UCCC).

Methods: Patients with a diagnosis of UCCC were identified from Surveillance, Epidemiology, and End Results (SEER) program from 1988 to 2007. Only surgically treated patients were included. Statistical analysis using Student t-test, Kaplan-Meier survival methods, and Cox proportional hazard regression were performed.

Results: One thousand three hundred eighty-five patients met the inclusion criteria; 955 patients (68.9%) underwent lymphadenectomy. Older patients (≥ 65) were less likely to undergo lymphadenectomy compared with their younger cohorts (64.3% vs. 75.9%, $p < 0.001$). The prevalence of nodal metastasis was 24.8%. Out of 724 women who had disease clinically confined to the uterus and underwent lymphadenectomy, 123 (17%) were found to have nodal metastasis. Lymphadenectomy was associated with improved survival. Patients who underwent lymphadenectomy were 39% (hazard ratio [HR], 0.61; 95% confidence interval [CI], 0.52 to 0.72; $p < 0.001$) less likely to die than patient who did not have the procedure. Moreover, more extensive lymphadenectomy correlated positively with survival. Compared to patients with 0 nodes removed, patients with more extensive lymphadenectomy (1 to 10 and > 10 nodes removed) were 32% (HR, 0.68; 95% CI, 0.56 to 0.83; $p < 0.001$) and 47% (HR, 0.53; 95% CI, 0.43 to 0.65; $p < 0.001$) less likely to die, respectively.

Conclusion: The extent of lymphadenectomy is associated with an improved survival of patients diagnosed with UCCC.

Keywords: Endometrial Neoplasms; Lymph Node Excision; Retrospective Studies; Survival Rate

INTRODUCTION

Endometrial cancer is the most common gynecologic malignancy in the United States. According to the latest statistics from the National Cancer Institute, it was estimated that 52,630 women will be diagnosed with endometrial cancer in 2014, and 8,590 will die of the disease [1]. Histologic cell type

has been recognized as an important prognostic factor that affect outcome in endometrial cancer.

Uterine clear cell cancer (UCCC) is a distinct histologic subtype of endometrial cancer that was first described in 1957 and further studied by Silverberg and De Giorgi [2], Kurman and Scully [3], and Kay [4]. UCCC accounts for 1% to 6% of all endometrial cancers [5-8]. Many studies have suggested the aggressive behavior and poor prognosis associated with UCCC [3,7-11]. UCCC has high propensity for extrauterine spread and high recurrence risk outside the pelvis especially upper abdomen and distant sites in two thirds of UCCC patients with recurrence [3,9,12]. Moreover, 40% to 50% of patients with disease clinically confined to the uterus were found to

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have extrauterine disease at the time of surgical staging [7,13]. The survival of patients with UCCC is poor and even lower than patients with grade 3 endometrioid endometrial cancer; however, UCCC may behave less aggressively than uterine serous cancer especially when the disease is confined to the uterus [7,9,11-14].

Because of their aggressive behavior and high rate of occult extrauterine spread, comprehensive surgical staging including lymphadenectomy is recommended for patients with clear cell endometrial cancer regardless of tumor size or depth of myometrial invasion [7,13]. In fact, women presumed to have early stage UCCC are often upstaged at the time of surgical staging. Matthews et al. [11] reported a 17% incidence of lymph node metastasis in patients diagnosed with UCCC. Similarly, a recent study by Thomas et al. [13] found that 20% of patients with disease clinically confined to the uterus had positive lymph nodes. However, because of its rarity previous reports on UCCC are limited by small numbers of patients, often combined with uterine serous cancer and did not elucidate the role of lymphadenectomy with surgical staging. Therefore, the objective of this study was to investigate the association of lymphadenectomy with survival in women diagnosed with UCCC using the population database of the Surveillance, Epidemiology, and End Results (SEER) program.

