



Lymph node dissection in endometrial cancer and clinical outcome: A population-based study in 5546 patients

M. Pölcher^{a,*,1}, M. Rottmann^{b,1}, S. Brugger^a, S. Mahner^c, C. Dannecker^c, M. Kiechle^d, C. Brambs^d, D. Grab^e, C. Anthuber^f, F. von Koch^g, A. Schnelzer^h, J. Engel^b

^a Department of Gynecologic Oncology and Minimally-invasive Surgery, Rotkreuzklinikum München, Frauenklinik Taxisstraße Munich, Germany

^b Munich Cancer Registry, Institute for Medical Information Processing, Biometry and Epidemiology, Ludwig-Maximilians-University (LMU), Munich, Germany

^c Department of Obstetrics and Gynecology, University Hospital, LMU Munich, Germany

^d Department of Obstetrics and Gynecology, University Hospital, Technical University Munich, Germany

^e Department of Obstetrics and Gynecology Städtisches Klinikum Harlaching Munich, Germany

^f Department of Obstetrics and Gynecology Klinikum Starnberg, Germany

^g Department of Obstetrics and Gynecology, Klinikum Dritter Orden, Munich, Germany

^h Department of Obstetrics and Gynecology, RoMed Kliniken, Rosenheim, Germany

HIGHLIGHTS

- Although it is recommended, a high proportion of patients had no lymph node surgery.
- The incidence of recurrence seems not to be related to lymph node dissection.
- The comorbidity status should be considered in analyses of lymph node surgery.
- The survival analysis challenges lymph node dissection in endometrial cancer.

ARTICLE INFO

Article history:

Received 2 January 2019

Received in revised form 1 April 2019

Accepted 2 April 2019

Available online 23 April 2019

Keywords:

Endometrial cancer
Lymph node dissection
Surgery
Sentinel lymph node
Survival
Comorbidity

ABSTRACT

Background. According to current treatment guidelines, comprehensive surgical staging procedures in endometrial cancer confined to the uterus depend on uterine risk factors: a systematic lymph node dissection (LND) is recommended in high risk patients and should be omitted in low risk patients. Its role in intermediate and high intermediate risk patients is inconclusive. The aim of this analysis was to review the implementation of this risk-adopted strategy.

Materials and methods. Data were provided by the population-based Munich Cancer Registry. Patients with endometrial cancer diagnosed between 1998 and 2016 were included.

Results. Of 5446 eligible patients, 58.5%, 30.1% and 11.4% belonged to the low risk, intermediate/high-intermediate and high risk group, respectively. Lymph node dissection was performed in 20.2%, 53.0% and 63.7% within these groups. Lymph node involvement was diagnosed in 1.7%, 9.6% and 19.3%, respectively. Within these risk groups, there was no significant difference in the time to local recurrence, lymph node recurrence or distant metastases between patients with and without LND. After adjusting for age and comorbidity-status, no significant difference in overall survival was found.

Conclusions. The application of a risk-adopted management of LND in early endometrial cancer in real-life is associated with a high rate of surgical under- and overtreatment. Corresponding survival data do not show a significant benefit of a systematic lymph node dissection. In order to improve the management and outcome of early endometrial cancer in the future, prospective trials, new surgical concepts and prognostic markers will be primary and necessary.

© 2019 Elsevier Inc. All rights reserved.

* Corresponding author at: Rotkreuzklinikum München, Frauenklinik Taxisstraße 3, 80637 München, Germany.

E-mail addresses: martin.poelcher@swmbrk.de (M. Pölcher), rotmann@ibe.med.uni-muenchen.de (M. Rottmann), sarah.brugger@swmbrk.de (S. Brugger), sven.mahner@med.uni-muenchen.de (S. Mahner), christian.dannecker@med.uni-muenchen.de (C. Dannecker), marion.kiechle@tum.de (M. Kiechle), christine.brambs@tum.de (C. Brambs), dieter.grab@klinikum-muenchen.de (D. Grab), christoph.anthuber@klinikum-starnberg.de (C. Anthuber), franz.koch@dritter-orden.de (F. von Koch), andreas.schnelzer@ro-med.de (A. Schnelzer), engel@ibe.med.uni-muenchen.de (J. Engel).

¹ The authors equally contributed to the paper.

1. Introduction

Endometrial cancer is the most common carcinoma of the female genital tract with over 300,000 new cases diagnosed each year worldwide [1]. Projections show an increasing incidence of this disease related to the ageing population as well as the increasing prevalence of obesity and metabolic syndromes [2]. Nodal involvement is one of the most relevant prognostic factors. Therefore, lymph node status is important to determine tumor stage and to consider adjuvant radiotherapy, chemotherapy or both [3]. Imaging techniques showed unfavorable sensitivity and specificity, thus, the current “gold standard” in the assessment of lymph node status remains comprehensive surgical staging, i.e. systematic pelvic and para-aortic lymph node dissection (LND) [4,5]. Since two randomized studies on endometrial cancer could not show a benefit in recurrence free survival (RFS) or overall survival (OS) for patients who underwent at least systematic pelvic LND compared to patients without LND, the necessity of LND is an ongoing controversy [6,7].

