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Original Research

Lymphadenectomy and pelvic irradiation in high-risk endometrioid endometrial cancer: a population-based retrospective analysis using the SEER databank

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The current role of lymphadenectomy in early-stage high-risk endometrioid endometrial cancer is to guide further adjuvant treatment according to lymph node status. Whether the procedure has any therapeutic role remains controversial. In this study we aimed to investigate the outcome of current practices by performing a population-based retrospective cohort analysis using the US population-derived freely accessible public Surveillance, Epidemiology and End Results program (SEER) database. SEER data from patients with endometrial cancer treated between 2004 and 2012 were accessed online on March 1, 2016. Kaplan-Meier estimators were used to describe the survival distribution and the log-rank (Mantel-Cox) test was used to perform overall and pairwise comparisons of the survival distributions. The cohort included 47,463 patients, 10,288 of whom fulfilled high-risk criteria. A higher lymph node yield count was associated with better overall survival, although the removal of more than 40 lymph nodes did not confer any further survival benefit. The application of pelvic irradiation without lymph node status confirmation did not provide a survival benefit. From this analysis, no evidence of a survival benefit associated with lymphadenectomy was found. However, the current role lymphadenectomy as a staging and guiding tool for further adjuvant treatment was supported. Well-designed prospective randomized trials are required to conclusively determine the prognostic and therapeutic value of lymphadenectomy in patients with high-risk endometrioid endometrial cancers.

Keywords

Endometrial cancer; Lymphadenectomy; High-risk endometrioid endometrial cancer; Pelvic irradiation

1. Introduction

Endometrial cancer is the most common gynecological malignancy in Germany, as well as in the developed world and globally [1–3]. Approximately 70% of patients with endometrial cancer present at an early stage, when the tumor remains confined to the corpus uteri, and have a very good 5-year-survival rate of over 80% [1, 4]. The surgical staging of endometrial cancer was first recommended by the Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) in 1988 [5], replacing the clinical staging that was earlier practiced and was based exclusively on clinical findings, reflecting a paradigm shift in disease management. Since the introduction of the new FIGO recommendations, discussions and debates have been ongoing about the value of lymphadenectomy not solely as a staging procedure, but as a treatment modality in itself. Randomized controlled trials have found no survival benefit associated with the procedure [6, 7], while some retrospective cohorts [8–10] as well as a meta-analysis [11] have found the contrary. In a recent Cochrane review, lymphadenectomy was regarded as a means of guiding the need for further treatment, such as irradiation, but not as a therapeutic means in itself [12].

Pelvic irradiation is complementary to the role of surgery in the treatment of endometrial cancer. Two large prospective studies (the PORTEC-trial and the GOG-99 trial) presented evidence that pelvic irradiation provides a benefit in the form of a longer disease-free interval but does not provide any overall survival benefit [13, 14]. Another randomized trial (PORTEC-2) showed that local irradiation using brachytherapy could be as effective as pelvic irradiation in reducing pelvic recurrences but had a significantly lower morbidity [15].

The Surveillance, Epidemiology and End Results program (SEER) includes data from 17 different cancer registries in the United States. The aim of this study was to evaluate the therapeutic role of lymphadenectomy and irradiation in the treatment algorithm of high-risk endometrioid endometrial cancer.

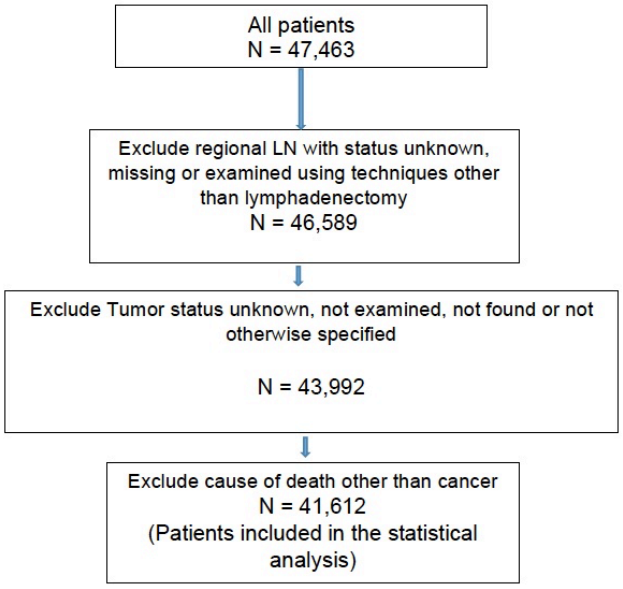

Fig. 1. Algorithm showing the process of patient selection for the statistical analysis from the SEER data set. The total number of patients included as well as those who were excluded according to the inclusion and exclusion criteria are thoroughly depicted.

