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The prognostic significance of aortic lymph node metastasis in endometrial cancer: Potential implications for selective aortic lymph node assessment

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HIGHLIGHTS

- Endometrial cancer with aortic lymph node metastasis portends a worse outcome.
- Older age and non-endometrioid histology are independent poor prognostic indicators in lymph node positive EC.
- Carcinosarcoma histology has the worse outcomes in lymph node positive EC.
- Compared to women with a pelvic-only LN dissection, women with pelvic and aortic dissections had lower EC mortality.

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ABSTRACT

Objectives. To evaluate the prognostic impact of aortic vs. pelvic lymph node (LN) metastasis among women with endometrial cancer (EC).

Methods. Using data from the SEER 18 Registries we identified 3650 women with LN positive (stage IIIC) EC. We used Kaplan-Meier curves and log-rank tests to compare mortality between women with stage IIIC1 and IIIC2 disease. We used Cox proportional hazards regression to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for associations between stage III sub-stage (IIIC1 vs. IIIC2) and survival.

Results. Endometrioid tumors were more common among women with stage IIIC1 than IIIC2 tumors (62.5% vs. 54.3%) while, non-endometrioid histologies were more common among stage IIIC2. In the multivariable model, stage IIIC2 was associated with higher all-cause (HR = 1.44, 95% CI = 1.22–1.69) and EC-specific mortality (HR = 1.49, 95% CI = 1.25–1.77) compared with IIIC1. Women with non-endometrioid EC had poor survival, in particular, women with carcinosarcomas had higher EC-specific mortality compared to women with endometrioid EC (HR = 3.32, 95% CI = 2.71–4.07). When stratifying women according to substage, older age and non-endometrioid histology were associated with higher EC-specific mortality. Compared to women with a pelvic-only LN dissection, women with pelvic and aortic dissections had lower all-cause (HR = 0.74, 95% CI = 0.63–0.88) and EC-specific (HR = 0.79, 95% CI = 0.66–0.95) mortality.

Conclusion. Women with aortic LN positive EC are more likely to die from their disease. Older women and non-endometrioid histologies are more likely to have aortic LN involvement. Compared to women with a pelvic-only LN dissection, women with pelvic and aortic dissections had lower EC mortality.

1. Introduction

Endometrial cancer (EC) is the most common gynecologic malignancy in the United States, with 63,320 new cases expected in 2018 [1]. The majority of ECs are diagnosed at an early stage after presentation and evaluation of abnormal vaginal bleeding [2]. The cornerstone of management for EC is surgery with hysterectomy, salpingo-oophorectomy and lymphadenectomy. Lymph node (LN) evaluation of the pelvic and para-aortic LN basins has been routinely performed in the United States despite data suggesting lack of survival benefit [3,4].

In 2009, FIGO divided stage IIIC (LN involved EC) into stage IIIC1 (pelvic LN involvement) and IIIC2 (aortic ± pelvic LN involvement) [5]. The separation made sense from an oncologic standpoint as

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involvement of the aortic LN chain likely suggests further progression, as most uterine drainage will be to the pelvic LNs [6,7]. Despite the rationale for the stage revision, there has been limited empirical data regarding the prognostic significance of aortic LN involvement.

Recently, the adoption of LN mapping and sentinel LN dissection has limited the performance of an aortic LN dissection since the majority of sentinel LNs will map to the pelvic LNs [8]. With the increasing utilization of sentinel LNs and lack of evidence that complete lymphadenectomy provides benefit, the utility of aortic LN dissection is questionable. We sought to evaluate the prognostic impact of aortic LN metastasis in EC utilizing the Surveillance, Epidemiology, End Results (SEER) database and to identify independent prognostic factors for women with LN positive disease.

2. Methods

2.1. Data source

The SEER Program is the source of population-based cancer information provided by the National Cancer Institute (NCI). We used data from 18 SEER registries which include Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, Utah, Los Angeles, San Jose-Monterey, Rural Georgia, Alaska Native, Greater California, Greater Georgia, Kentucky, Louisiana, and New Jersey. Information on all incident cancers (excluding basal or squamous cell skin cancer) occurring within these regions is collected by the SEER Program. Data from these registries covers approximately 28% of the U.S. population [9].