MATERIALS AND METHODS

Subjects with a diagnosis of UCCC were identified using SEER data from 1988 to 2007 [15]. All patients with known lymphadenectomy status at the time of primary surgical treatment were included. Patients who underwent lymphadenectomy were grouped in lymph node dissection+ (LND+) category whereas those who did not have lymphadenectomy were grouped in LND (-) category. The inclusion criteria were: surgical treatment with hysterectomy with or without lymphadenectomy, clear cell histology, known age, and active follow-up. Patients with histology types other than clear cell histology were excluded. Other exclusion criteria were patients with unknown age, unknown status of lymphadenectomy, absence of surgical treatment, and a diagnosis by autopsy or death certificate. Stage I/II who had lymphadenectomy, and stage III/IV in this manuscript represent the actual FIGO stage. In patients with stage I and II disease who did not have lymphadenectomy, the stage is determined based on surgical and pathologic factors available with no information on lymph node status. To assess the impact of the extent of lymphadenectomy, all the patients who underwent lymphadenectomy were divided into two groups based on

the number of lymph nodes reported (1 to 10 nodes and >10 nodes). Demographic, clinicopathologic, treatment, and survival information were extracted using the “Case Listing” option of the SEER Stat software. No record of chemotherapy appears in SEER database.

Table 1. Key variables in patients with uterine clear cell cancer by the status of lymphadenectomy (n=1,385)

Variable	No LND (%) (n=430)	LND (%) (n=955)	p-value
Age (yr)			<0.001
Median age	71	67	
<65	133 (24.1)	420 (76.0)	
≥65	297 (35.7)	535 (64.3)	
Race			0.474
White	347 (32.0)	737 (68.0)	
African American	49 (28.8)	121 (71.2)	
Asian	31 (26.3)	87 (73.7)	
Other	3 (23.1)	10 (76.9)	
Stage			<0.001
I	226 (32.3)	473 (67.7)	
II	48 (27.3)	128 (72.7)	
III	38 (13.2)	251 (86.9)	
IV	97 (49.5)	99 (50.5)	
Unknown	21 (84.0)	4 (16.0)	
Stage			<0.001
Early (I–II)	274 (31.3)	601 (68.7)	
Late (III–IV)	135 (27.8)	350 (72.2)	
Radiation			<0.001
No	290 (38.0)	473 (62.0)	
Yes	131 (21.9)	466 (78.1)	
Unknown	9 (36.0)	16 (64.0)	
Extent (node)			
0	430	-	
1–10	-	376 (39.4)	
>10	-	482 (50.5)	
Unknown number	-	97 (10.2)	
No. of positive nodes			
1	-	91 (38.4)	
2–5	-	81 (34.2)	
>5	-	44 (18.6)	
Unknown number	-	21 (8.9)	
Status			<0.001
Dead	259 (60.2)	378 (39.6)	
Alive	171 (39.8)	577 (60.4)	

LND, lymph node dissection.

Associations between categorical covariates were assessed using chi-square tests. Group differences in continuous measures were assessed using Student t-test. Survival curves were estimated using the Kaplan-Meier method. Comparisons in survival among different groups were made using log rank statistics. Cox proportional hazard regression was used to adjust for age, race, stage, extent of lymphadenectomy and adjuvant radiation therapy. All p-values are reported as raw values for single comparisons and a p-value of <0.05 was considered statistically significant. STATA 10.0 program (StataCorp, College Station, TX, USA) was used for the analysis of the data.

RESULTS

A total of 1,385 patients met the inclusion criteria. Nine hundred fifty-five (68.95%) had lymphadenectomy whereas 430 (31.05%) did not. Of the 955 patients who had lymphadenectomy, 237 (24.8%) had positive nodes. The median number of nodes recovered was 13 (range, 1 to 89). For patients with positive nodes, the median number of positive nodes was 2 (range, 1 to 38) and the median number of total nodes removed was 12 (range, 1 to 76). Patient characteristics are listed in **Table 1**.