2. Methods

This was a population-based retrospective cohort analysis using the freely accessible public SEER database. SEER data from patients with endometrial cancer treated between 2004 and 2012 were accessed online on March 1, 2016 after obtaining the required authorization (SEER ID: 14859-Nov2015). Program version 8.2.1 was used, which included data collected prior to the November 2014 submission.

3. Patient dataset

Patients were selected from the SEER database records from the period 2004-2012 who were registered with the diagnosis of endometrial endometrioid cancer. Patients who had incomplete records such as unknown or missing regional lymph node status, those with lymph node status examined using techniques other than lymphadenectomy, those with tumor status unknown, not examined or not found were excluded. Patients with cause of death other than cancer were also excluded. Between 2004 and 2012, there were 47,463 registered patients with endometrial cancer of the endometrioid type, of whom only 41,612 were available for statistical analysis after excluding patients not meeting the inclusion criteria (Fig. 1).

3.1 Statistical analysis

Using the variables tumor extent and tumor grade, the patients of the cohort were subdivided as follows: advanced if T = T_{3a}, T_{3b}, or T_4; high risk if G_2 & T_{1c} or T_{2b}, or G_3& T_{1a}, T_{1b}, T_{1c}, T_{1NOS}, T_{2a}, T_{2b}, or T_{2NOS}; and low risk if otherwise. (NOS: non otherwise specified). All T_{1NOS} tumors that were not accompanied by a G3 histology, were excluded from the statistical analysis.

The high-risk group of patients was stratified into six subgroups according to; (i) whether or not a lymphadenectomy had been performed, (ii) the extent of any lymph node involvement (for those who received a lymphadenectomy), and (iii) whether or not patients had received irradiation.

Statistical analyses were performed to compare the overall survival between the different study groups. The primary variable that was compared between the groups was the overall survival time (in months) calculated since diagnosis. The survival period was calculated as the time interval between diagnosis and the last registered follow-up visit or the time interval between diagnosis and death due to endometrioid cancer. Further variables in the analysis included age at diagnosis (years), race, tumor extent (T), tumor grade, lymph node involvement (not examined, positive and negative nodes), and radiotherapy.

Kaplan-Meier estimators were used to describe the survival distribution for patients having different demographic and clinical traits. The log-rank (Mantel-Cox) test was used to perform overall and pairwise comparisons of the survival distribution among different groups of patients according to the chosen variables. Confidence intervals for the mean survival time for patients in the different groups were also compared to further assess the practical significance of the differences.

All statistical analyses were performed using IBM SPSS Statistics software for Windows, version 24.0 (IBM Corp., Armonk, N.Y., USA). All confidence intervals had a 95% confidence level. All statistical tests were two-sided and tests with a P-value < 0.05 were considered statistically significant.

4. Results

The mean age in the patient dataset $\pm$ standard deviation (SD) was 60.14 $\pm$ 11.36 years. A total of 10,288 patients were of high risk, 27,411 were of low risk, and 3,913 were of advanced stage. Mean survival $\pm$ SD was 45.5 $\pm$ 30.61 months, ranging from 0-107 months. The demographic data, stage, lymph node status, and irradiation status of the patients who met the inclusion criteria are shown in Table 1.

Among the 26,339 (63.3%) patients who underwent lymphadenectomy, 2,427 (9.2%) had positive lymph nodes, whereas in the high-risk group 1,080 (13.2%) had positive lymph nodes. In the high-risk group, 8,292 (80.6%) patients underwent lymphadenectomy whereas 1,996 (19.4%) patients did not receive an operative examination of the lymph node status. Among those, 1,052 did not receive any sort of adjuvant treatment while 944 received irradiation. The survival outcome of the high-risk patients who were divided into six groups were compared pairwise and the results are shown in Table 2. Kaplan-Meier survival curves for the six subgroups, in addition to the low-risk and advanced disease groups, are shown in Fig. 2. Patients in the high-risk group who received a lymphadenectomy that showed lymph node involvement but did not receive pelvic irradia-

Table 1. Characteristics of the patients included in the analysis.

