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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

# 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

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## Abstract

**Purpose** The recommended therapy for type I FIGO IB endometrial cancer (EC) is hysterectomy and adnexectomy, but the therapeutic benefits of additional pelvic and paraaortic lymph node dissection (LND) are still under discussion. In this study, we retrospectively evaluated overall survival (OAS) and recurrence-free survival (RFS) among patients with type I FIGO IB EC who did undergo systematic or elective lymphadenectomy or none at all.

**Methods** We selected 299 individuals from the database of the German Tumor Centre Regensburg who were diagnosed between 1998 and 2015 with endometrial adenocarcinoma of the uterus type I FIGO IB. We applied multivariable Cox regression to the selected patient data and estimated hazard ratios for OAS and RFS against the performed intervention. Further, we carried out risk adjustments with respect to clinicopathological parameters, and performed model selection using conditional stepwise forward selection.

**Results** We observed significant benefits of LND in the unadjusted survival analysis; however, we did not confirm this effect in multivariable regression analysis upon risk adjustment. In this case, hazard ratio (HR) for OAS in patients without LND versus patients with LND is reduced to 1.214 (95% CI 0.771–1.911; $p = 0.402$), HR for RFS is 1.059 (95% CI 0.689–1.626; $p = 0.795$). Similarly, we were also able to eliminate the statistical benefit of systematic versus elective LND by risk adjustment.

**Conclusions** In contrast to previous observations in high-grade EC, our study provides compelling evidence that LND, in particular systematic lymphadenectomy, is not beneficial for patients with type I FIGO IB EC in terms of long-term OAS and RFS.

**Keywords** Endometrial cancer · Lymphadenectomy · Outcome · Overall survival · Recurrence

## Introduction

Endometrial carcinoma (EC) is the most common genital cancer in the Western world (Thaker and Sood 2017). Type II EC is associated with higher mortality, although it constitutes only a fifth of all cases of EC (Saso et al. 2011). The

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poor outcome of the post-menopausal type II EC is based on its aggressive and invasive tumor biology (Bokhman 1983; Gottwald 2010). By contrast, the majority of all diagnosed cases of EC fall into category type I, which usually occurs after menopause (Saso et al. 2011). Type I EC is an invasive malignancy associated with a good long-term prognosis (Denschlag et al. 2010; Morice et al. 2016).

Type I carcinomas are endometrioid carcinomas, typically develop under the influence of hyperestrogenism on atypical endometrial hyperplasia and are characterized for the most part by a low stage and a favorable course. Their relation to estrogens is also expressed by the usually high expression of estrogen and progesterone receptors. Its pathogenesis goes through adenocarcinoma sequence with subsequent progression from a low to a higher degree of malignancy.

Type II carcinomas typically arise on the bottom of an atrophic endometrium or within (glandular cystic) endometrial polyps. Histologically, these include non-endometrioid carcinomas, in particular the serous and currently also the clear cell carcinomas. An expression of estrogen and progesterone receptors is usually absent or weak, which lacks a clear pathogenetic relation to the female sex hormones (Onkologisches Leitlinienprogramm 2017).

The current standard intervention for EC is hysterectomy and adenexectomy. The recommendation for additional pelvic and paraaortic lymph node dissection (LND) depends on tumor type (type I or II). The German S3 guideline states that if LND is indicated, no lymph node sampling but systematic lymphadenectomy should be performed. LND of normal lymph nodes is highly suggested in endometrial carcinoma type II if macroscopic R0 resection can be achieved. In type I carcinoma without clinically suspicious nodes recommendations depend on tumor stage and grade: According to this German guideline, LND should not be performed in pT1a, G1/2 cases, is optional in pT1a, G3 or pT1b, G1/2 cases, and should be performed in pT1b, G3 tumors. This weak statement for pT1b tumors, which is reflected in other recommendations is based on low evidence for a benefit of lymphadenectomy in these patients (Leitlinienprogramm Onkologie 2017; May et al. 2010; Frost et al. 2017; Kitchener et al. 2009). Systematic LND is a severe intervention and, hence, is associated with a high risk for the patient (Achouri et al. 2013). Therefore, it is imperative to identify all relevant clinical parameters to choose optimal treatment for the patient.