2.2. Study population

We included women ≥18 years of age at the time of a first primary diagnosis of stage IIIC1 or IIIC2 EC (C54.0-C54.9, C55.9) between 2010 and 2014 ($n = 4005$). We created a case listing that included the following variables: age at diagnosis, race, year of diagnosis, International Classification of Diseases for Oncology, Third Edition (ICD-O-3) morphology, surgery, radiation treatment, chemotherapy, vital status, cause of death, and survival time. We categorized ICD-O-3 codes into the following histological categories: endometrioid/adenocarcinoma/mucinous (8380–8383, 8140, 8210, 8211, 8560, 8260, 8262, 8263, 8570, 8261, 8480–8482), serous (8441, 8460, 8461), carcinosarcoma (8950, 8951, 8980, 8981), clear cell (8310), and mixed epithelial (8323, 8255). We excluded women with missing information on follow-up time ($n = 12$),with other ICD-O-3 histology codes (8000, 8010, 8013, 8020, 8041, 8045, 8050, 8071, 8072, 8082, 8246, 8313, 8370, 8510, 8574, 8575, $n = 93$), with implausible values for lymph node dissection (e.g. pelvic and aortic nodes coded as 'not examined' but with stage IIIC disease, $n = 228$), or unknown information on dissection of pelvic or aortic basins, $n = 22$), resulting in a final sample of 3650.

2.3. Statistical analysis

Distributions of age at diagnosis (18–34, 35–44, 45–54, 55–64, 65–74, ≥75), race (White, Black, Other), histology (endometrioid, serous, carcinosarcoma, clear cell, mixed epithelial), surgery (no cancer-directed surgery, total hysterectomy, other), lymph node dissection (pelvic only, aortic only, pelvic and aortic dissection), radiation treatment (no/unknown vs. yes), and chemotherapy (no/unknown vs. yes) according to stage III sub-stage (IIIC1 vs. IIIC2) were compared with chi-square tests. We also compared the number of lymph nodes examined and the number of positive nodes for each basin according to substage using Kruskal-Wallis tests.

Follow-up time was computed from the date of surgery to date of death or end of follow-up. Kaplan–Meier estimates and log-rank tests were used to compare survival distributions according to stage III substage. We used Cox proportional hazards regression models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between stage III sub-stage, EC-specific-, and all-cause mortality in models adjusted for age, race, histology, surgery, extent of lymph node dissection, radiation treatment, and chemotherapy. We conducted a sensitivity analysis examining the association between stage III substage and mortality in the subgroup of women with complete, i.e. pelvic and aortic, lymph node dissections. We also examined predictors of EC-specific mortality in Cox regression models stratified by sub-stage.

All analyses were completed using SEER Stat and SAS/STAT software (version 9.4 of the SAS System for Windows, SAS Institute, Cary, NC, USA). This study was considered exempt by the Institutional Review Board of the Ohio State University as all data are de-identified and intended for public use.

3. Results

3.1. Study population

Of the 3650 study participants with LN positive disease, 61.9% had stage IIIC1 compared to 38.1% with stage IIIC2 disease. Distributions of patient characteristics according to stage III sub-stage are shown in Table 1. Age at EC diagnosis and race were similar, with median age of diagnosis of 63 years and approximately 75% of women in both substages being white. Histology differed between women with stage IIIC1 and IIIC2 EC ($p < 0.0001$). Endometrioid tumors were more common among women with stage IIIC1 than IIIC2 tumors (62.5% vs. 54.3%) while serous, clear cell, carcinosarcoma, or mixed epithelial tumors were more commonly represented in the stage IIIC2 category than IIIC1. More than 95% of women in both sub-stages underwent cancer directed surgery. Women with stage IIIC2 disease more commonly had pelvic and aortic lymph node dissections compared to women with stage IIIC1 (90.9% vs. 51.5%). Radiation therapy significantly differed, with stage IIIC1 patients more commonly receiving radiation. No difference in use of chemotherapy was noted (Table 1).

3.2. Stage III sub-stage and mortality

Among 3650 EC patients with a median follow-up of 1.7 years (range: 0–4.9 years), there were 864 deaths, of which, 738 (85.4%) were EC-related. Compared to women with stage IIIC1, women with stage IIIC2 had higher all-cause (log-rank $p < 0.0001$) and EC-specific mortality (log-rank $p < 0.0001$) (Figs. 1 and 2). In Cox regression models adjusted for age, race, histology, year of diagnosis, SEER registry, surgery, extent of lymph node evaluation, and adjuvant treatment, stage IIIC2 was associated with higher all-cause (HR = 1.44, 95% CI = 1.22–1.69) and EC-specific mortality (HR = 1.49, 95% CI = 1.25–1.77) compared with stage IIIC1, (Table 2).