According to treatment guidelines and international consensus statements, a risk adapted management strategy is applied in the current clinical concept: In patients classified as *low risk* for lymph node involvement and recurrence (risk stratification see Table 1), with a tumor confined to the uterus, no conspicuous intra-abdominal findings and the absence of risk factors, it includes a simple hysterectomy and bilateral salpingo-oophorectomy without lymph node assessment [8,9]. In patients with high risk factors a systematic LND is recommended due to a higher prevalence of nodal involvement. In cases of intermediate/high intermediate risk factors, the best practice remains controversial, resulting in the recommendation that LND “may be” performed or not [9]. The role of systematic lymph node dissections is becoming increasingly controversial in modern oncology [10–12].

Furthermore, stratification criteria in endometrial cancer are often not valid pre- or intraoperatively: grading may change after final histopathologic examination, and the depth of myometrial invasion can differ compared to initial findings of preoperative imaging or fresh frozen section during surgery. The decision for adequate lymph node assessment therefore poses a fundamental challenge in the clinical management of these patients: is a “one stop” surgical approach justified or is a secondary lymph node operation after final histopathologic assessment more reliable?

Longer operative times are necessary for a systematic lymph node dissection and can be associated with considerable short- and long-time morbidity. Increased blood loss, thromboembolic complications and impairment of wound healing are more common after LND, and lymphocele formation or edema of the limb with a leg volume change over 10% in up to 34% of patients are long-term adverse events [13,14]. Therefore, the extent of surgical staging is a consideration of its associated risks: the benefit of the knowledge about nodal involvement has to be balanced against the adverse events of comprehensive surgical staging. Today, there is a wide range of surgical staging

practices in endometrial cancer. The spectrum of lymph node assessment may consist of sentinel lymph node mapping, systematic pelvic or pelvic and paraaortic lymph node dissection [9,15].

Even though measurable criteria for omitting LND are lacking, it is likely that comprehensive surgical staging is rarely performed in patients with severe comorbidities. In addition to limited life expectancy, the restricted surgical treatment may also be due to a lack of adjuvant treatment. Therefore, the cohort of patients with LND may have an intrinsically favorable health status and better access to the recommended adjuvant treatment.

The aim of this study was to determine the status quo of surgical management of endometrial cancer in this large patient population. How many patients were surgically treated in accordance to the risk adopted algorithm consisting of the avoidance of an unnecessary LND in low risk patients and the performance of a reliable lymph node assessment in high risk patients. Also, how many patients with and without LND were diagnosed with loco-regional relapse or distant failure? And what is the correlation of LND and survival once the comorbidity status is considered?

2. Material and methods

2.1. Data collection

The Munich Cancer Registry (MCR) is a population-based clinical cancer registry representing Upper Bavaria and a region of Lower Bavaria in southern Germany [16]. The registry catchment area has grown to 4.8 million inhabitants over time. Pathology reports of solid tumors from all pathology laboratories in the catchment area are available and provide the total number of patients in the region as well as primary prognostic factors associated with the patients' disease. The clinicians provide data concerning patient age, primary disease characteristics (e.g. stage and histology), comorbidities and therapies. The survival status of patients with cancer diagnoses is updated systematically through death certificates. All data and outcome measurements (e.g. death, local recurrence, metastases) are documented according to the guidelines of the International Agency for Research in Cancer (IARC). Tumors are classified according to the staging criteria of the 7th edition (2009) of the Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) based on the TNM Classification of Malignant Tumors [17]. The FIGO stage of tumors that had been classified according to the former 5th edition (1997) or 6th edition (2002) was adjusted according to the 7th edition (2009), i.e. stage IB was changed to stage IA and stage IC was changed to IB, respectively.

2.2. Patients

Between 1998 and 2016, a total number of 9468 patients were diagnosed with tumors originating from the endometrium within the catchment area (Fig. 1). Patients with non-invasive carcinoma ($n = 34$), sarcoma or lymphoma ($n = 384$) as well as cases registered by death certificates only ($n = 33$) or those who did not undergo a hysterectomy ($n = 664$) were excluded from the analysis. Furthermore, patients with evidence of previous or synchronous malignant tumors ($n = 1318$) were excluded in order to eliminate conflicting treatment decisions and overlapping tumor effects. The analysis of the remaining patients provided a population-based survey of patients with a carcinoma of the endometrium ($n = 7035$). To evaluate the effects of the lymph node dissection (LND), analyses were limited to patients with stage pT1 disease without any evidence of distant metastases at the time of diagnosis. Risk groups were classified according to the European Society for Medical Oncology system, and intermediate and high intermediate risk groups were merged (cohort 1, $n = 5446$) [8]. An intraoperative frozen section was not mandatory in order to assess uterine risk factors. Secondary lymph node dissection after final pathology was at the discretion of the treating physician. LND was defined as pelvic or pelvic

Table 1
Risk groups according to ESMO-ESGO-ESTRO Consensus Conference [8].

	Grading	Histological type	Stage	LVSI
Low risk	G1, G2	Endometrioid	IA	Negative
Intermediate risk	G1, G2	Endometrioid	IA	Positive
	G1, G2	Endometrioid	IB	Negative
High-intermediate risk	G3	Endometrioid	IA	Negative
	G3	Endometrioid	IA	Positive
High risk	G1, G2	Endometrioid	IB	Positive
	G3	Endometrioid	IB	Negative/positive
	G3	Non-endometrioid	IA/B	Negative/positive
			II	Negative/positive

Stage: IA = myometrial invasion <50%; IB = myometrial invasion ≥50%;

Stage II = cervical involvement, LVSI = lymphovascular space invasion.