		Range	Mean	SD
Age		20-100	60.14	11.36
Survival time (months)		0-107	45.5	30.61
			Number (percentage)	
Disease related deaths			2,443 (5.9%)	
Race	White		35,235 (84.7%)	
	Black		2,662 (6.4%)	
	Other		3,715 (8.9%)	
T-stage	T1a		10,978 (26.4%)	
	T1b		17,084 (41%)	
	T1c		6,208 (14.9%)	
	T2a		1,563 (3.8%)	
	T2b		1,866 (4.5%)	
	T3a		2,888 (6.9%)	
	T3b		667 (1.6%)	
	T4		358 (0.9%)	
Grading	G1		21,739 (52.2%)	
	G2		13,805 (33.2%)	
	G3		6,068 (14.6%)	
Irradiation	No irradiation		31,442 (75.6%)	
	Refused irradiation		262 (0.6%)	
	Irradiation form	Beam therapy	3,688 (8.9%)	
		Radioactive implants	3,946 (9.5%)	
		Combination	2,088 (5%)	
		Other	186 (0.4%)	
Lymphadenectomy and lymph node involvement	No lymphadenectomy		15,273 (36.7%)	
	Negative regional lymph nodes		23,912 (57.5%)	
	Lymph node involvement (according to percentage of involved lymph nodes from total extracted lymph nodes)	$< 10\%$	871 (2.1%)	
		10%-30%	896 (2.2%)	
		30%-50%	357 (0.9%)	
		$> 50\%$	303 (0.7%)	
Risk stratification	Low		27,411 (65.9%)	
	High		10,288 (24.7%)	
	Advanced		3,913 (9.4%)	

tion had the worst overall survival (median overall survival of 80 months) among the entire high-risk group. This group's survival rate was comparable to that of patients in the advanced disease group.

Table 3 shows the survival outcomes of patients subdivided according to lymph node status and percentage of involved lymph nodes out of the total number of lymph nodes removed. In keeping with the expected prognostic value of surgical staging overall survival was inversely proportional to the percentage of lymph nodes involved in a statistically significant manner. A similar outcome was observed for the high-risk group of patients yielding an. Please see Table 4 for full statistical details of all patient groups.

Table 5a and Table 5b show the survival outcomes of patients according to the total count of the lymph nodes removed in both the whole cohort and in the high-risk group of patients, respectively. Among the whole patient cohort, a consistent significant rise in overall survival was observed with increasing count of the lymph node yield until a count of 40 lymph nodes was reached. A lymph node yield greater than 40 did not confer any further significant overall survival benefit. A similar pattern was also observed in the high-risk group of patients. Fig. 3 (a) shows Kaplan-Meier Curves of the overall survival according to the number of lymph nodes removed in the entire cohort and (b) in the high-risk group of patients. Table 6a and Table 6b show the survival outcomes of patients according to the absolute number of infiltrated lymph nodes in the patient cohort as a whole and in the high-risk subgroup of patients, respectively. A significant worsening in overall survival was observed with increasing infiltrated lymph node count, both within the patient cohort as a whole and within the high-risk sub-group.

The survival outcome for the high-risk group, with respect to lymph node status and type of radiation received, if any, revealed a statistically significant effect on survival in the group of patients who received external beam irradiation after lymphadenectomy in comparison with those who did not receive any type of radiation (Table 7a, Table 7b and Ta-

Table 2. Survival outcomes of low-risk, high-risk, and advanced patients with and without lymphadenectomy, irradiation, and lymph node involvement.

		Total number	Number of events (percentage survival)	Mean survival (months)	95% CI of survival (months)	*P*-value for log-rank test					
						H 1	H 2	H 3	H 4	H 5	H 6
Low risk		27,411									
High Risk	H 1	1,052	136 (87.1%)	92.1	89.75-94.4		0.28	< 0.001	0.01	< 0.001	< 0.001
	H 2	944	116 (87.7%)	93.66	91.42-95.9	0.28		< 0.001	< 0.001	< 0.001	< 0.001
	H 3	437	93 (79.7%)	80.31	75.84-84.77	< 0.001	< 0.001		0.025	< 0.001	< 0.001
	H 4	643	124 (81.7%)	86.3	83.14-89.46	0.01	< 0.001	0.025		< 0.001	< 0.001
	H 5	3,438	179 (94.9%)	100.92	100.1-101.78	< 0.001	< 0.001	< 0.001	< 0.001		0.003
	H 6	3,774	261 (93.1%)	98.84	97.9-99.78	< 0.001	< 0.001	< 0.001	< 0.001	0.003	
Advanced		3,913									

H1: no Lymphadenectomy & no irradiation, H2: no lymphadenectomy & irradiation, H3: positive lymph nodes & no irradiation, H4: positive lymph nodes & irradiation, H5: negative lymph nodes & no irradiation, H6: negative lymph nodes & irradiation.