In sensitivity analyses restricted to the 2428 women who had a pelvic and aortic lymph node dissection, effect estimates comparing stage IIIC2 vs. IIIC1 were similar to the overall model (all-cause mortality: HR = 1.46, 95% CI = 1.22–1.74); EC-specific mortality: HR = 1.52, 95% CI = 1.26–1.84, data not tabled).

3.3. Other predictors of mortality among LN positive women (IIIC1 and IIIC2)

Older age was associated with higher all-cause (HR >75 years vs. 18–34 years = 4.86, 95% CI = 1.54–15.29) and EC-specific mortality (HR = 4.11, 95% CI = 1.30–12.96). Black women also experienced higher all-cause (HR = 1.34, 95% CI = 1.10–1.62) and EC-specific (HR = 1.36, 95% CI = 1.10–1.68) mortality than white women. Non-endometrioid histology was independently associated with higher mortality. Compared to women with endometrioid tumors, those with carcinosarcoma had the highest all-cause (HR = 3.10, 95% CI = 2.56–3.76) and EC-specific mortality (HR = 3.32, 95% CI = 2.71–4.07). Women with serous, clear cell, or mixed epithelial histology had between 28%

Table 1
Characteristics of women with stage IIIC endometrial cancer according to sub-stage: surveillance, epidemiology, and end results 18 registries, 2010–2014.

	Stage IIIC1	Stage IIIC2	p
	n = 2259	n = 1391	
	n (%)		
Age at EC diagnosis (years)			0.22
18–34	19 (0.8)	9 (0.6)	
35–44	93 (4.1)	40 (2.9)	
45–54	318 (14.1)	181 (13.0)	
55–64	851 (37.7)	524 (37.7)	
65–74	656 (29.0)	442 (14.0)	
75+	322 (14.2)	195 (14.0)	
Median (interquartile range)	63 (56–70)	63 (57–70)	
Race			0.09
Black	274 (12.1)	199 (14.3)	
White	1741 (77.1)	1029 (74.0)	
Other	244 (10.8)	163 (11.7)	
Histology			<0.0001
Endometrioid	1412 (62.5)	755 (54.3)	
Serous	295 (13.1)	265 (19.0)	
Carcinosarcoma	238 (10.5)	162 (11.6)	
Clear cell	50 (2.2)	44 (3.2)	
Mixed epithelial	264 (11.7)	165 (11.9)	
Surgery			0.07
No cancer-directed surgery	9 (0.4)	11 (0.8)	
Total hysterectomy	1906 (84.4)	1140 (82.0)	
Other cancer-directed surgery	344 (15.2)	240 (17.2)	
Lymph node dissection			<0.0001
Pelvic only	1088 (48.2)	51 (3.7)	
Aortic only	7 (0.3)	76 (5.5)	
Pelvic and aortic	1164 (51.5)	1264 (90.9)	
Pelvic lymphadenectomy			
Number of nodes removed, median (range)[a]	12 (1–81)	13 (1–67)	0.008
Number of positive nodes, median (range)[a]	1 (1–29)	3 (1–66)	<0.0001
Aortic lymphadenectomy			
Number of nodes removed, mean (range)[a]	4 (1–45)	6 (1–90)	<0.0001
Number of positive nodes, mean (range)[a]	–	2 (1–35)	–
Radiation treatment			0.004
None/unknown	1076 (47.6)	731 (52.5)	
Any radiation	1183 (52.4)	660 (47.4)	
Chemotherapy treatment			0.47
None/unknown	538 (23.8)	317 (22.8)b	
Any chemotherapy	1721 (76.2)	b1074 (77.2)	

[a] Among women with a nodal dissection and number of nodes documented.

and 90% higher EC-specific mortality than women with endometrioid tumors (Table 2). Women who did not undergo cancer-directed surgery had worse outcomes than women who had a total hysterectomy or other cancer-directed surgery. Compared to women with a pelvic-only lymph node dissection, women with pelvic and aortic dissections had lower all-cause (HR = 0.74, 95% CI = 0.63–0.88) and EC-specific (HR = 0.79, 95% CI = 0.66–0.95) mortality. Finally, radiation treatment and chemotherapy were each associated with lower all-cause and EC-specific mortality for women with lymph node positive disease.