ESMO: European Society of Medical Oncology, ESGO: European Society of Gynecologic Oncology, ESTRO: European Society for Radiotherapy and Oncology

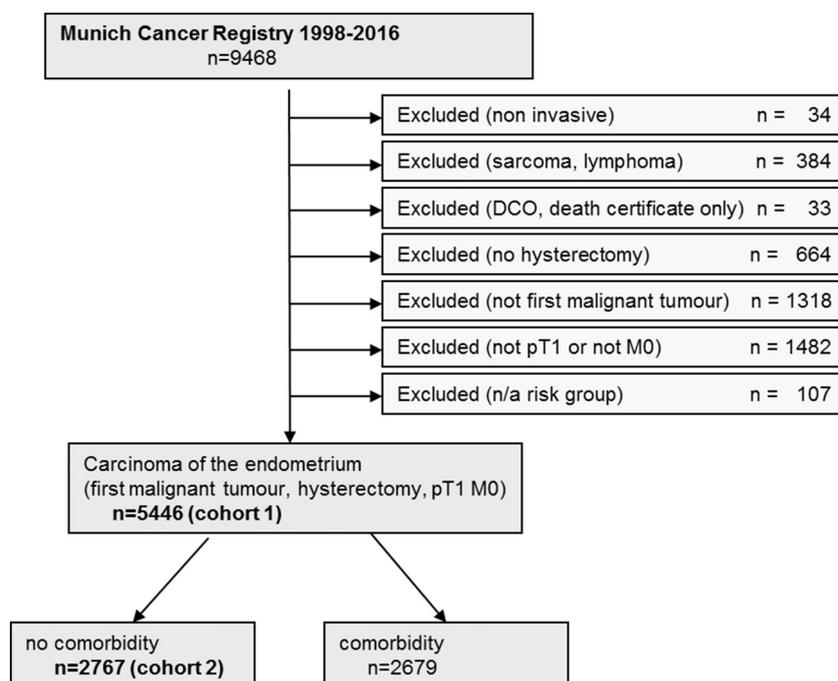


Fig. 1. Patient cohorts.

and para-aortic lymph node dissection. In cases of no specification the removal of at least 10 lymph nodes was required. Lower lymph node counts, lymph node samplings and sentinel lymph node dissections (SLND) were not considered as a sufficient lymph node assessment within the analysis and therefore analyzed as patients without LND.

One of the main reasons for omitting the LND may be a decreased medical condition and life-time affecting comorbidities. To reduce the impact of selection effects on overall survival, multivariate analyses were performed for patients without listed comorbidities (cohort 2; $n = 2767$).

2.3. Treatment recommendations within the study period

The interdisciplinary Munich Tumour Centre as well as the German Cancer Society have been developing guidelines on endometrial carcinoma since 1994 and 1999, respectively [18,19]. All these guidelines recommend at least a systematic pelvic LND for patients with intermediate/high intermediate or high risk uterine factors.

2.4. Adjuvant treatment

Postoperatively, women were managed with surveillance, vaginal brachytherapy, external beam radiation, combined radiotherapy, chemo-radiation or platinum- and taxane-based chemotherapy alone, reflecting individualized treatment decisions and developing national standards in adjuvant treatment recommendations within the study period.

2.5. Statistical analysis

The chi-square and Fisher's exact test were used to examine frequency data. To account for competing risks [20], a cumulative incidence (CI) analysis was used to calculate the time to progression (TTP). Differences among the subgroups were assessed by Gray's Test for Equality of Cumulative Incidence Functions. To determine the association of LND and overall survival (OS), independent factors were analyzed using a Cox proportional hazards model. The significance level for all analyses was set at 5%. Analyses were conducted using SAS software, version 9.4 (SAS Institute, Cary, N.C.).

3. Results

The overall detection rate of lymph node involvement in the entire cohort of pT1 tumors was 170 of 5446 patients (3.1%). Out of all LND ($n = 1906$) the vast majority of 91.1% ($n = 1736$) had no nodal involvement and lymph node metastases were found in 8.9% ($n = 170$). Median lymph node count was 29 (Range 10 to ≤ 99). In 3188 patients with low risk factors, a LND was performed in 20.2% ($n = 643$). Within these patients, 1.7% ($n = 11$) were node-positive. In 1639 patients with intermediate/high intermediate risk factors, the LND was performed in 53.0% ($n = 869$) to find 9.6% ($n = 83$) node-positive patients. In 619 stage pT1 high risk patients, an LND was performed in 63.7% ($n = 394$) whereof 19.3% ($n = 76$) of the patients were node-positive (Table 2). These results confirm the increasing risk of lymph node involvement according to uterine risk factor groups. Patients without comorbidities ($n = 2767$; 50.8%) had a significantly higher rate of LND compared to patients with no comorbidities ($n = 2679$; 49.2%) in the intermediate/high intermediate risk group ($p = 0.007$) and in the high risk group ($p = 0.001$) (Table 2).

The cumulative incidence of lymph node recurrence, local recurrence and distant metastasis did not differ significantly for patients without LND compared to patients with LND (Table 3 and Fig. 2).