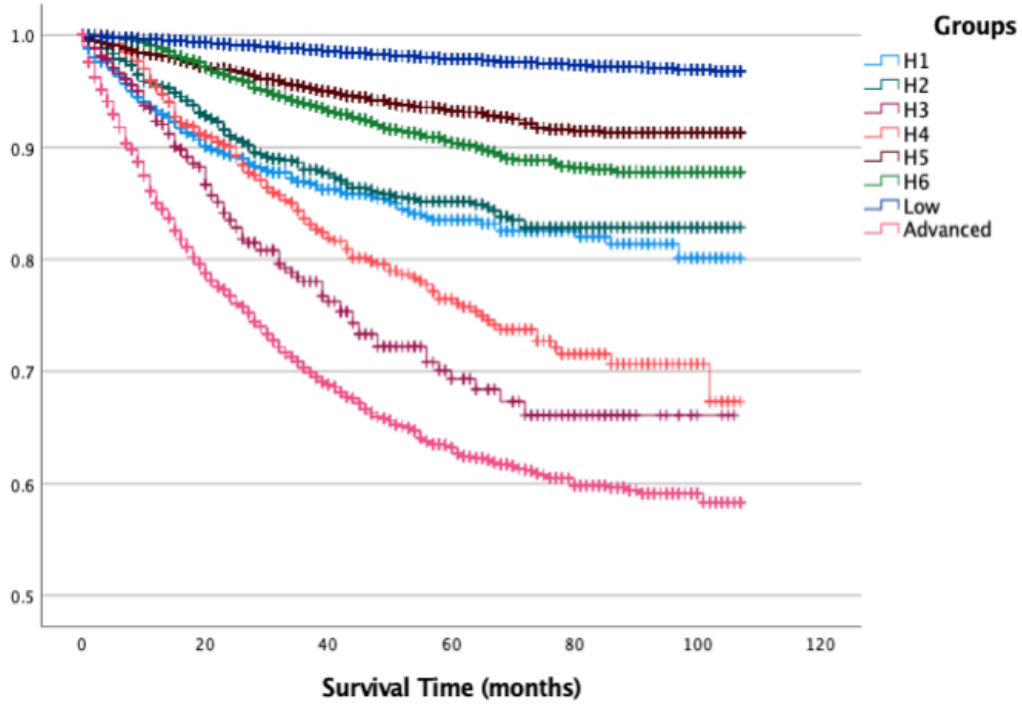

Fig. 2. Kaplan-Meier curves showing the overall survival in the patients with low-risk, high-risk and advanced disease. The high-risk patients were divided into six groups: H1: no Lymphadenectomy & no irradiation, H2: no lymphadenectomy & irradiation, H3: positive lymph nodes & no irradiation, H4: positive lymph nodes & irradiation, H5: negative lymph nodes & no irradiation, H6: negative lymph nodes & irradiation. Patients in the high-risk group who received a lymphadenectomy that showed lymph node involvement but did not receive pelvic irradiation (group H3) had the worst overall survival.

ble 7c).

5. Discussion

Since the introduction of systematic lymphadenectomy to the operative staging process for endometrial cancer in 1988 [5], the therapeutic value of this procedure has been highly debated. Prospective randomized trials have shown no survival benefit for lymphadenectomy [6, 7]. However, these trials have been heavily criticized for being underpowered, for not having clearly defined the role of lymphadenectomy in guiding therapy, and for the suboptimal quality of the lymphadenectomy procedure used [16–18].

Our data analysis produced some apparently contradictory results. On the one hand, a mean overall survival of 80 months was demonstrated in the high-risk group of patients with lymph node involvement who had not received any form of adjuvant treatment. This group of patients showed the worst prognosis among the high-risk collective, despite the average overall survival of 80 months, reflecting some therapeutic benefit associated with the procedure or, perhaps, could be explained by the dormant biological nature of lymph node metastasis. On the other hand, while analyzing the survival outcome in the high-risk group with respect to the percentage of lymph node involvement to the total number of

Table 3. Survival outcomes of patients who underwent lymphadenectomy according to the percentage of involved lymph nodes out of the total number of lymph nodes removed.

	Total number of patients	Number of cancer-related deaths	Mean survival in months (percentage survival)	95% CI of survival in months	*P*-value for log rank test					
					A 1	A 2	A 3	A 4	A 5	A 6
A 1	23,912	916	102.52 (96.2%)	102.24-102.8		< 0.001	< 0.001	0.01	< 0.001	< 0.001
A 2	871	124	89.66 (85.8%)	86.93-92.39	< 0.001		< 0.001	< 0.001	< 0.001	< 0.001
A 3	896	222	78.21 (75.3%)	75.1-81.34	< 0.001	< 0.001		< 0.001	< 0.001	< 0.001
A 4	357	125	67.1 (65%)	61.74-72.35	< 0.001	< 0.001	< 0.001		< 0.001	< 0.001
A 5	303	160	48.1 (47.2%)	42.38-53.78	< 0.001	< 0.001	< 0.001	< 0.001		< 0.001
A 6	15,273	896	100.29 (94.2%)	99.86-100.71	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	

A1: no lymph node involvement, A2: < 10% lymph node involvement, A3: 10%-30%, A4: 30%-50%, A5: > 50%, A6: no lymphadenectomy.

