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Lymph node micrometastases and outcome of endometrial cancer

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HIGHLIGHTS

- We investigated the survival impact of lymph node micrometastases in endometrial cancer.
- Lymph node micrometastases are associated with adverse outcome in endometrial cancer.
- Adjuvant therapy might improve disease-free survival of patients with micrometastases.

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ABSTRACT

Background. The relationship between nodal micrometastases and clinical outcome of endometrial cancer is unclear.

Patients and methods. We performed a multicenter, retrospective registry-based study of 2392 patients with endometrial cancer with and without nodal micrometastases. The primary outcome measure was disease-free survival.

Results. After exclusions, the final study involved 428 patients: 302 (70.6%) with node-negative endometrial cancer, who did not receive adjuvant treatment, 95 (22.2%) with nodal micrometastases who received adjuvant treatment, and 31 (7.2%) with nodal micrometastases who did not receive adjuvant treatment. The median follow-up was 84.8 months. Without adjuvant therapy the disease-free survival in the cohort of patients with micrometastases was significantly reduced as compared with disease-free survival in the node-negative cohort ($p = 0.0001$). With adjuvant therapy the median disease-free survival of patients with nodal micrometastases was similar with those of node-negative patients ($p = 0.648$). The adjusted hazard ratio for disease events among patients with micrometastases and no adjuvant therapy, as compared with node-negative patients, was 2.23 (95% confidence interval [CI] 1.26–3.95). In the cohort with micrometastases the relative risk of events was significantly decreased by adjuvant therapy (HR 0.29, 95%CI 0.13–0.65) even after adjustment for age at diagnosis, myometrial invasion, histological grade and type, and performance status.

Conclusions. Nodal micrometastases are associated with decreased disease-free survival of patients with endometrial cancer. Adjuvant therapy was associated with improved disease-free survival of patients with micrometastases.

1. Introduction

Endometrial cancer is the most common gynecologic cancer in the world [1]. In 1988 the International Federation of Gynecology and Obstetrics (FIGO) established criteria for accurate surgical staging in endometrial cancer patients including abdominal exploration, hysterectomy with salpingo-oophorectomy and pelvic and para-aortic lymphadenectomy [2]. The status of the pelvic and paraaortal lymph nodes is an important prognostic factor in endometrial cancer [1] and should be considered during treatment decision. Standard procedure to evaluate the lymph node status is pelvic and paraaortal lymph node dissection [3]. A new very promising strategy to obtain an accurate lymph

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node status represents the sentinel-node biopsy [4]. The increasing use of this technique is associated with an increasing rate of detection of nodal micrometastases [5,6]. It has been suggested in a small cohort, that nodal micrometastases are associated with reduced survival [6,7]. Nevertheless, the guidelines regarding nodal micrometastases in endometrial cancer and especially the recommendation of adjuvant treatment are insufficient. The high rate of assumed nodal micrometastases [8,9], suggests the importance of further investigation of this topic.

The aim of this work was to evaluate the influence of nodal micrometastases on patient outcome in regard to adjuvant therapy.

2. Patients and methods

We investigated cases of endometrial cancer included in the prospectively maintained regional cancer registry of Saxony-Anhalt, a federal state of Germany. The tumor registry contains prospectively collected information on diagnosis, age, tumor stage, receptor status, tumor grading, lymph node status, date of diagnosis, date of disease recurrence, site of recurrence, date of death and the treatment regimens used [10,11]. The registry covers a population of 1.2 million people in north Sachsen-Anhalt. The information about the date and cause of death is automatically updated into the system by the main health department shortly after death [12]. In this cohort study we analyzed women who were diagnosed with endometrial cancer between January 2000 and September 2017 in 10 hospitals in Sachsen-Anhalt [13]. Among these women, we selected only patients with a final nodal status with micrometastases (n = 126) (Fig. 1). Patients without lymph node metastases and no adjuvant treatment (radiation and/or chemotherapy) (n = 302) were used as a control. Patients with unknown lymph node status (n = 131) and not performed lymph node evaluation (n = 831), with distant metastases (n = 32), or patients with nodal macrometastases (n = 261) were excluded. Patients without lymph node metastases treated with adjuvant therapy (n = 747) were also excluded from further investigation.

The patients eligible for analysis were divided into three groups: patients with nodal negative endometrial cancer who did not receive adjuvant treatment, women with nodal micrometastases who did not receive adjuvant treatment, and patients with nodal micrometastases who underwent adjuvant treatment. Lymph node status was defined as follows: lymph nodes without tumor infiltration were reported as negative; micrometastases were defined as tumor in lymph node with a size between >0.2 mm and ≤2.0 mm; tumor in lymph node measured larger than 2.0 mm was reported as macrometastasis.