Adjuvant treatment was not used to compensate for a missing lymph node status as the number of patients who underwent postoperative radiotherapy or chemotherapy was much lower in patients without LND. Survival analysis was performed in patients with and without comorbidities. A comparison of patients with LND to those without LND did not show significant survival differences in patients without comorbidities after adjusting for age (Table 4).

4. Discussion

This population-based cohort study presents a valid indication for the limitation of the current risk-adopted algorithm and the surgical intervention of a systematic lymph node dissection in early stage endometrial cancer. It suggests that the current concept is potentially associated with a high proportion of surgical over- and under-treatment. In 29% of the entire cohort, surgical staging differed from guideline recommendations. Treatment recommendations do not

Table 2
Patient characteristics and treatment.

		LND		no LND		Total		p-Value	
		n	%	n	%	n	%		
Cohort 1 (n = 5446)	Risk group							<0.001	
	Low	643	20.2	2545	79.8	3188	58.5		
	Intermediate/high Interm.	869	53.0	770	47.0	1639	30.1		
	High	394	63.7	225	36.4	619	11.4		
	Lymph node involvement								
	Low	11	1.7	–		11	0.4		
	Intermediate/high Interm.	83	9.6	–		83	5.1		
	High	76	19.3	–		76	12.9		
	Age								<0.001
	<60 years	503	36.6	871	63.4	1374	25.2		
	60–69	761	41.6	1069	58.4	1830	33.6		
70–79	564	35.0	1046	65.0	1610	29.6			
≥80	78	12.3	554	87.7	632	11.6			
Comorbidities							0.020		
Yes	895	47.0	1784	50.4	2679	49.2			
No	1011	53.0	1756	49.6	2767	50.8			
Cohort 2 (n = 2767) (No comorbidity)	Risk group							<0.001	
	Low	332	20.2	1311	79.8	1643	59.4		
	Intermediate/high Interm.	439	56.5	338	43.5	777	28.1		
	High	240	69.2	107	30.8	347	12.5		
	Radiotherapy								
	Low	114	34.3	223	17.0	337	20.5		
	Intermediate/high interm.	320	72.9	140	41.4	460	59.2		
	High	129	53.8	36	33.6	165	47.6		
	Chemotherapy								
	low	0	0.0	0	0.0	0	0.0		
	Intermediate/high interm.	2	0.5	0	0.0	2	0.3		
	High	11	4.6	0	0.0	11	3.2		
	Radiotherapy and chemotherapy								
	Low	1	0.1	1	0.1	2	0.1		
	Intermediate/high interm.	15	3.4	5	1.5	20	2.6		
High	30	12.5	1	0.9	31	8.9			

Table 3
Cumulative incidence of lymph node recurrence, local recurrence and distant metastasis in patients with and without LND after 5 years (cohort 1).

	Low risk			Intermediate/high intermediate risk			High risk		
	LND	No LND	p	LND	No LND	p	LND	No LND	p
lymph node-recurrence	0.6	0.7	n.s.	2.1	2.3	n.s.	4.4	4.2	n.s.
local recurrence	2.1	2.4	n.s.	6.7	6.9	n.s.	11.2	9.7	n.s.
distant metastasis	2.5	3.0	n.s.	9.5	10.9	n.s.	25.4	25.0	n.s.

LND: Lymph node dissection.

include an LND in the low risk group. However, about every fifth low risk patient underwent an LND. In contrast, more than one third of the patients who do not fall into the low risk group had no surgical lymph node assessment.

Patients with a tumor confined to the uterine corpus had no lymph node involvement after lymph node dissection in 91% and were exposed to the potential morbidity of comprehensive surgery.

This study raises doubts regarding a potential measurable treatment effect of systematic LND. Omitting lymph node dissection entirely suggests a similar rate of nodal involvement in the cohort of patients without LND compared to those with LND. A detrimental effect may be expected due to the need for adjuvant treatment guided by node positive disease. In patients with undetected stage IIIC disease, the need for adequate adjuvant treatment is withheld and the prognosis therefore considered inferior. The comparison of time to recurrence within each risk group did not show a significant difference between the cohorts with LND compared to those without LND challenging the term “therapeutic lymph node dissection” in endometrial cancer.

Furthermore, this study provides strong evidence of the substantial correlation between age as well as comorbidity status and overall survival. Age is an independent prognostic factor, and younger patients were more often treated by LND than older patients. Patients with comorbidities may have a limited life expectancy regardless of their malignant tumor. The univariate analysis showed favorable OS for patients with compared to those without LND in intermediate/high intermediate and high risk groups, suggesting a survival benefit as a treatment effect of the surgical procedure. However, after adjusting for age and excluding patients with comorbidities, the Cox regression model did not show superior survival data in patients with LND compared to patients without LND.

The inability to account for confounding factors, i.e. comorbidity that influence survival is an important limitation of retrospective studies. Chan et al. evaluated the extent of lymph node dissection in 12,333 patients of the SEER database with endometrioid uterine carcinoma and found improved overall survival rates associated with systematic LND in stage I-IV disease [21]. Trimble et al. reported a significant positive

Fig. 2. Time to lymph node recurrence, local recurrence and distant metastasis (cumulative incidence) by risk group and lymph node dissection (LND) (cohort 1) a) lymph node recurrence b) local recurrence c) distant metastasis.