3.4. Predictors for EC-specific mortality stratified by sub-stage

We also examined predictors of EC-specific mortality stratified by sub-stage (Table 3). Older age was associated with higher EC-specific mortality among women with stage IIIC1 (≥75 vs. ≤44 HR = 3.24, 95% CI = 1.71–6.13) and IIIC2 EC (≥75 vs. ≤44 HR = 4.63, 95% CI = 1.6–12.89). Black as compared to white race was associated with higher

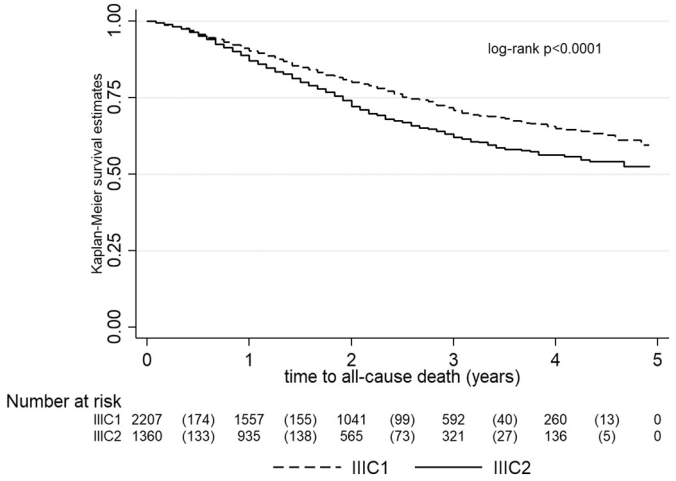

Fig. 1. All-cause mortality according to stage III EC sub-stage.

EC-specific mortality in the IIIC1 group (HR = 1.50, 95% CI = 1.13–2.01), but not among women in the IIIC2 group. Histology was an important prognostic factor for women in both subgroups. Compared to women with endometrioid tumors, women with carcinosarcoma had significantly higher EC-specific mortality among women with IIIC1 (HR = 4.22, 95% CI = 3.21–5.56) or IIIC2 (HR = 2.56, 95% CI = 1.86–3.51) EC. Compared to women with endometrioid tumors, women with serous histology had significantly higher EC-specific mortality among women with IIIC1 (HR = 1.99, 95% CI = 1.49–2.65) or IIIC2 (HR = 1.85, 95% CI = 1.38–2.49) EC. Among women with a stage IIIC1 diagnosis, a pelvic and aortic dissection was associated with significantly lower mortality compared to a pelvic-only dissection (HR = 0.81, 95% CI = 0.66–0.99). As expected, women with IIIC1 or IIIC2 EC who received cancer-directed surgery, chemotherapy or radiation had lower EC-specific mortality than women who did not receive these treatments ($p < 0.0001$ for each, Table 3).

4. Discussion

Surgical staging including pelvic and aortic LN dissection is routine practice in surgical staging for EC. In 2009, FIGO updated EC staging criteria to separate stage IIIC (LN metastasis) into those with pelvic (IIIC1) and those with aortic with or without pelvic LN metastasis (IIIC2) [5]. Distinguishing pelvic from aortic involvement seems reasonable from a prognostic standpoint; however, data supporting the change are limited. Our data confirms that aortic LN metastasis confers

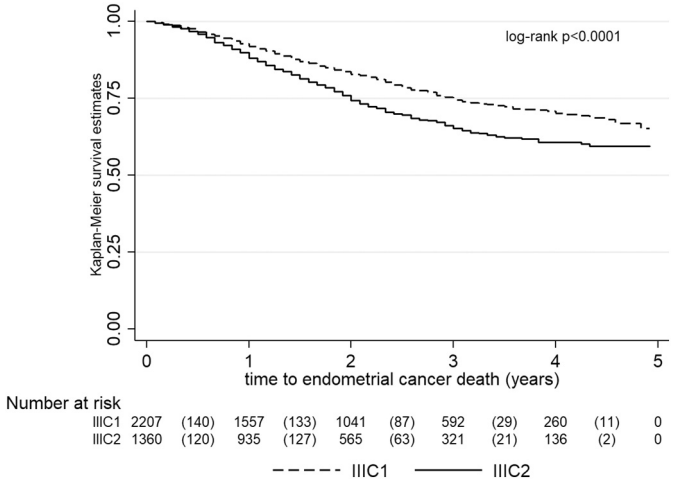

Fig. 2. Endometrial cancer-specific mortality according to stage III EC sub-stage.