The effect of micrometastases on the patient outcome was investigated by the comparison of survival between patients with nodal negative disease and patients with nodal micrometastases without adjuvant treatment. The effect of adjuvant treatment was investigated by comparison of survival between patients with nodal micrometastases without and with adjuvant treatment. The primary outcome measure was the rate of disease-free survival (DFS). It has been defined as the period from the date of diagnosis to local and/or regional recurrence, distant metastases or death from disease, whichever occurred first. Patients who died of other causes or patients with an unknown cause of death were censored. The follow-up either ends with the patient's death, the last follow-up at 15.09.2014 or the last available information in the tumor registry. The median follow-up was 84.8 months (range, 1–214 months).

The manuscript was prepared in accordance with the STROBE statement criteria [14]. The Ethical Committee of the Otto-von-Guericke University, Magdeburg, Germany concluded that no informed consent was required for this retrospective, observational study. Before analysis, patient data were anonymized.

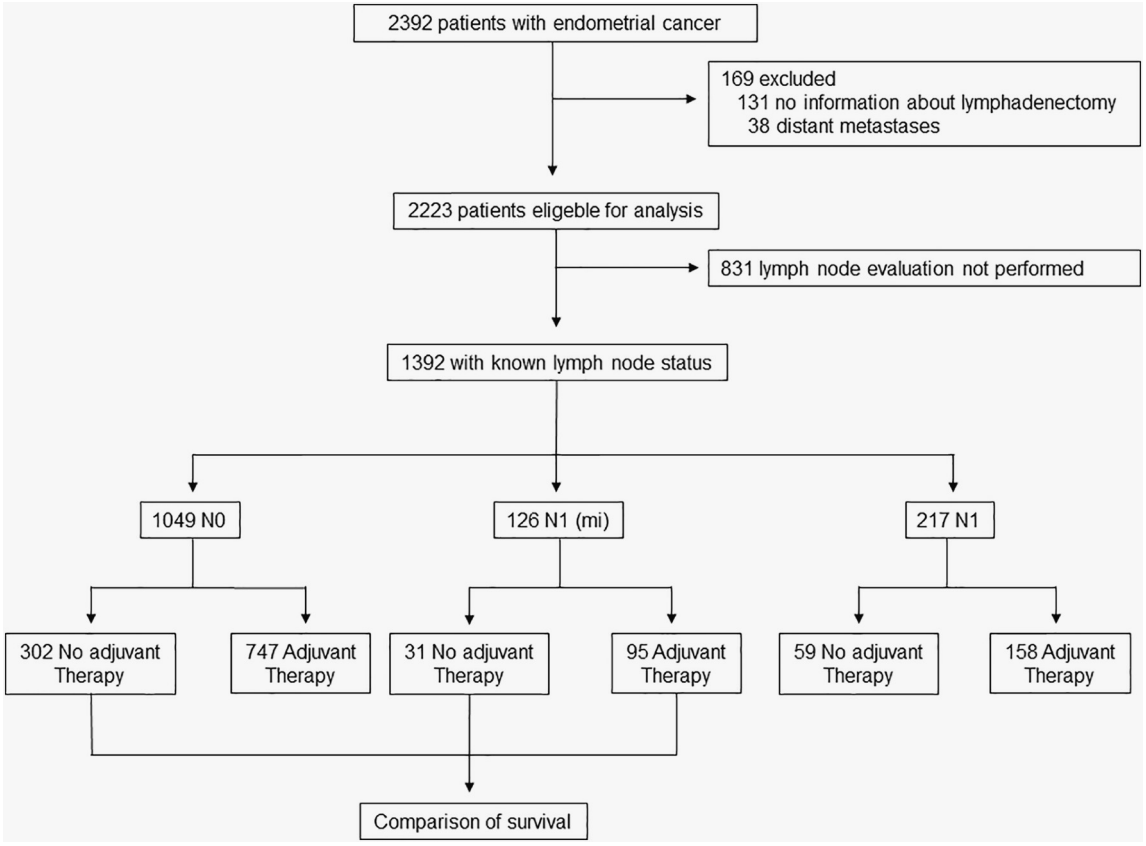

Fig. 1. Study design.

2.1. Statistical analysis

The statistical calculations were performed using SPSS version 22.0 (SPSS, Chicago, IL, USA). Correlation of variables was assessed using Chi-square test and Student's *t*-test for continuous variables. Survival probability was studied using the Kaplan-Meier method. The equality of survival curves was tested by the log rank test. Multivariate Cox proportional hazard regression analysis was used to compare the cohorts and to adjust for known prognostic factors. The statistical analyses were two sided and *p*-values of <0.05 were considered statistically significant.