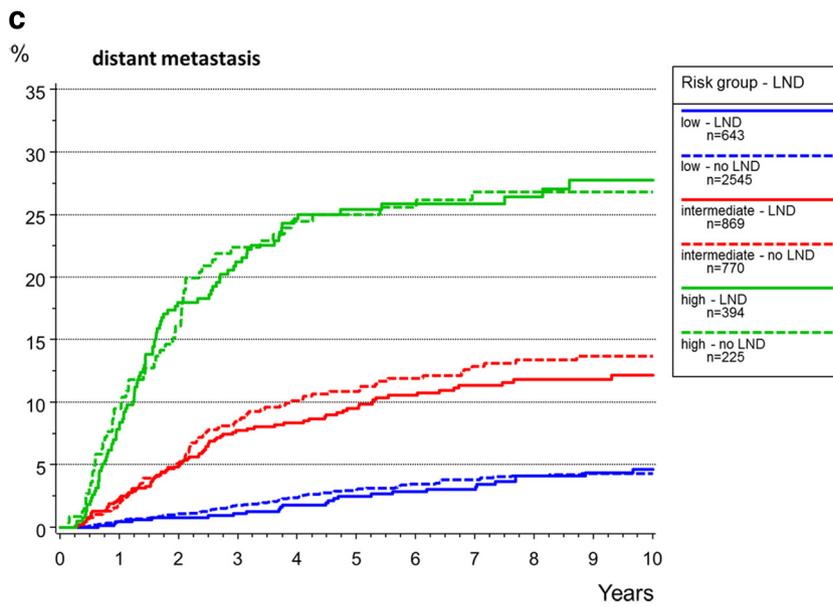
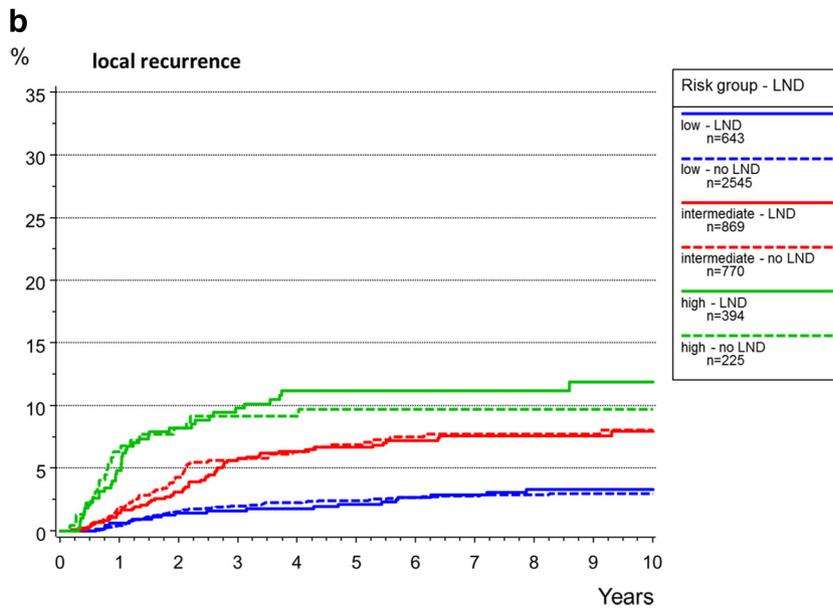
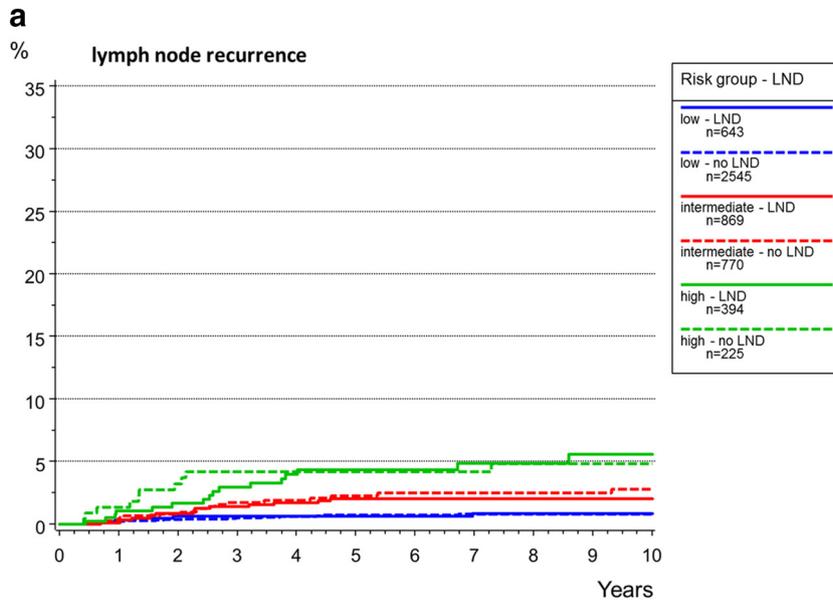


Table 4
Multivariate analysis (overall survival) of lymph node dissection (LND) for patients without comorbidities (cohort 2: n = 2767).