Whereas recent studies indicate a significant benefit for this intervention in patients with high-grade EC (Papathemelis 2017; Cragun et al. 2005; Mariani et al. 2000; Fujimoto et al. 2007), the benefit is questioned in patients with type I FIGO IB EC because the available data are inconclusive (Rani et al. 2017; Frost et al. 2017). The recently launched prospective study "Endometrial Cancer Lymphadenectomy Trial" (ECLAT) is aimed to provide the necessary data for this therapeutic recommendation, but the results will not be available for the next years. (ECLAT 2018). We therefore sought out to retrospectively evaluate the survival benefit of pelvic and paraaortic LND for patients with this most debated stage type I FIGO IB EC.

## Patients and methods

### Study design and data source

Our data source is described earlier (Papathemelis 2017). We accessed patient data from 2,398 cases of endometrial cancer (ICD-10 C54) between January 1998 and December 2015 from the Tumor Centre Regensburg (Bavaria, Germany) (Tumorzentrum Regensburg 2018). The database, founded in 1991, contains information about diagnosis, course of disease, therapeutic modalities and long-term follow-up data from 53 regional hospitals from Upper Palatinate including university hospitals, gynecologic cancer centers and more than 1000 physicians with oncological patient care. This population-based regional cancer registry covers a population of approximately 1.1 million people and collects cross-sectional documentation of all EC patients in this area.

### Patient inclusion and exclusion criteria

For this population-based, retrospective cohort study, we selected all female patients in the cancer registry who were diagnosed with type I EC G1-2 Grading and FIGO stage IB defined by a myometrial invasion of more than 50% (Fig. 1). FIGO Stage IB was defined according to the revised criteria of the year 2009 (Creasman 2009) representing solely a myometrial invasion of the outer one-half of the myometrium. Prior to 2009 outer myometrial invasion was classified as stage IC. The previous FIGO stages IA and IB in 2009 were combined to form the revised FIGO Stage IA; these cases were excluded from our analysis. We excluded patients with malignant previous or synchronous secondary tumors from this study. We also dismissed patients who did not undergo a uterus extirpation. A further exclusion criterion was the lack of sufficient follow-up data. Finally, we disregarded patients with incomplete tumor resection (R1 or R2).

### Statistical analysis

Continuous data were expressed as means, range and standard deviation, whereas categorical data were expressed as frequency counts and percentages. Comparison of means was performed by Student's *t* test in case of normally distributed data. Chi-square test was used for comparisons between individual categorical variables. OS was calculated from the date of cancer diagnosis to the date of death from any cause.

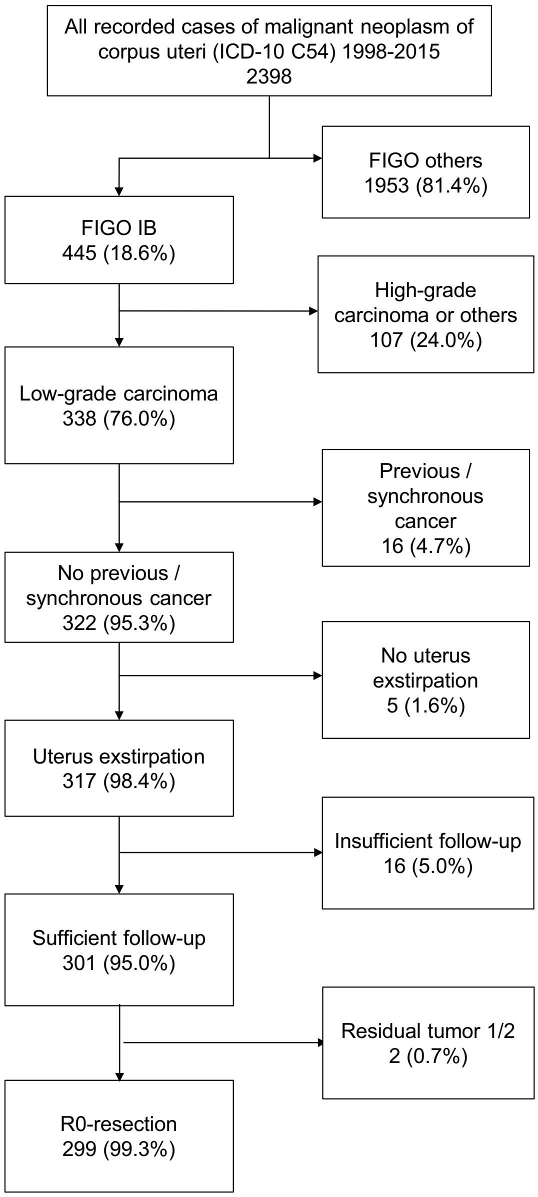


**Fig. 1** Flow-chart showing inclusion and exclusion criteria

RFS includes local relapse, as well as subsequent regional and distant metastases. Vital status of all patients was validated using death certificates and information from registration offices. Patients without an event or patients with limited follow-up were censored. All patients were uniformly censored at a maximum cut-off date May 31 2016.