Table 4. Survival outcomes of high-risk patients who underwent lymphadenectomy according to the percentage of involved lymph nodes out of the total number of lymph nodes removed.

	Total number	Number of events	Mean survival in months (percentage survival)	95% CI of survival (months)	*P*-value for log-rank test				
					B 1	B 2	B 3	B 4	B 5
B 1	7,212	440	99.83 (93.9%)	99.19-100.48		< 0.001	< 0.001	0.01	< 0.001
B 2	445	67	88.88 (84.9%)	85.24-92.52	< 0.001		0.02	< 0.001	< 0.001
B 3	423	89	82.96 (78.9%)	78.85-87.08	< 0.001	0.02		0.05	0.04
B 4	136	37	74.60 (72.8%)	66.31-82.89	< 0.001	< 0.001	0.05		0.68
B 5	76	24	68.99 (68.4%)	59.09-78.90	< 0.001	< 0.001	0.04	0.68	
Total	8,292	657	97.75 (92.1%)	97.08-98.42					

B1: No lymph node involvement, B2: > 10% lymph node involvement, B3: 10%-30%, B4: 30%-50%, B5: > 50%.

extracted lymph nodes, we demonstrated a significant linearly progressive worsening in survival with increasing percentage of involved lymph nodes. This finding is also consistent with the results of two prospective studies [6, 7] as well as a recent retrospective study [19]. We consider this finding to negate the therapeutic value of lymphadenectomy. If the procedure had provided a survival benefit, it would have been manifested in observing a better or at least comparable survival rate between groups regardless of the percentage of lymph node involvement.

As regards the quality or efficiency of the lymphadenectomy procedure itself, our results showed a positive correlation between survival and increasing lymph node yield until a plateau of 40 or more lymph nodes was reached, above which the extraction of additional lymph nodes did not provide any further survival benefit to the patient. Chan *et al.* (2006) have also reported a limited survival benefit associated with the extraction up to a maximum threshold number of lymph nodes; in their study the threshold above which no further survival benefit of lymph node removal in high risk endometrial cancer patients occurred at 20 lymph nodes [20]. Although the threshold observed in our study's patients was twice as high as that reported in the Chan *et al.,* study the overall finding of a limited survival benefit for lymphadenectomy is consistent between them.

Lymphadenectomy in early-stage high-risk endometrial cancer is considered an important tool in guiding further adjuvant treatment modalities. Prospective randomized trials have shown no survival benefit for radiotherapy in intermediate/high-risk endometrial cancer patients [13, 14], but have demonstrated a significant progression-free interval that could be attained by brachytherapy alone without external pelvic irradiation [15]. Our results, derived from a US population-based database, are concordant with these findings. Our results indicate that administering radiotherapy to high-risk patients without determining lymph node status did not provide any survival benefit, supporting the current role of lymphadenectomy in the diagnostic algorithm of endometrial cancer. In fact, in this study's cohort, administering external beam irradiation without having determined lymph node status by lymphadenectomy was associated with a marginally worse overall survival.

Our study's findings reflect the implications of treatment recommendations on a US based population. Many patients with histologically defined disease-free lymph nodes received pelvic irradiation, while other high-risk patients that should have received lymphadenectomy did not undergo this procedure but were nonetheless treated with pelvic irradiation that marginally worsened the outcome. We were unfortunately unable to extract the basis for such decisions from the data.

Limitations of this study include the retrospective nature of the analysis, missing information regarding standardization of indications as well as likely variation in the performance efficiency of the lymphadenectomy procedure itself. Furthermore, the extent of regional lymph node resection

Table 5a. Survival outcomes of patients who underwent lymphadenectomy according to the absolute number of removed lymph nodes.