The median age of the lymphadenectomy group was 67 years compared with 71 years for those who did not have lymphadenectomy (p<0.001). Younger women (<65 years) were more likely to have lymphadenectomy compared with the older group (≥65 years; 75.95% vs. 64.30%, p<0.001). There was no significant difference in performing lymphadenectomy among all racial groups; however, African American women were more likely to have positive lymph nodes than white women (40% vs. 23%, p<0.001). Almost two thirds of patients

(875 or 63.17%) presented with disease confined to the uterus (stage I and II).

Among 724 patients with disease clinically confined to the uterus who underwent lymphadenectomy, 123 (17%) were upstaged due to nodal metastasis. African American women with clinical early stage UCCC were more likely to have nodal metastasis compared with their white counterparts (31% vs. 15%, respectively, p<0.001). There was no significant difference in the rate of nodal metastasis among younger (<65) and older women (≥65) (16% vs. 18%, respectively, p=0.5).

Overall 5-year survival was significantly higher for lymphadenectomy group compared to the group who did not have the procedure (62% vs. 48%, p<0.001) (**Fig. 1A**). Higher survival rates for the lymphadenectomy group were seen in early stage (77% vs. 61%, p<0.001) (**Fig. 1B**) as well as advanced stage disease (35% vs. 18%, p<0.001). In a multivariate analysis including age, race, stage, extent of lymphadenectomy and adjuvant radiation therapy, women who underwent lymphadenectomy were 39% (hazard ratio [HR], 0.61; 95% confidence interval [CI], 0.52 to 0.72; p<0.001) less likely to die than women who did not have lymphadenectomy. Similarly, women with early stage disease in the lymphadenectomy group were 38% (HR, 0.62; 95% CI, 0.49 to 0.77; p<0.001) less likely to die compared with their counterparts who underwent no lymphadenectomy.

The number of lymph nodes removed had a significant impact on the 5-year survival rates (48% in patients with no lymph nodes, 55% in those with 1 to 10 nodes, 67% in those >10 nodes, p<0.001) (**Table 2, Fig. 2A**). These data were consistent when included only patients with early stage (I to II) disease (p<0.001) (**Fig. 2B**). Furthermore, the extent of lymphadenectomy positively correlated with 5-year survival in patients with pathologically negative nodes (64% vs. 75%