In order to estimate hazard ratios (HR) for OAS and RFS, univariable and multivariable Cox regression analyses were applied to compare patients who did not underwent LND and patients in which LND was performed. The second group was further differentiated into systematic (removal of 25 + lymph nodes according to German Guidelines), elective (removal of 1–24 lymphnodes) and unclassified LND. Risk-adjustment was performed in multivariable analyses to adjust for confounding factors: age at diagnosis, year of diagnosis, comorbidity, obesity, region of lymphadenectomy, lymph vessel invasion, vein invasion, oophorectomy, radiotherapy and chemotherapy. Comorbidity was adjusted for using Charlson Comorbidity Index CCI, categorized in a group with at least one disease and a group without any disease listed in the CCI list (Charlson et al 1987). Model selection in multivariable Cox regression was performed using conditional stepwise forward selection. HR was considered significant if the corresponding confidence interval (CI) excluded 1, and the $p$ value of the log-rank test was $<0.05$. All analyses were performed using IBM SPSS Statistics Version 24.0 (Chicago, EUA).

## Results

### Description of patient cohort and performed interventions

From 2398 patients registered in the cancer registry, 299 matched the selection criteria for this study (Fig. 1). All patients were diagnosed with type I G1-2 FIGO IB EC, underwent primary surgery and did not suffer from previous or synchronous cancer at the time of selection. (Supplementary Table 1). The majority of the patients selected for this study were between 60 and 80 years old (Table 1, mean age 68.7, median 69.4). Our statistical analysis revealed that the likelihood of undergoing LND is higher in younger patients (Chi-square $p=0.001$, $t$ test $<0.001$) (Table 1). In particular, systematic LND is preferentially performed among younger patients ($p<0.001$) (Table 2). Distribution of the Charlson Comorbidity Index in the patient cohort was independent of the performed lymphadenectomy (Tables 1, 2). Similarly, the distribution of obesity, oophorectomy, and primary therapy did not display any significant difference against the performed intervention. The majority of the patients were of normal weight (88.3%) and underwent an oophorectomy (90.0%). The primary therapy for 65.6% of the patients was a combination of surgery and radiotherapy, mostly vaginal afterloading, and for the remaining 33.8% only surgery. Only two patients received a combination of surgery and chemotherapy.

The analysis of the patient characteristics presents that LND, in particular systematic LND, were mostly performed in recent times ($p<0.001$) (Tables 1, 2). Elective LND mostly comprised the removal of pelvic LN, whereas systematic LND also included the removal of paraaortic LN ($p<0.001$) (Table 2).

Two-thirds of the patients did not display lymph vessel and vein invasion (L0, V0), which is in agreement with the selection of type I EC; nonetheless, we observed