	HR [95%-CI]	p-Value
Low risk no LND vs. LND	1.12 [0.77;1.61]	0.560
Age		
<60	1.00	<0.001
60–69	2.23 [1.38;3.60]	
70–79	6.17 [3.90;9.77]	
≥80	21.29 [12.82;35.34]	
Intermediate/high interm. risk no LND vs. LND	HR [95%-CI] 0.91 [0.65;1.26]	p-Value 0.557
Age		
<60	1.00	<0.001
60–69	1.09 [0.64;1.86]	
70–79	2.83 [1.70;4.69]	
≥80	7.91 [4.61;13.59]	
High risk no LND vs. LND	HR [95%-CI] 1.44 [0.98;2.11]	p-Value 0.066
Age		
<60	1.00	<0.001
60–69	1.49 [0.67;3.29]	
70–79	4.92 [2.41;10.03]	
≥80	6.30 [2.95;13.43]	

HR: Hazard ratio; CI: confidence interval.

correlation for lymph node sampling and 5 year OS in stage I/II G3 [22]. Cragun et al. described a correlation between the extent of LND and prognosis, with a longer OS when >11 lymph nodes were removed [23]. Todo et al. compared pelvic LND with pelvic and paraaortic LND and found significantly more favorable OS associated with a more comprehensive staging [24]. These studies advocate for a more radical approach of lymph node surgery. However, all these retrospective studies did not incorporate comorbidity as a confounding factor.

More recently, several studies evaluated the role of LND with attention to the comorbidity status of the patients. Matched pair analyses did not show survival benefits in patients with stage I intermediate risk cancer or high risk cancer, and a study considering the comorbidity status within a multivariable analysis did not find survival differences in stage IB patients with endometrioid carcinoma [25–27]. Two randomized phase 3 studies on lymph node dissection in endometrial cancer reported no differences in survival [6,7]. Concerns have been raised over these results because a high proportion of low risk patients may have led to a concealment of survival differences in patients who were at higher risk. In the current study, three risk groups were therefore analyzed independently in order to focus on potential effects specific to each risk group. Another main criticism of these phase 3 studies was the absence of a standardized adjuvant treatment strategy within the studies. However, until today clinical trials have failed to demonstrate that adjuvant radiotherapy improves overall survival, although it reduces the number of pelvic recurrences [5,28,29]. Therefore, we did not adjust for different adjuvant therapies.

Some limitations have to be addressed. The drawbacks of a cohort study with missing values and absent randomization offer restricted evidence. A centralized pathologic slide review was not available. The extent of the influence of the comorbidity status on treatment decisions is unclear. We therefore focused on patients without comorbidities. There is no standardized coverage of the comorbidity status in the data entry form of the MCR, i.e. the report contains a dichotomizing “yes” or “no”. This may result in differences between reporting centers. More detailed information like the *Charlson Comorbidity Index* would be preferable. Additionally, preoperative imaging was not mandatory and may have influenced the decision for LND in cases of suspected nodal involvement. The cut-off to define a comprehensive surgical staging (10 lymph nodes) was arbitrarily chosen and may not actually identify a radical surgical approach. In addition the treatment recommendations and clinical management concepts concerning LND have changed throughout the long study period, and the lymph node assessment may vary between the participating centers as well as over time.

A growing body of evidence of randomized studies in other cancers like breast cancer, lung cancer, malignant melanoma or ovarian cancer suggests that the prognostic information of lymph node dissection is useful but the surgical removal of lymph nodes has no impact on survival [10–12,30]. A new randomized trial was launched to address the role of systematic LND in intermediate and high risk endometrial cancer compared to no lymph node assessment at all [31].

Sentinel lymph node dissection (SLND) can serve as a useful tool whenever a reduction of surgical morbidity can be achieved while gaining information on nodal involvement, adjuvant treatment and prognosis [32,33]. More than 70% of patients with endometrial cancer are potentially eligible for SLND [34]. First prospective multicenter studies were reported with encouraging results [35,36]. During the observation period of this study, SLND was not an important issue as it was implemented in <1.4%. First treatment recommendations rated SLND as a reasonable approach for lymph node assessment in endometrial cancer [15].

Endometrial cancer is a heterogeneous group including various histological types and stages of disease. New findings in genetic profiling suggest different subtypes in endometrial cancer independent of histomorphological features [37,38]. Attention will be turned to new prognostic factors and therapeutic differences within these groups and may influence classifications and surgical treatment decisions in the future. Further randomized trials will be focused on investigating the role of systematic lymph node dissection for patients with endometrial cancer to direct adjuvant treatment and the role of sentinel lymph node biopsy.

Abbreviations

95%-CI	95% Confidence interval
DCO	Death certificate only
ESGO	European Society of Gynecologic Oncology
ESMO	European Society of Medical Oncology
ESTRO	European Society for Radiotherapy and Oncology
HR	Hazard ratio
LND	Lymph node dissection
MCR	Munich Cancer Registry
NCCN	National Comprehensive Cancer Network
OS	Overall survival
SEER	Surveillance, Epidemiology, and End Results Program
SLND	Sentinel Lymph Node Dissection

Conflict of interest

The authors have no conflict of interest concerning this paper.

General conflict of interest

MP reports personal fees for serving on advisory boards and lecture honoraria from AstraZeneca, Teva and Roche. SM reports grants and personal fees from AstraZeneca, personal fees from Clovis, grants and personal fees from Medac, grants and personal fees from MSD, personal fees from Novartis, grants and personal fees from PharmaMar, grants and personal fees from Roche, personal fees from Sensor Kinetics, grants and personal fees from Tesaro, grants and personal fees from Teva, outside the submitted work; CB reports personal fees for serving on advisory boards and lecture honoraria from Teva and Roche. FK reports lecture honoraria from Roche; AS reports personal fees for serving on advisory boards and lecture honoraria from AstraZeneca, Teva, Omniamed, Gedeon Richter, Tesaro and Roche.