	Number	Mean survival (months)	95% CI for survival (months)							
				0	**1-10**	**11-20**	**21-30**	**31-40**	**41-50**	**51-60**	**> 60**
0	15,273	100.29	99.86-100.71		**0.01***	**0.017***	**0.032***	0.336	0.545	0.455	0.21
1-10	10,207	99.26	98.71-99.81	**0.01***		**< 0.001***	**< 0.001***	**0.04***	0.87	0.79	0.38
11-20	8,904	100.9	100.36-101.44	**0.017***	**< 0.001***		0.78	0.75	0.15	0.18	0.07
21-30	4,552	100.93	100.17-101.69	**0.032***	**< 0.001***	0.78		0.624	0.13	0.17	0.07
31-40	1,710	100.65	99.38-101.91	0.336	**0.04***	0.75	0.624		0.29	0.27	0.12
41-50	612	99.41	97.16-101.67	0.545	0.87	0.15	0.13	0.29		0.75	0.39
51-60	224	98.49	94.51-102.47	0.455	0.79	0.18	0.17	0.27	0.75		0.61
> 60	130	97.18	91.67-102.69	0.21	0.38	0.07	0.07	0.12	0.39	0.61	

Table 5b. Survival outcomes of high-risk patients who underwent lymphadenectomy according to the absolute number of removed lymph nodes.

	Total number	Number of events	Mean survival in months (percentage survival)	95% CI of survival (months)	*P*-value for log-rank test					
					1-10	11-20	21-30	31-40	41-50	> 51
1-10	2,892	272	96.36 (90.6%)	95.17-97.55		**0.03**	**0.002**	**0.03**	0.83	0.53
11-20	2,877	214	98.13 (92.6%)	96.99-99.26	**0.03**		0.16	0.29	0.27	0.98
21-30	1,546	101	99.35 (93.5%)	97.92-100.78	**0.002**	0.16		0.96	0.07	0.57
31-40	607	37	99.35 (93.1%)	96.98-101.71	**0.03**	0.29	0.96		0.11	0.56
41-50	221	22	95.72 (90.1%)	91.32-100.11	0.83	0.27	0.07	0.11		0.56
> 51	149	11	97.28 (92.4%)	92.35-102.2	0.53	0.98	0.57	0.56	0.56	
Total	8,292	657	97.75 (92.1%)	97.1-98.42						

Table 6a. Survival outcomes of patients who underwent lymphadenectomy according to the absolute number of involved lymph nodes.

	Total number (percentage)	Mean survival (months)	95% CI of survival (months)	*P*-value for log-rank test							
				C 1	C 2	C 3	C 4	C 5	C 6	C 7	C 8
C 1	23,912 (57.5%)	102.52	102.24-102.8		**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**
C 2	995 (2.4%)	82.28	79.45-85.11	**< 0.001**		**0.01**	0.81	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**
C 3	561 (1.3%)	76.1	72.02-80.02	**< 0.001**	**0.01**		0.12	0.31	0.1	**< 0.001**	**< 0.001**
C 4	285 (0.7%)	81.39	75.97-86.82	**< 0.001**	0.81	0.12		**0.03**	**0.01**	**< 0.001**	**< 0.001**
C 5	165 (0.4%)	72.76	65.17-80.35	**< 0.001**	**< 0.001**	0.31	**0.03**		0.58	**0.01**	**< 0.001**
C 6	120 (0.3%)	67.65	58.69-76.59	**< 0.001**	**< 0.001**	0.1	**0.01**	0.58		0.1	**< 0.001**
C 7	301 (0.7%)	59.58	53.59-65.57	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**	**0.01**	0.1		**< 0.001**
C 8	15,273 (36.7%)	100.29	99.86-100.71	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**	

C1: no lymph node involvement, C2: 1 lymph node involved, C3: 2 lymph nodes involved, C4: 3 lymph nodes involved, C5: 4 lymph nodes involved, C6: 5 lymph nodes involved, C7: 6-90 lymph nodes involved, C8: no lymphadenectomy.

was not clearly defined in the source data, meaning that we could not conclude whether para-aortal lymph node dissection was performed in all cases, as recommended [21, 22], and as shown in a recent retrospective analysis to provide a survival benefit in high-risk endometrial cancer patients [23]. Another weakness of this study is that there was no information recorded regarding the type of radiation therapy performed and this is likely to have varied.

6. Conclusions

From this analysis, we could not provide clear evidence that lymphadenectomy confers a survival benefit to patients with endometrioid endometrial cancer. However, the current role of lymphadenectomy in staging and as a tool for guiding further adjuvant treatment was supported. Well-designed prospective randomized trials are required to determine the therapeutic value of lymphadenectomy in patients with high-risk endometrioid endometrial cancers.

Table 6b. Survival outcomes of high-risk patients who underwent lymphadenectomy according to the absolute number of involved lymph nodes.