3. Results

Between January 2000 and September 2017, 2392 women with endometrial cancer were identified. The flow-diagram reports the study design and the number of patients at each stage of the study (Fig. 1). After exclusions the final study involved 428 patients: 302 (70.6%) with node-negative endometrial cancer, who did not receive adjuvant treatment, 95 (22.2%) with nodal micrometastases who received adjuvant treatment, and 31 (7.2%) with nodal micrometastases who did not receive adjuvant treatment. The clinical and pathological characteristics of the three groups are shown in Table 1. In the node-negative, no adjuvant therapy group as compared with the group with micrometastases and no adjuvant therapy, the patients were younger ($p = 0.0018$), the tumors with an myometrial invasion of <50% were more frequent ($p = 0.012$), and more of the patients received an minimal invasive surgery ($p = 0.003$) and lymph-node dissection ($p = 0.001$). To note, SnB was more frequently observed in the group of patients with micrometastases. The ultrastaging procedure during sentinel node mapping is often associated with detection of most micrometastases. Notably, between node-positive no adjuvant therapy cohort and node-positive adjuvant therapy cohort the baseline characteristics were equally distributed (Table 1).

Next, the survival effect of micrometastases was investigated. The DFS in the group of patients with micrometastases and no adjuvant therapy was significantly reduced as compared with DFS in the node-negative no adjuvant therapy cohort (Fig. 2A). In this cohort of patients without adjuvant therapy the DFS rate during the follow up period was 32.3% and 73.2% for patients with and without micrometastases, respectively ($p = 0.0001$). Interestingly, the rate of DFS was similar among node-negative patients without adjuvant treatment and patients with micrometastases who received an adjuvant therapy (Fig. 2B). The rates of DFS were 73.2% and 78.9%, respectively ($p = 0.648$). Adjuvant radiotherapy received 88 (92.6%) of women, of whom 67 (76.2%) were treated with external beam radiotherapy. In 21 (23.8%) cases vaginal brachytherapy was added to external beam radiotherapy. Chemotherapy was administered to 35 (35.8%) of patients with micrometastases. In all cases, platinum-based systemic treatment was used.

After adjustment for other prognostic covariates (Table 2), the number of events was significantly increased in the node-positive no adjuvant therapy cohort as compared with the node-negative no adjuvant therapy cohort (HR 2.23, 95% CI 1.26–3.95). However, the rate of vaginal recurrence was equal between two groups. Age at diagnosis >69 years old, low histological grade and non-endometrioid type were also associated with risk of events. In the group of patients with micrometastases the rate of events was significantly decreased by adjuvant therapy (HR 0.29, 95% CI 0.13–0.65) even after adjustment for age at diagnosis, myometrial invasion, histological grade and type, and performance status (Table 2). Notably, age at diagnosis, myometrial invasion, histological grade and type, and performance status were not associated with the rate of events.

Table 1
Baseline characteristics of the patients.

Variable	All patients (N = 428)	N0 no adjuvant therapy (N = 302)	N1 (mi) no adjuvant therapy (N = 31)	*P* value[&]	N1 (mi) adjuvant therapy (N = 95)	*P* value[§]
Age at diagnosis (yr)				0.0018		0.070
Median	69	69	73		69	
Range	29–96	33–94	55–89		36–92	
Myometrial invasion				0.012		0.151
≤50%	240	204 (72.1)	12 (46.2)		24 (28.9)	
>50%	152	79 (27.9)	14 (53.8)		59 (71.1)	
Histological grade				0.380		0.252
1	145	122 (40.8)	8 (27.6)		15 (16.5)	
2	174	119 (39.8)	14 (48.3)		41 (45.1)	
3	100	58 (19.4)	7 (24.1)		35 (38.5)	
Histological type				1.000		0.359
Endometrioid	399	283 (94.0)	30 (96.8)		86 (92.5)	
Non-endometrioid	26	18 (6.0)	1 (3.2)		7 (7.5)	
ECOG status				0.454		0.800
0 to 1	348	248 (83.2)	24 (77.4)		76 (80.0)	
2 to 4	76	50 (16.8)	7 (22.6)		19 (20.0)	
Type of surgery				0.003		0.095
Minimal invasive	347	275 (91.1)	22 (71.0)		50 (52.6)	
Laparotomy	81	27 (8.9)	9 (29.0)		45 (47.4)	
Type of lymphadenectomie				0.0001		0.137
SnB	12	8 (2.6)	0 (0)		3 (3.2)	
SnB and LND	42	3 (1.0)	6 (19.4)		33 (34.7)	
LND	375	291 (96.4)	25 (80.6)		59 (62.1)	
No. of lymph nodes removed				0.624		0.208
Mean		22	21		24	
Range		2–72	2–43		2–57	
Adjuvant therapy						
Radiotherapy	60	NA	NA		61 (64.2)	
Systemic therapy	7	NA	NA		7 (7.4)	
Both	27	NA	NA		27 (28.4)	