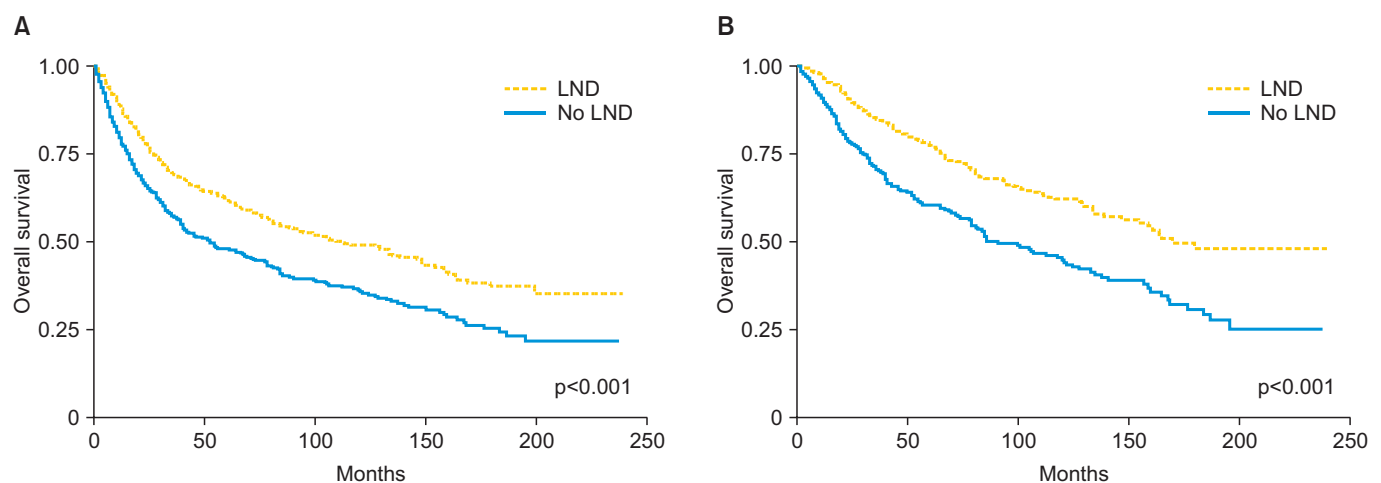


Fig. 1. Overall survival based on lymph node dissection (LND) in uterine clear cell cancer (A) and early stage uterine clear cell cancer (B).

Table 2. Five-year survival for uterine clear cell cancer based on the extent of lymphadenectomy and clinicopathologic characteristics (n=1,288)

Variable	Percentage (95% confidence interval)			Log rank
	No lymphadenectomy (n=430)	1–10 nodes (n=376)	>10 nodes (n=482)	
Overall	48 (43–53)	55 (49–61)	67 (62–72)	<0.001
Age (yr)				
<65	63 (54–71)	70 (61–78)	77 (70–83)	0.19
≥65	42 (36–48)	46 (39–53)	57 (49–64)	<0.001
Stage				
Early (I–II)	61 (54–66)	71 (63–77)	80 (74–84)	<0.001
Late (III–IV)	18 (12–26)	32 (24–41)	39 (30–48)	<0.001
Race				
White	51 (45–56)	57 (51–63)	67 (61–72)	<0.001
African American	32 (19–46)	45 (30–58)	58 (39–73)	0.039
Asian	48 (28–65)	60 (38–76)	73 (54–85)	0.055

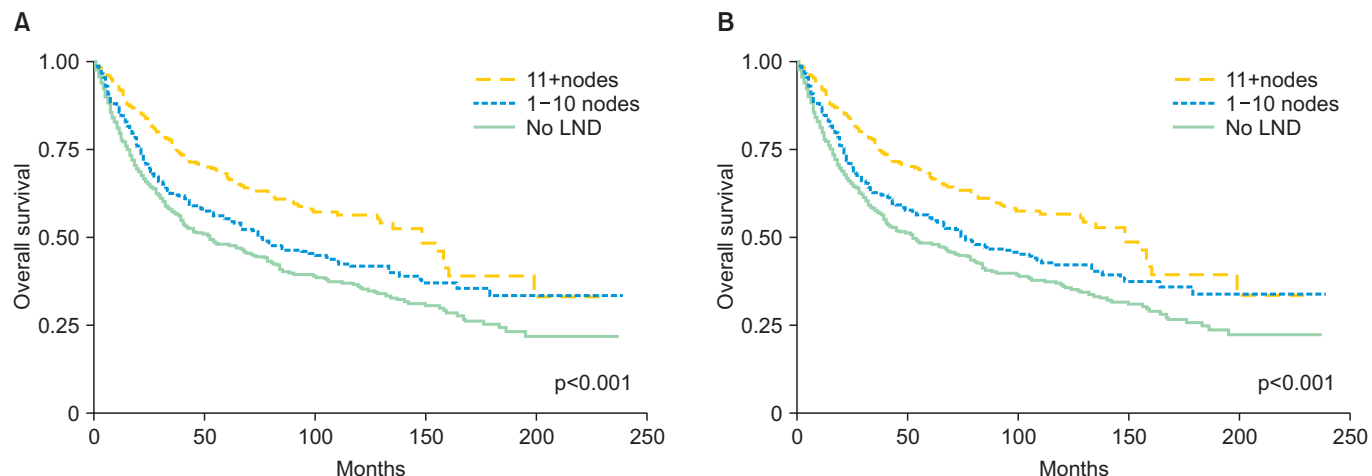


Fig. 2. Overall survival based on lymph node dissection (LND) in uterine clear cell cancer (A), and early stage uterine clear cell cancer (B).

for 1 to 10 vs. >10 nodes removed, respectively; $p=0.002$). In an analysis of 237 patients with stage IIIc-IV who have nodal metastases, the removal of a total of 1 to 10 and >10 lymph nodes was associated with 5-year survival rates of 29% and 37%, respectively ($p=0.04$).