MR, SB, MK, DG, CD, CA, JE are reporting no general conflict of interest.

Acknowledgements

We thank all the hospitals, departments, and practitioners that participated in the documentation of the data of the Munich Cancer Registry.

Contributors

MP and MR drafting of the manuscript, MR and JE planned, performed and wrote the statistical analyses, all other authors were responsible for patient recruitment, documentation and wrote and approved the final article.

References

- [1] WHO. GLOBOCAN, Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012, (01 June 2017, date last accessed) 2012 2012.
- [2] M.A. Sheikh, A.D. Althouse, K.E. Freese, S. Soisson, R.P. Edwards, S. Welburn, et al., USA endometrial cancer projections to 2030: should we be concerned? *Future Oncol.* 10 (2014) 2561–2568.
- [3] J. Zhou, Z.Y. He, F.Y. Li, J.Y. Sun, H.X. Lin, S.G. Wu, et al., Prognostic value of lymph node ratio in stage IIIC epithelial ovarian cancer with node-positive in a SEER population-based study, *Oncotarget* 7 (2016) 7952–7959.
- [4] T.J. Selman, C.H. Mann, J. Zamora, K.S. Khan, A systematic review of tests for lymph node status in primary endometrial cancer, *BMC Womens Health* 8 (2008) 8.
- [5] H.M. Keys, J.A. Roberts, V.L. Brunetto, R.J. Zaino, N.M. Spirtos, J.D. Bloss, et al., A phase III trial of surgery with or without adjuvant external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study, *Gynecol. Oncol.* 92 (2004) 744–751.
- [6] P. Benedetti Panici, S. Basile, F. Maneschi, A. Alberto Lissoni, M. Signorelli, G. Scambia, et al., Systematic pelvic lymphadenectomy vs. no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial, *J. Natl. Cancer Inst.* 100 (2008) 1707–1716.
- [7] H. Kitchener, A.M. Swart, Q. Qian, C. Amos, M.K. Parmar, Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study, *Lancet* 373 (2009) 125–136.
- [8] N. Colombo, C. Creutzberg, F. Amant, T. Bosse, A. Gonzalez-Martin, J. Ledermann, et al., ESMO-ESGO-ESTRO consensus conference on endometrial Cancer: diagnosis, treatment and follow-up, *Int. J. Gynecol. Cancer* 26 (2016) 2–30.
- [9] Leitlinienprogramm Onkologie, (Deutsche Krebsgesellschaft DK, AWMF). Diagnostik, Therapie und Nachsorge der Patientinnen mit Endometriumkarzinom, AWMF Registernummer: 032/034-OL, 2018.
- [10] G.E. Darling, M.S. Allen, P.A. Decker, K. Ballman, R.A. Malthaner, R.I. Inculat, et al., Randomized trial of mediastinal lymph node sampling versus complete lymphadenectomy during pulmonary resection in the patient with N0 or N1 (less than hilar) non-small cell carcinoma: results of the American College of Surgery Oncology Group Z0030 Trial, *J. Thorac. Cardiovasc. Surg.* 141 (2011) 662–670.
- [11] P. Harter, J. Sehoul, D. Lorusso, A. Reuss, I. Vergote, C. Marth, et al., A randomized trial of lymphadenectomy in patients with advanced ovarian neoplasms, *N. Engl. J. Med.* 380 (2019) 822–832.
- [12] U. Leiter, R. Stadler, C. Mauch, W. Hohenberger, N. Brockmeyer, C. Berking, et al., Complete lymph node dissection versus no dissection in patients with sentinel lymph node biopsy positive melanoma (DeCOG-SLT): a multicentre, randomised, phase 3 trial, *Lancet Oncol.* 17 (2016) 757–767.
- [13] N.R. Abu-Rustum, K. Alektiar, A. Iasonos, G. Lev, Y. Sonoda, C. Aghajanian, et al., The incidence of symptomatic lower-extremity lymphedema following treatment of uterine corpus malignancies: a 12-year experience at Memorial Sloan-Kettering Cancer Center, *Gynecol. Oncol.* 103 (2006) 714–718.
- [14] J.W.K.J. Carlson, A. Hutson, J. Carter, J.A. Armer, S. Lockwood, S. Nolte, L. Wenzel, J.L. Walker, A.C. Fleury, A.J. Bonebrake, J.T. Soper, C.A. Mathews, O. Zivanovic, W.E. Richards, D.S. Alberts, R.R. Barakat, GOG 244, the lymphedema and gynecologic cancer (LEG) study: incidence and risk factors in newly diagnosed patients, 49th Annual Meeting of the Society of Gynecologic Oncology Gynecologic Oncology (June 2018) 6–7.
- [15] NCCN, Clinical Practice Guidelines in Oncology, Uterine Neoplasms. National Comprehensive Cancer Network, 2017.
- [16] MCR: Munich Cancer Registry. Catchment Area of MCR, 2018.
- [17] L.W. Sobin, in: International union against Cancer (UICC) (Ed.), C. TNM Classification of Malignant Tumours, Wiley-Liss, New York, 2009.