**Table 1** Demographic and clinic-pathological characteristics of patients who did or did not undergo lymphadenectomy

| | Lymphadenectomy | | | | | | |
|---|---|---|---|---|---|---|---|
| | LND yes | | LND no | | Total | | Chi-square |
| | *n* | % | *n* | % | *n* | % | *p* |
| Age at diagnosis | | | | | | | |
| < 60 | 41 | 18.9 | 7 | 8.5 | 48 | 16.1 | |
| 60–69 | 86 | 39.6 | 25 | 30.5 | 111 | 37.1 | 0.001 |
| 70–79 | 77 | 35.5 | 35 | 42.7 | 112 | 37.5 | |
| 80 + | 13 | 6.0 | 15 | 18.3 | 28 | 9.4 | |
| Charlson Comorbidity Index | | | | | | | |
| 0 | 201 | 92.6 | 68 | 82.9 | 269 | 90.0 | |
| 1 | 15 | 6.9 | 11 | 13.4 | 26 | 8.7 | 0.008 |
| 2 | 0 | 0.0 | 3 | 3.7 | 3 | 1.0 | |
| 4 | 1 | 0.5 | 0 | 0.0 | 1 | 0.3 | |
| Obesity | | | | | | | |
| Yes | 27 | 12.4 | 8 | 9.8 | 35 | 11.7 | 0.519 |
| No | 190 | 87.6 | 74 | 90.2 | 264 | 88.3 | |
| Year of diagnosis | | | | | | | |
| 1998–2003 | 44 | 20.3 | 36 | 43.9 | 80 | 26.8 | |
| 2004–2009 | 87 | 40.1 | 24 | 29.3 | 111 | 37.1 | < 0.001 |
| 2010–2015 | 86 | 39.6 | 22 | 26.8 | 108 | 36.1 | |
| Region of lymphonodectomy | | | | | | | |
| LND paraaortic + pelvic | 89 | 41.0 | 0 | 0.0 | 89 | 29.8 | |
| LND pelvic only | 128 | 59.0 | 0 | 0.0 | 128 | 42.8 | < 0.001 |
| No LND | 0 | 0.0 | 82 | 100.0 | 82 | 27.4 | |
| Lymph vessel invasion | | | | | | | |
| L0 | 144 | 66.4 | 41 | 50.0 | 185 | 61.9 | |
| L1 | 23 | 10.6 | 7 | 8.5 | 30 | 10.0 | 0.007 |
| LX/kA | 50 | 23.0 | 34 | 41.5 | 84 | 28.1 | |
| Vein invasion | | | | | | | |
| V0 | 159 | 73.3 | 44 | 53.7 | 203 | 67.9 | |
| V1 | 2 | 0.9 | 2 | 2.4 | 4 | 1.3 | 0.005 |
| VX/kA | 56 | 25.8 | 36 | 43.9 | 92 | 30.8 | |
| Primary therapy | | | | | | | |
| Surgery + rad | 142 | 65.4 | 54 | 65.9 | 196 | 65.6 | |
| Surgery + CTX | 2 | 0.9 | 0 | 0.0 | 2 | 0.7 | 0.683 |
| Surgery only | 73 | 33.6 | 28 | 34.1 | 101 | 33.8 | |
| Oophorectomy | | | | | | | |
| Yes | 194 | 89.4 | 75 | 91.5 | 269 | 90.0 | 0.596 |
| No/ns | 23 | 10.6 | 7 | 8.5 | 30 | 10.0 | |
| Radiotherapy | | | | | | | |
| Tele- and brachytherapy | 10 | 4.6 | 15 | 18.3 | 25 | 8.4 | |
| Brachytherapy | 86 | 39.6 | 20 | 24.4 | 106 | 35.5 | |
| Teletherapy | 14 | 6.5 | 9 | 11.0 | 23 | 7.7 | 0.001 |
| Radiotherapy ns | 32 | 14.7 | 10 | 12.2 | 42 | 14.0 | |
| No radiotherapy | 75 | 34.6 | 28 | 34.1 | 103 | 34.4 | |
| Total | 217 | 100.0 | 82 | 100.0 | 299 | 100.0 | |

**Table 2** Patient characteristics according to number of lymph nodes examined (systematic LND = 25 + lymph nodes removed, elective LND = 1–24 lymph nodes removed)