A multivariate Cox proportional hazard models that included age, race, stage, extent of lymphadenectomy and adjuvant radiation therapy were used to examine the impact of the extent of lymphadenectomy on survival of UCCC patients (Table 3). When the entire cohort was included, those patients who had 1 to 10 nodes removed were 32% (HR, 0.68; 95% CI, 0.56 to 0.83; $p<0.001$) less likely to die than patient who had 0 nodes removed and those patients who had >10 nodes removed were 47% (HR, 0.53; 95% CI, 0.43 to 0.65; $p<0.001$) less likely to die than who had 0 nodes removed. Among stage

IIIC–IV patients with nodal disease, those who underwent more extensive lymphadenectomy (>10 nodes) were 32% (HR, 0.68; 95% CI, 0.47 to 0.98; $p=0.03$) less likely to die than those who had 1 to 10 nodes removed. Finally, in patients with early stage disease, the extent of lymphadenectomy persisted as an independent predictor of improved survival. The hazard ratio of death was 0.68 (95% CI, 0.51 to 0.90; $p=0.007$) for those who had 1 to 10 nodes removed and 0.58 (95% CI, 0.43 to 0.77; $p<0.001$) for those who had >10 nodes removed (Table 3).

DISCUSSION

UCCC represents a distinct histologic subtype of endometrial carcinoma. A significant proportion of patients with appar-

Table 3. Multivariate analysis for uterine clear cell cancer

Variable	All patients		Early stage (I–II)	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (yr)		<0.001		<0.001
Age<65	Reference		Reference	
Age≥65	2.3 (1.92–2.81)		3.5 (2.6–4.7)	
Race				
White	Reference		Reference	
African American	1.2 (0.96–1.53)	0.095	1.5 (1.11–2.16)	0.009
Asian	0.9 (0.62–1.19)	0.392	0.8 (0.45–1.39)	0.400
Stage		<0.001		
Early (stage I–II)	Reference		-	
Late stage (III–IV)	3.7 (3.15–4.44)		-	
Extent of lymphadenectomy (number of removed lymph nodes)				
0	Reference		Reference	
1–10	0.68 (0.56–0.83)	<0.001	0.68 (0.51–0.90)	
>10	0.53 (0.43–0.65)	<0.001	0.58 (0.43–0.77)	
Adjuvant radiation		0.007		0.400
No	Reference		Reference	
Yes	0.8 (0.14–0.73)		1.2 (0.91–1.46)	

HR, hazard ratio; CI, confidence interval.

ently early stage disease are upstaged at surgical assessment. In the study of 99 patients with uterine clear cell carcinoma, Thomas et al. [13], found that 52% (36/69) of patients with disease clinically confined to the uterus were found to have extrauterine disease after surgical staging. Similarly, Cirisano et al. [7] reported that 39% of patients with clinically early stage UCCC were upstaged to surgical stage III to IV [7]. Considering the high rate of surgical upstaging and the inability to reliably predict the extrauterine extension of the disease, many authors recommended routine comprehensive surgical staging when uterine clear cell pathology is suspected [7,13,16].