Table 2
Hazard ratios (HRs) and 95% confidence intervals (CIs) for predictors of survival among women with stage IIIC EC.

	All-cause mortality ($N = 3650$, all deaths = 864)			Endometrial cancer-specific mortality ($N = 3650$, EC deaths = 738)		
	Deaths, n (%)[a]	HR (95% CI)[b]	p	Deaths, n (%)[a]	HR (95% CI)[b]	p
Sub-stage			<0.0001			<0.0001
IIIC1	484 (21.4)	1.00		402 (17.8)	1.00	
IIIC2	380 (27.3)	1.44 (1.22, 1.69)		336 (24.2)	1.49 (1.25, 1.77)	
Age at diagnosis			<0.0001			<0.0001
18–34	3 (10.7)	1.00		3 (10.7)	1.00	
35–44	13 (9.8)	1.25 (0.35, 4.41)		12 (9.0)	1.16 (0.33,4.16)	
45–54	89 (17.8)	2.44 (0.77, 7.76)		78 (15.6)	2.12 (0.67,6.77)	
55–64	277 (20.2)	2.75 (0.88, 8.63)		243 (17.7)	2.42 (0.77, 7.61)	
65–74	276 (25.1)	3.17 (1.01, 9.96)		233 (21.2)	2.72 (0.87, 8.56)	
75+	206 (39.9)	4.86 (1.54, 15.29)		169 (32.7)	4.11 (1.30, 12.96)	
Race			0.005			0.01
White	626 (22.6)	1.00		530 (19.1)	1.00	
Black	166 (35.1)	1.34 (1.10, 1.62)		142 (30.0)	1.36 (1.10, 1.68)	
Other	72 (17.7)	0.84 (0.64, 1.11)		66 (16.2)	0.89 (0.67, 1.19)	
Histology			<0.0001			<0.0001
Endometrioid		1.00		313 (14.4)	1.00	
Serous	181 (32.3)	1.89 (1.57, 2.28)		154 (27.5)	1.90 (1.55 2.33)	
Carcinosarcoma	170 (42.5)	3.10 (2.56, 3.76)		153 (38.3)	3.32 (2.71 4.08)	
Clear cell	32 (34.0)	1.51 (1.04, 2.18)		23 (24.5)	1.28 (0.83, 1.98)	
Mixed epithelial	110 (25.6)	1.49 (1.19, 1.85)		95 (22.1)	1.53 (1.21, 1.93)	
Surgery			<0.0001			<0.0001
No cancer-directed surgery	15 (75.0)	1.00		13 (65.0)	1.00	
Total hysterectomy		0.10 (0.05, 0.17)		579 (19.0)	0.09 (0.05, 0.16)	
Other cancer-directed surgery	164 (28.1)	0.12 (0.07, 0.21)		146 (25.0)	0.11 (0.06, 0.20)	
Lymph node dissection			0.002			0.05
Pelvic only	289 (25.4)	1.00		234 (20.5)	1.00	
Aortic only	28 (33.7)	0.94 (0.62, 1.43)		22 (26.5)	0.87 (0.55, 1.39)	
Pelvic and aortic	547 (22.5)	0.74 (0.63, 0.88)		482 (19.9)	0.79 (0.66, 0.95)	
Radiation treatment			<0.0001			<0.0001
None/unknown	525 (29.1)	1.00		441 (24.4)	1.00	
Any radiation	339 (18.4)	0.66 (0.57, 0.76)		297 (16.1)	0.69 (0.59, 0.80)	
Chemotherapy treatment			<0.0001			<0.0001
None/unknown	287 (33.6)	1.00		234 (27.4)	1.00	
Any chemotherapy	577 (20.6)	0.64 (0.56, 0.75)		504 (18.0)	0.67 (0.57 0.80)	

[a] Row percentage.
[b] HR and 95% CI adjusted for all variables shown in the table, year of diagnosis, and SEER registry.

worse outcomes compared with pelvic LN metastasis alone. Furthermore, our data highlights important prognostic factors for women with lymph node positive endometrial cancer. We identified older age and non-endometrioid histology as independent prognostic factors among women with LN positive disease. In particular, women with carcinosarcoma histology had the worst outcomes.