	Total number	Number of events	Mean survival in months (percentage survival)	95% CI of survival (months)	*P*-value for log-rank test						
					D 1	D 2	D 3	D 4	D 5	D 6	D 7
D 1	7,212	440	99.83 (93.9%)	99.19-100.48		**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**
D 2	463	83	86.25 (82.1%)	82.51-89.99	**< 0.001**		0.41	0.76	**0.02**	**0.02**	0.07
D 3	263	54	83.90 (79.5%)	78.65-89.15	**< 0.001**	0.41		0.37	0.10	0.08	0.24
D 4	139	22	82.50 (84.2%)	76.34-88.67	**< 0.001**	0.76	0.37		**0.04**	**0.02**	0.08
D 5	72	20	75.66 (72.2%)	64.74-86.58	**< 0.001**	**0.02**	0.1	**0.04**		0.79	0.65
D 6	49	15	65.93 (69.4%)	54.90-76.97	**< 0.001**	**0.02**	0.08	**0.02**	0.79		0.54
D 7	94	23	76.07 (75.5%)	66.40-85.73	**< 0.001**	0.07	0.24	0.08	0.65	0.54	
Total	8,292	657	97.75 (92.1%)	97.08-98.42							

D1: no lymph node involvement, D2: 1 lymph node involved, D3: 2 lymph nodes involved, D4: 3 lymph nodes involved, D5: 4 lymph nodes involved, D6: 5 lymph nodes involved, D7: 6-90 lymph nodes involved.

Table 7a. Survival outcomes of high-risk patients who did not undergo any lymphadenectomy according to the type of radiation received (if any).

						P-value for log-rank test (no lymphadenectomy)			
Node status	Radiation	Number of cases	Number of events	Mean survival in months (percentage survival)	95% CI of survival (months)	No radiation	Refused radiation	External beam	Brachytherapy
No lymphadenectomy	No radiation	1,030	131	92.32 (87.3%)	89.99-94.64		0.1	0.6	**0.04**
	Refused radiation	22	5	74.68 (77.3%)	55.68-93.68	0.1		0.2	**0.01**
	External beam	469	71	91.2 (84.9%)	87.85-94.55	0.6	0.2		**0.03**
	Brachytherapy	475	45	95.09 (90.5%)	92.12-98.07	**0.04**	**0.01**	**0.03**	
	Overall	1,996	252	92.83 (87.4%)	91.22-94.44				

Table 7b. Survival outcomes of high-risk patients who underwent lymphadenectomy that revealed no lymph node involvement, according to radiation type (if any).

						P-value for log-rank test (negative lymph nodes)			
Node status	Radiation	Number of cases	Number of events	Mean survival in months (percentage survival)	95% CI of survival (months)	No radiation	Refused radiation	External beam	Brachytherapy
Negative lymph nodes	No radiation	3,350	174	100.95 (94.2%)	100.08-101.82		0.7	**0.001**	0.4
	Refused radiation	88	5	99.95 (94.3%)	93.99-105.91	0.7		0.4	0.8
	External beam	1,114	118	96.3 (89.4%)	94.5-98.11	**0.001**	0.4		**0.001**
	Brachytherapy	2,660	143	100.11 (94.6%)	99.02-101.21	0.4	0.8	**0.001**	
	Overall	7,212	440	99.83 (93.9%)	99.19-100.48				

Table 7c. Survival outcomes of high-risk patients who underwent lymphadenectomy that revealed lymph node involvement, according to radiation type (if any).

						P-value for log-rank test (positive lymph nodes)			
Node status	Radiation	Number of cases	Number of events	Mean survival in months (percentage survival)	95% CI of survival (months)	No radiation	Refused radiation	External beam	Brachytherapy
Positive lymph nodes	No radiation	417	91	79.72 (78.2%)	75.13 - 84.32		0.3	**0.003**	0.5
	Refused radiation	20	2	84.05 (90%)	69.84 - 98.26	0.3		0.7	0.4
	External beam	370	61	89.49 (83.5%)	85.56 - 93.42	**0.003**	0.7		**0.02**
	Brachytherapy	273	63	81.02 (76.9%)	75.92 - 86.12	0.5	0.4	**0.02**	
	Overall	1,080	217	84.16 (79.9%)	81.54 - 86.77				