| | Lymphadenectomy LND | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Systematic LND | | Elective LND | | Unclassified LND | | No LND | | Total | | Chi-square |
| | *n* | % | *n* | % | *n* | % | *n* | % | *n* | % | *p* |
| Age at diagnosis | | | | | | | | | | | |
| < 60 | 25 | 24.3 | 8 | 12.7 | 8 | 15.7 | 7 | 8.5 | 48 | 16.1 | |
| 60–69 | 44 | 42.7 | 22 | 34.9 | 20 | 39.2 | 25 | 30.5 | 111 | 37.1 | < 0.001 |
| 70–79 | 33 | 32.0 | 23 | 36.5 | 21 | 41.2 | 35 | 42.7 | 112 | 37.5 | |
| 80 + | 1 | 1.0 | 10 | 15.9 | 2 | 3.9 | 15 | 18.3 | 28 | 9.4 | |
| Charlson Comorbidity Index | | | | | | | | | | | |
| 0 | 98 | 95.1 | 56 | 88.9 | 47 | 92.2 | 68 | 82.9 | 269 | 90.0 | |
| 1 | 5 | 4.9 | 6 | 9.5 | 4 | 7.8 | 11 | 13.4 | 26 | 8.7 | 0.059 |
| 2 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 3 | 3.7 | 3 | 1.0 | |
| 4 | 0 | 0.0 | 1 | 1.6 | 0 | 0.0 | 0 | 0.0 | 1 | 0.3 | |
| Obesity | | | | | | | | | | | |
| Yes | 15 | 14.6 | 5 | 7.9 | 7 | 13.7 | 8 | 9.8 | 35 | 11.7 | 0.535 |
| No | 88 | 85.4 | 58 | 92.1 | 44 | 86.3 | 74 | 90.2 | 264 | 88.3 | |
| Year of diagnosis | | | | | | | | | | | |
| 1998–2003 | 10 | 9.7 | 12 | 19.0 | 22 | 43.1 | 36 | 43.9 | 80 | 26.8 | |
| 2004–2009 | 35 | 34.0 | 36 | 57.1 | 16 | 31.4 | 24 | 29.3 | 111 | 37.1 | < 0.001 |
| 2010–2015 | 58 | 56.3 | 15 | 23.8 | 13 | 25.5 | 22 | 26.8 | 108 | 36.1 | |
| Region of lymphadenectomy | | | | | | | | | | | |
| LND paraaortic + pelvic | 71 | 68.9 | 15 | 23.8 | 3 | 5.9 | 0 | 0.0 | 89 | 29.8 | |
| LND pelvic only | 32 | 31.1 | 48 | 76.2 | 48 | 94.1 | 0 | 0.0 | 128 | 42.8 | < 0.001 |
| No LND | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 82 | 100.0 | 82 | 27.4 | |
| Lymph vessel invasion | | | | | | | | | | | |
| L0 | 75 | 72.8 | 41 | 65.1 | 28 | 54.9 | 41 | 50.0 | 185 | 61.9 | |
| L1 | 9 | 8.7 | 6 | 9.5 | 8 | 15.7 | 7 | 8.5 | 30 | 10.0 | 0.019 |
| LX/kA | 19 | 18.4 | 16 | 25.4 | 15 | 29.4 | 34 | 41.5 | 84 | 28.1 | |
| Vein invasion | | | | | | | | | | | |
| V0 | 82 | 79.6 | 45 | 71.4 | 32 | 62.7 | 44 | 53.7 | 203 | 67.9 | |
| V1 | 1 | 1.0 | 0 | 0.0 | 1 | 2.0 | 2 | 2.4 | 4 | 1.3 | 0.014 |
| VX/kA | 20 | 19.4 | 18 | 28.6 | 18 | 35.3 | 36 | 43.9 | 92 | 30.8 | |
| Primary therapy | | | | | | | | | | | |
| Surgery + rad | 75 | 72.8 | 39 | 61.9 | 28 | 54.9 | 54 | 65.9 | 196 | 65.6 | |
| Surgery + CTX | 1 | 1.0 | 0 | 0.0 | 1 | 2.0 | 0 | 0.0 | 2 | 0.7 | 0.266 |
| Surgery only | 27 | 26.2 | 24 | 38.1 | 22 | 43.1 | 28 | 34.1 | 101 | 33.8 | |
| Oophorectomy | | | | | | | | | | | |
| Yes | 92 | 89.3 | 55 | 87.3 | 47 | 92.2 | 75 | 91.5 | 269 | 90.0 | 0.797 |
| No/ns | 11 | 10.7 | 8 | 12.7 | 4 | 7.8 | 7 | 8.5 | 30 | 10.0 | |
| Radiotherapy | | | | | | | | | | | |
| Tele/brachytherapy | 2 | 1.9 | 3 | 4.8 | 5 | 9.8 | 15 | 18.3 | 25 | 8.4 | |
| Brachytherapy | 49 | 47.6 | 25 | 39.7 | 12 | 23.5 | 20 | 24.4 | 106 | 35.5 | |
| Teletherapy | 4 | 3.9 | 2 | 3.2 | 8 | 15.7 | 9 | 11.0 | 23 | 7.7 | < 0.001 |
| Radiotherapy ns | 20 | 19.4 | 9 | 14.3 | 3 | 5.9 | 10 | 12.2 | 42 | 14.0 | |
| No radiotherapy | 28 | 27.2 | 24 | 38.1 | 23 | 45.1 | 28 | 34.1 | 103 | 34.4 | |
| Total | 103 | 100.0 | 63 | 100.0 | 51 | 100.0 | 82 | 100.0 | 299 | 100.0 | |

slight differences in the distribution of lymph vessel and vein invasion within the different LND treatment regiments' (Tables 1, 2). Brachytherapy was the most common therapeutical procedure after surgery ($p = 0.001$); patients who underwent systematic LND were more likely to receive brachytherapy alone ($p < 0.001$) (Tables 1, 2).