ECOG, Eastern Co-operative Oncology Group; LND, lymphadenectomy; SnB, sentinel node biopsy.
[&] *P* value is for the comparison of N0 no adjuvant therapy cohort with N1 no adjuvant therapy cohort.
[§] *P* value is for the comparison of N1 no adjuvant therapy cohort with the N1 adjuvant therapy cohort.

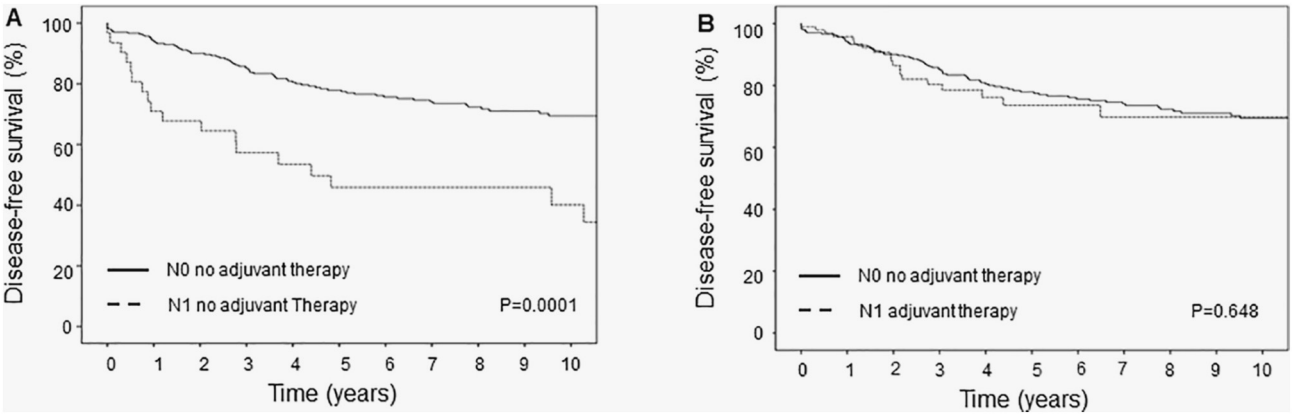

Fig. 2. Kaplan-Meier analysis of disease-free survival for node-negative and positive patients without adjuvant therapy (A) and for node-negative patients without adjuvant therapy and patients with micrometastases and adjuvant therapy (B).

4. Discussion

In the present study, we found that nodal micrometastases were associated with a reduction of DFS of patients with endometrial cancer. The risk of events during the follow-up period increased 2-fold in comparison with node negative patients. Interestingly, the adjuvant therapy improved DFS after adjustment for risk factors and reduced the relative risk of events by 71%.

Nevertheless, the clinical impact of our findings remains unclear, because this is the first work clearly demonstrating a benefit of adjuvant treatment for endometrial cancer. The association of nodal micrometastases and unfavorable clinical outcome has been already investigated for other cancers [15–22]. Conversely, various reports have not found any significant influence of micrometastases on patients' survival [23,24]. Concluding that the importance of micrometastases for survival of patients with endometrial cancer is not well understood yet. However, the ever-increasing role of sentinel-node biopsy in treatment of endometrial cancer is associated with rising rates of detection of micrometastases and isolated tumor cells in lymph nodes [4]. This will provoke the need for additional knowledge in this topic. The existing data are still unsatisfactory and additional data regarding nodal micrometastases and patients' outcome are necessary.

Table 2
Cox proportional-hazards model of the effect of variables on events.