Systemic lymphadenectomy as a part of comprehensive surgical staging is important to define the extent of the disease and to guide postoperative adjuvant therapy in patients with UCCC. Our data revealed that patients who underwent lymphadenectomy have survival advantage that persisted in patients with early stage disease who have negative lymph nodes. The survival difference observed may simply be due to the comparison of patients with true early stage disease after a thorough staging procedure with inaccurately staged patients with true stage III disease. In fact, our data showed that 17% of UCCC patients with disease clinically confined to the uterus were upstaged due to finding of nodal metastasis. Similarly, prior studies have shown that up to 17% to 20% of patients

who were presumed to have early stage UCCC were found to have nodal metastasis during their staging procedures [11,13].

Our data showed several disparities in performing lymphadenectomy. Older women (≥65 years) were less likely than younger women (<65 years) to undergo lymphadenectomy. Several studies have documented that older women are less likely to receive surgical or radiation therapy [17,18]. In our cohort there was no significant racial difference in performing lymphadenectomy; however, African American women were more likely to have nodal metastasis than their white counterparts. Previous studies showed that endometrial carcinoma is often more aggressive in African American women compared to white women [19,20].

The correlation between the number of pathologically negative nodes and survival has been described in several solid cancers including breast, rectal, and cervical cancers [21–23]. In endometrial cancer, Cragun et al. [24] in a single institutional review of 509 patients including only 40 patients with serous or clear cell histology, showed that patients with poorly differentiated stage I and stage IIA disease having more than eleven pelvic nodes removed had an improved overall and progression-free survival than those with eleven or fewer nodes resected. In a SEER analysis of patients with stage I–IV endometrioid endometrial cancer, the survival was

significantly improved in patients with intermediate/high risk group who had more nodes removed [25]. The current report is the largest series to date on UCCC patients showing a survival benefit in subsets of patients who had a more extensive lymphadenectomy. In a recent study by Thomas et al. [13], among patients with stage I/II UCCC; those (22 patients) who underwent systemic lymphadenectomy (>20 nodes) had no peritoneal, lymphatic or hematologic failure but one patient with vaginal recurrence (4.5%) with median follow up of 44 months whereas those (27 patients) who had no or suboptimal lymphadenectomy, nine experienced recurrence (33%) including four vaginal, four pelvic, two lymphatic, and one hematologic recurrences. Furthermore in patients with nodal disease, our data showed that more extensive nodal resection was associated with improved survival. These findings suggest that survival advantage associated with the extent of lymphadenectomy may not simply be related to stage migration. An extensive lymphadenectomy may improve survival by removing occult nodal micrometastasis, not readily detected by routine histopathologic methods that may be resistant to chemotherapy (pharmacologic Sanctuary theory).

This study suffers from some limitations that include lack of information regarding central pathology review, surgeon subspecialty, location of lymphadenectomy, use and type of adjuvant chemotherapy, medical comorbidities, date and treatment of recurrences. Furthermore, we lacked information on patients' medical and surgical factors that may have impacted the decision to perform lymphadenectomy. Patients with significant comorbidities or certain body habitus may have no or less extensive lymphadenectomy; thus, representing patients with poor prognostic cancers. Moreover, patients with gross bulky nodal disease or those with advanced stage cancers may undergo a selective nodal sampling or debulking rather than a thorough staging lymphadenectomy. However, the strengths of this study include examination of large number of patients with UCCC. SEER data are representative of the United States population with less selection and surveillance biases often associated with single academic institutional studies.

In conclusion, our findings suggest that lymphadenectomy is associated with survival benefit in patients diagnosed with UCCC even after adjusting for age, stage, race, and adjuvant radiation therapy. Furthermore, the extent of lymphadenectomy performed in this patient population influences survival when a greater number of lymph nodes are removed. While our data are limited by its retrospective nature and lack of information on chemotherapy and comorbidity index; our study generates a hypothesis that lymphadenectomy may play a significant role in the treatment of UCCC. This hypoth-

esis warrants a need for multi-institutional prospective study or randomized trial to assess the impact of lymphadenectomy on outcome of patients with high risk endometrial cancer including uterine clear cell histology.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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