From a management perspective LN involvement is usually managed with chemotherapy, radiation or a combination of the two [10]. The known involvement of aortic LNs may influence radiation fields, guide additional work-up (e.g. chest imaging) and may change a clinician's surveillance strategy. Additionally, aortic LN involvement provides important prognostic information to the patient. Our data also suggests a possible therapeutic benefit of aortic lymph node dissection with women receiving pelvic and aortic lymph node dissections having a lower all-cause and EC-specific mortality (HR = 0.79).

Sentinel LN dissection has been adopted in EC. The benefit of sentinel LNs has previously been reported in several cancer types and recent data in EC highlight the benefits of sentinel LN dissection in EC with improved identification of LN positive individuals, decreased surgical complications and decreased lymphedema [11–15]. While the majority of ECs are identified at an early stage, approximately 1 in 5 women with EC will have LN involvement [1]. Furthermore, approximately 3% of EC cases with sentinel LN dissection will identify an aortic LN as the sentinel LN which is consistent with previous data describing isolated aortic metastases [6–8]. As most women have uterine-confined disease and the incidence of isolated aortic LNs is low, sentinel lymph dissection of the pelvic LNs would seem to be an appropriate management strategy. Consequently, the majority of women that undergo a sentinel LN dissection will not have their aortic LNs evaluated unless the LN mapping identifies sentinel aortic LNs.

Our data may help guide clinicians to identify those women undergoing sentinel LN dissection that may benefit from additional aortic LN assessment (in the absence of sentinel LN mapping to this region) to assist in counseling and additional risk stratification. Based on our data surgeons performing a sentinel LN dissection could consider aortic LN dissection if there is no mapping to aortic sentinel LNs, or pre-operative imaging for older patients and those with high risk histologies, especially carcinosarcomas. The strategy of pelvic sentinel LN biopsy and aortic LN dissection may allow for the most comprehensive prognostic information while limiting morbidity of lymphedema from a complete pelvic and aortic LN dissection.

Previous reports have not identified that performance of sentinel LNs reduces survival in women with EC; even those with high risk histologies [16,17]. Additionally, there does not appear to be a therapeutic benefit of lymphadenectomy in EC [3,4]. With this in mind one may question the role of lymphadenectomy in EC patients at all. Recently, PORTEC-3 [18] reported their results which did not identify an improvement in overall survival with the addition of chemotherapy to pelvic radiation in high risk EC. While the high risk population as a whole in PORTEC-3 did not have a benefit in overall survival the sub-group of stage III EC did have an improved progression-free survival (HR = 0.66; $p = 0.031$) [18]. Conversely, GOG258 which evaluated the addition of radiation to chemotherapy did not demonstrate a survival benefit with the addition of radiation [19]. Taken together it is important to note that the management of stage IIIC endometrial cancer may not differ regardless of aortic

Table 3
Hazard ratios (HRs) and 95% confidence intervals (CIs) for predictors of EC-specific mortality stratified by stage III substage.