- [18] Leitlinien zum Zervixkarzinom, zum Endometriumkarzinom und zu den Trophoblasttumoren., W. Zuckschwert Verlag, München Wien New York, 2008.
- [19] T. München, Endometriumkarzinom. Empfehlungen zur Diagnostik, Therapie und Nachsorge onkologischer Erkrankungen, Tumorzentrum München, München, 1994.
- [20] J. Kalbfleisch, R. Prentice, The Statistical Analysis of Failure Time Data, John Wiley, New York, 1980.
- [21] J.K. Chan, M.K. Cheung, W.K. Huh, K. Osann, A. Husain, N.N. Teng, et al., Therapeutic role of lymph node resection in endometrioid corpus cancer: a study of 12,333 patients, *Cancer* 107 (2006) 1823–1830.
- [22] E.L. Trimble, C. Kosary, R.C. Park, Lymph node sampling and survival in endometrial cancer, *Gynecol. Oncol.* 71 (1998) 340–343.
- [23] J.M. Cragun, L.J. Havrilesky, B. Calingaert, I. Synan, A.A. Secord, J.T. Soper, et al., Retrospective analysis of selective lymphadenectomy in apparent early-stage endometrial cancer, *J. Clin. Oncol.* 23 (2005) 3668–3675.
- [24] Y. Todo, H. Kato, M. Kaneuchi, H. Watari, M. Takeda, N. Sakuragi, Survival effect of Para-aortic lymphadenectomy in endometrial cancer (SEPAL study): a retrospective cohort analysis, *Lancet* 375 (2010) 1165–1172.
- [25] P.J. Coronado, M. Fasero, L. Baquedano, M.A. Martinez-Maestre, A. Casado, J.A. Vidart, et al., Impact of the lymphadenectomy in high-risk histologic types of endometrial cancer: a matched-pair study, *Int. J. Gynecol. Cancer* 24 (2014) 703–712.
- [26] P.J. Coronado, A. Rychlik, M.A. Martinez-Maestre, L. Baquedano, M. Fasero, A. Garcia-Arreza, et al., Role of lymphadenectomy in intermediate-risk endometrial cancer: a matched-pair study, *J. Gynecol. Oncol.* 29 (2018) e1.
- [27] T. Papathelemis, D. Hassas, M. Gerken, M. Klinkhammer-Schalke, A. Scharl, M.P. Lux, et al., Is there a benefit of lymphadenectomy for overall and recurrence-free survival in type I FIGO IB G1–2 endometrial carcinoma? A retrospective population-based cohort analysis, *J. Cancer Res. Clin. Oncol.* (2018) 2019–2027.
- [28] J. Aalders, V. Abeler, P. Kolstad, M. Onsrud, Postoperative external irradiation and prognostic parameters in stage I endometrial carcinoma: clinical and histopathologic study of 540 patients, *Obstet. Gynecol.* 56 (1980) 419–427.
- [29] C.L. Creutzberg, W.L. van Putten, P.C. Koper, M.L. Lybeert, J.J. Jobsen, C.C. Warlam-Rodenhuis, et al., Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma, *Lancet* 355 (2000) 1404–1411.
- [30] N. Bromham, M. Schmidt-Hansen, M. Astin, E. Hasler, M.W. Reed, Axillary treatment for operable primary breast cancer, *Cochrane Database Syst. Rev.* 1 (2017), CD004561.
- [31] Endometrial Cancer Lymphadenectomy Trial (ECLAT)2018.
- [32] M. Ballester, G. Dubernard, F. Lecuru, D. Heitz, P. Mathevet, H. Marret, et al., Detection rate and diagnostic accuracy of sentinel-node biopsy in early stage endometrial cancer: a prospective multicentre study (SENTI-ENDO), *Lancet Oncol.* 12 (2011) 469–476.
- [33] N.R. Abu-Rustum, Sentinel lymph node mapping for endometrial cancer: a modern approach to surgical staging, *J. Natl. Compr. Cancer Netw.* 12 (2014) 288–297.
- [34] S. Brugger, M. Hamann, M. Mosner, M. Beer, M. Braun, M. Polcher, Endometrial cancer-how many patients could benefit from sentinel lymph node dissection? *World J. Surg. Oncol.* 16 (2018) 95.
- [35] R.W. Holloway, N.R. Abu-Rustum, F.J. Backes, J.F. Boggess, W.H. Gottlieb, W. Jeffrey Lowery, et al., Sentinel lymph node mapping and staging in endometrial cancer: a Society of Gynecologic Oncology literature review with consensus recommendations, *Gynecol. Oncol.* 146 (2017) 405–415.
- [36] E.C. Rossi, L.D. Kowalski, J. Scalici, L. Cantrell, K. Schuler, R.K. Hanna, et al., A comparison of sentinel lymph node biopsy to lymphadenectomy for endometrial cancer staging (FIRES trial): a multicentre, prospective, cohort study, *Lancet Oncol.* 18 (2017) 384–392.
- [37] Cancer Genome Atlas Research N, C. Kandath, N. Schultz, A.D. Cherniack, R. Akbani, Y. Liu, et al., Integrated genomic characterization of endometrial carcinoma, *Nature* 497 (2013) 67–73.
- [38] A. Talhouk, M.K. McConechy, S. Leung, W. Yang, A. Lum, J. Senz, et al., Confirmation of ProMISe: a simple, genomics-based clinical classifier for endometrial cancer, *Cancer* 123 (2017) 802–813.