Variable	No adjuvant therapy		Micrometastases	
	Hazard ratio for events (95% CI)	*P* value	Hazard ratio for events (95% CI)	*P* value
Micrometastases				
No	1.00	0.006	–	NA
Yes	2.23 (1.26–3.95)		–	
Adjuvant therapy				
No	–	NA	1.00	0.002
Yes	–		0.29 (0.13–0.65)	
Age at diagnosis (yr)				
≤69	1.00	0.002	1.00	0.857
>69	2.27 (1.37–3.76)		1.08 (0.47–2.51)	
Myometrial invasion				
≤50%	1.00	0.274	1.00	0.565
>50%	1.28 (0.82–2.00)		1.25 (0.58–2.71)	
Histological grade				
1, 2	1.00	0.016	1.00	0.091
3	1.77 (1.11–2.81)		1.95 (0.900–4.22)	
Histological type				
Endometrioid	1.00	0.001	1.00	0.209
Non-endometrioid	3.14 (1.55–6.36)		2.26 (0.63–8.02)	
ECOG status				
0, 1	1.00	0.441	1.00	0.519
2, 3, 4	0.22 (0.74–2.02)		1.34 (0.55–3.29)	

ECOG, Eastern Co-operative Oncology Group; LND, lymphadenectomy; SnB, sentinel node biopsy.

Similar to our data, St. Clair and co-workers have found that the oncological outcome of patients with micrometastases is improved by using adjuvant therapy [6]. Isolated tumor cells and micrometastases were identified in 14.8% patients, and the presence of low volume metastases was an independent risk factor. Most of the patients with isolated tumor cells and micrometastases received adjuvant treatment. In the mentioned retrospective analysis, patients with low volume metastases were treated as node positive, making an evaluation of treatment effect difficult. In our study, a third of the patients did not receive adjuvant therapy. Thus, we were able to evaluate the survival of patients with untreated micrometastases. We observed a significant improvement of DFS using an adjuvant treatment. After correction for different cofactors, such as age, myometrial invasion, histological grade, histological type, ECOG status, the unfavorable role of micrometastases regarding patients' survival was confirmed. The role of micrometastases as a prognostic factor was investigated in another retrospective study with 63 patients. Based on the small number of patients no significant difference was observed between survival of patients with and without micrometastases [7]. However, micrometastases were identified as unfavorable prognostic factor. In the opposite to all these findings, Plante et al. have found that progression-free survival of patients with micrometastases is similar to the survival of node negative patients [5]. Additionally, patients with isolated tumor cells only have excellent prognosis without adjuvant therapy. This discrepancy to our observation might be due to the low rate of micrometastases identified by Plante and co-workers (2.1%) or the fact that most patients received an adjuvant therapy, improving patients' survival. Notably, in this study isolated tumor cells and not micrometastases were investigated and could additionally explain the discrepancy to our results. The improved survival of patients with nodal micrometastases by adjuvant therapy observed in our study has been already confirmed for breast cancer [22].

Limitation of our study is its retrospective character and lack of information on isolated tumor cells in extirpated lymph nodes. Another limitation is the fact that adjuvant therapy was based on decision of a physician. However, the adjustment for important risk factors influencing treatment decision was performed to reduce the selection bias to a minimum. However, the exact reason to omit adjuvant therapy in a case of micrometastases, such as patient refusal or reduced performance status [10] was not investigated and should be considered during the interpretation of the data. Although cases with ITC were not included in our study, the presence of not detected ITC in the patients is possible and belongs to the limitations of our study. The strengths of the present study are: i) large sample size with a long follow-up; ii) large number of patients with micrometastases who did not receive adjuvant treatment;

iii) high level of external validity as nodal status was investigated multicentric and the study population was similar to the general population; and iv) the exclusion criteria were kept to a minimum. An ideal trial to investigate the survival benefit of adjuvant therapy for patients with micrometastases should be multi-centric and including patients randomized to adjuvant and no adjuvant therapy. However, for ethical reasons, such a trial would not be tolerable. Therefore, the knowledge about the therapeutic benefit in endometrial cancer with low volume of nodal metastases should be addressed by similar large retrospective trials with high external validity.

In conclusion, the present study demonstrates that nodal micrometastases are associated with worse DFS and this unfavorable effect is increased by adjuvant therapy including radiation and chemotherapy. The adjuvant therapy of patients with nodal micrometastases should be further evaluated to avoid unnecessary morbidity caused by the aggressive adjuvant therapy.

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Author contribution

AI, carried out the study design and statistical analysis and participated in drafting the manuscript, CL, collected the data and participated in analysis of the clinical data; TI, participated in collecting the data analysis of the clinical data; SI, participated in study design and analysis of the clinical data; RK, participated in designing the study and analysis of the clinical data; TP, participated in designing the study and analysis of the clinical data; OO, participated in designing the study and contributed methodological knowhow; HE, participated in designing of the study, analysis of the data and drafting the manuscript. All authors read and approved the final version of the manuscript.

Declaration of Competing Interest

The authors declare no conflict of interest.

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