	IIIC1 ($n = 2259$, EC deaths = 402)			IIIC2 ($n = 1391$, EC deaths = 336)		
	Deaths n (%)[a]	HR (95% CI)[b]	p	Deaths n (%)[a]	HR (95% CI)[b]	p
Age at diagnosis			<0.0001			0.005
18–44	11 (9.8)	1.00		4 (8.2)	1.00	
45–54	36 (11.3)	1.43 (0.72, 2.82)		42 (23.2)	2.77 (0.98, 7.81)	
55–64	126 (14.8)	1.67 (0.89, 3.12)		117 (22.3)	3.16 (1.15, 8.67)	
65–74	130 (19.8)	2.13 (1.14, 3.99)		103 (23.3)	2.98 (1.09, 8.19)	
75+	99 (30.7)	3.24 (1.71, 6.13)		70 (35.9)	4.63 (1.66, 12.89)	
Race			0.02			0.26
White	295 16.94	1.00		235 (22.8)	1.00	
Black	76 (27.7)	1.50 (1.13, 2.01)		66 (33.2)	1.28 (0.93, 1.78)	
Other	31 (12.7)	0.95 (0.62, 1.44)		35 (21.5)	0.90 (0.59, 1.37)	
Histology			<0.0001			<0.0001
Endometrioid	174 (12.3)	1.00		139 (18.4)	1.00	
Serous	74 (25.1)	1.99 (1.49, 2.65)		80 (30.2)	1.85 (1.38, 2.49)	
Carcinosarcoma	91 (38.2)	4.22 (3.21, 5.56)		62 (38.3)	2.56 (1.86, 3.51)	
Clear cell	9 (18.0)	1.19 (0.60, 2.37)		14 (31.8)	1.42 (0.80, 2.52)	
Mixed epithelial	54 (20.5)	1.72 (1.26, 2.35)		41 (24.9)	1.32 (0.91, 1.91)	
Surgery			<0.0001			<0.0001
No cancer-directed surgery	7 (77.8)	1.00		6 (54.6)	1.00	
Total hysterectomy	327 (17.2)	0.02 (0.01, 0.05)		252 (22.1)	0.16 (0.07, 0.40)	
Other cancer-directed surgery	68 (19.8)	0.02 (0.01, 0.04)		78 (32.5)	0.25 (0.10, 0.63)	
Lymph node dissection			0.08			0.64
Pelvic only	216 (19.9)	1.00		18 (35.3)	1.00	
Aortic only	3 (42.9)	1.57 (0.47, 5.21)		19 (25.0)	0.83 (0.42, 1.62)	
Pelvic and aortic	183 (15.7)	0.81 (0.66, 0.99)		299 (23.7)	0.79 (0.47, 1.30)	
Radiation treatment			0.003			0.001
None/unknown	231 (21.5)	1.00		210 (28.7)	1.00	
Any radiation	171 (14.5)	0.73 (0.59, 0.90)		126 (19.1)	0.67 (0.53, 0.85)	
Chemotherapy treatment			0.007			<0.0001
None/unknown	128 (23.8)	1.00		106 (33.4)	1.00	
Any chemotherapy	274 (15.9)	0.73 (0.58, 0.92)		230 (21.4)	0.57 (0.44 0.74)	

[a] Row percentage.
[b] Multivariable-adjusted HRs adjusted for all variables shown in the table, SEER registry, and year of diagnosis.

lymph node disease as the benefit of radiation in this population is questionable and all patients will likely receive chemotherapy. An important caveat would be that carcinosarcomas, which portended the worse outcomes, were not included in either trial.

The role of selective aortic lymphadenectomy in women with EC may extend beyond prognostic information as well. Our data demonstrated a survival benefit in women receiving a pelvic and aortic lymph node dissection over pelvic lymph node dissection alone. Data from Todo et al. [20] as part of the SEPAL study reported that overall survival was significantly longer in those patients in whom pelvic and para-aortic lymphadenectomy was performed versus pelvic lymphadenectomy alone. While both their data as well as ours is retrospective in nature it calls into question whether there may be some therapeutic benefit as well in women undergoing surgery for EC. There currently is no prospective data evaluating the role of selective aortic lymphadenectomy in combination with sentinel pelvic lymphadenectomy.

Our data is limited by the intrinsic weaknesses of retrospective databases. However, this is the largest data collection evaluating aortic LN metastasis in EC. Additional strengths of our work include the ability to parse out populations that have the highest risks of mortality among women with pelvic and aortic LN metastasis.

Sentinel LNs are emerging as the standard of care in EC and while there are certainly many advantages to the technique, we are likely to lose the benefit of knowing the aortic LN status in the majority of patients. Additionally, as the technique is increasingly adopted, formal training in aortic lymphadenectomy in EC is likely to be diminished as well [21]. Surgeons may consider selective aortic lymphadenectomy in those women who are most likely to have aortic LN metastasis as an adjunct to sentinel pelvic LN dissection.

5. Conclusions

Women with aortic LN positive EC are more likely to die from their disease. Older women and non-endometrioid histologies are more likely to have aortic lymph node involvement as well as have poorer outcomes if they have pelvic and/or aortic LN involvement. While women with non-endometrioid tumors have worse outcomes, carcinosarcoma portends the worst outcomes in both pelvic and aortic lymph node positive women. Compared to women with a pelvic-only LN dissection, women with pelvic and aortic dissections had lower EC mortality and may be an area of additional research interest.

Conflict of interest disclosure

None of the authors have a conflict of interest to disclose.

Authors contributions

Concept and design (CC, DC, AF); acquisition, analysis, or interpretation of data (all authors); drafting of the manuscript (CC, AF). Critical revision of the manuscript for important intellectual consent (all authors); statistical and data analysis (CC, AF, JR); study supervision (CC, AF, DC.)

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