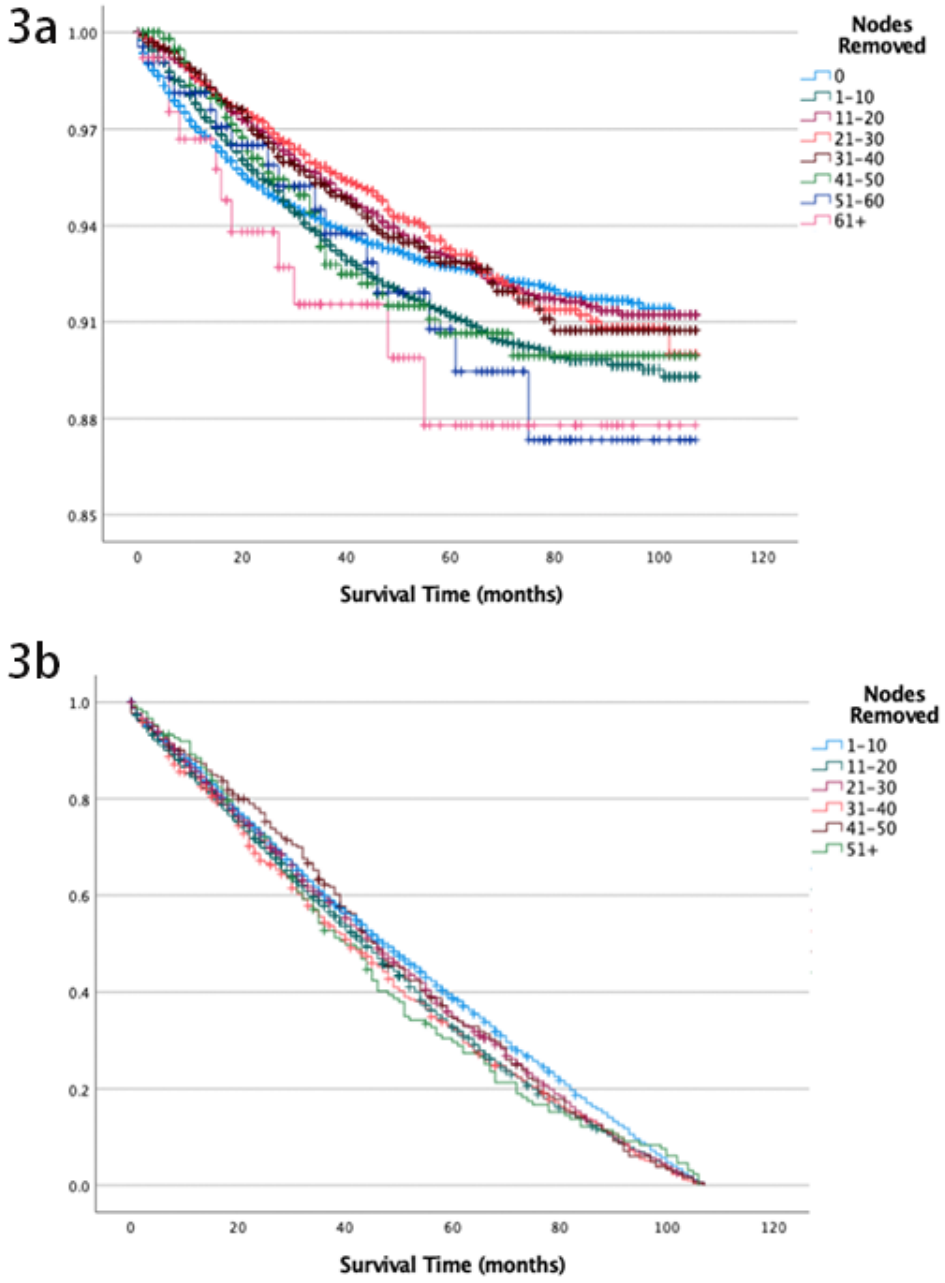

Fig. 3. (a). Kaplan-Meier curves showing the overall survival in the patients who received a lymphadenectomy according to the number of removed lymph nodes and (b). Kaplan-Meier curves showing the overall survival in the high-risk patients who received a lymphadenectomy according to the number of removed lymph nodes. A lymph node yield greater than 40 did not confer any further significant overall survival benefit.

Abbreviations

AGO, German workgroup on gynecologic oncology (Arbeitsgemeinschaft Gynäkologische Onkologie); CI, confidence interval; FIGO, Fédération Internationale de Gynécologie et d'Obstétrique; OS, overall survival; SD, standard deviation; SEER, Surveillance, Epidemiology and End Results program.

Author contributions

All authors contributed to study design and idea formulation. AAS, MSS, SAM, SA, AN and BR were responsible for data acquisition and tabulation. AAS, MSS, SAM, OG and EM contributed to statistical analysis and data editing. All authors contributed to manuscript writing, revision and finalizing in its current form, and are hence responsible for the work in its current form.

Ethics approval and consent to participate

This article does not contain any studies with human participants performed by any of the authors.

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Conflict of interest

The authors declare no competing interests.

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