### Lymphadenectomy does not influence hazard ratios upon risk adjustment

We investigated the impact of LND on patient survival in the cohort. Patients' numbers and portions according to type of intervention, life status and recurrence status are shown in Supplementary Table 2. Next, we performed univariable Cox regression analysis, in which we defined LND and systemic LND as reference values (Table 3). Our analysis presents an apparent disadvantage in OAS with regard to absence of LND in patients with type I FIGO IB EC (HR 1.673, 95% CI 1.096–2.555, $p=0.017$), whereas there were no significant differences in regard to RFS (HR 1.488, 95% CI 0.992–2.231, $p=0.055$). Furthermore, we observed that systematic LND as reference holds a significant advantage for OAS over both elective LND (HR 2.653, 95 CI 1.331–5.288, $p=0.006$) and absence of LND (HR 2.872, 95% CI 1.488–5.545, $p=0.002$). We observed similar differences in regard to RFS: the advantage of systematic LND against elective LND (HR 2.794, 95% CI 1.469–5.313, $p=0.002$), unclassified LND (HR 2.087, 95% CI 1.044–4.171, $p=0.037$) or absence of LND (HR 2.753, 95% CI 1.486–5.101, $p=0.001$) was statistically significant.

Finally, we carried out a multivariable Cox regression analysis including risk adjustment for confounding factors, e.g., age at diagnosis, year of diagnosis, comorbidity, obesity, region of lymphadenectomy, lymph vessel invasion, vein invasion, oophorectomy, radiotherapy and chemotherapy. After risk adjustment, the previously identified survival benefits (both OAS and RFS) associated with LND and especially systematic LND could not be confirmed (Table 3).

We found no statistically significant difference in OAS between patients who received an LND (reference) and patients who did not undergo such intervention (HR 1.214, 95% CI 0.771–1.911, $p=0.402$; Table 3; Fig. 2). Similarly, we were not able to detect any statistically significant difference for RFS in our adjusted datasets of the two patient subgroups defined by presence of absence of LND (HR 1.059, 95% CI 0.689–1.626, $p=0.795$) (Table 3; Fig. 3). Furthermore, the benefit of systematic LND as opposed to elective and no LND did not persist in multivariable regression analyses for OAS and RFS (Table 3).

## Discussion

EC is a major challenge for the Western population since increasing life expectancy and rising obesity contribute to the increasing prevalence (Frost et al. 2015; Cramer 2012). In order to provide optimal patient care for patients with EC, efficacy and benefit of LND as standard therapy has to be evaluated. In recent years, there has been a considerable debate about the recommendation of systematic LND for the treatment of type I FIGO IB EC (Rani et al. 2017; Frost et al. 2017). Notably, recent studies suggest that the benefit of this intervention is not proven; however, the shortcomings of these studies are the limited patient data (Frost et al. 2017; Benedetti-Panici et al. 2008). Another drawback of these studies is that they pooled type I and type II EC patients for analysis, eventually influencing the outcome.

There have been two randomized controlled trials addressing the effect of lymphadenectomy in early FIGO I endometrial cancer. An Italian trial by Benedetti-Panici et al. (2008) (NCT 00482300) randomized 514 eligible patients with FIGO I endometrial cancer. Patients were assigned to undergo pelvic systematic lymphadenectomy ($n=264$) or no lymphadenectomy ($n=250$). A median number of 26 pelvic lymph nodes were removed in patients of the lymphadenectomy arm. The extent of lymphadenectomy did not systematically include paraaortic lymph nodes. Furthermore, there was a lack of strict criteria for adjuvant therapies. The use of adjuvant therapies was left to the discretion of the treating physicians. Finally, 87 patients in the lymphadenectomy arm had a myometrial invasion less than 50% of the uterus which implicates a possible surgical overtreatment in these cases, since pelvic lymph node metastasis is extremely rare in this early stage of the disease (Creasmanet al. 1987).

The second randomized trial addressing the effect of lymphadenectomy was the MRC ASTEC trial (Kitchener et al. 2009). Again, although the reports of ASTEC have been a valuable contribution due the large number of patients randomized ($n=1408$), interpretation of conclusions should be done with caution due to pitfalls of the study design. 51% of patients in the lymphadenectomy arm ($n=686$) had a myometrial invasion of less than 50% of the uterus. In 60% of the surgeries of the lymphadenectomy arm, less than 15 nodes have been removed. In another 35% of the cases less than ten nodes have been removed. Main reason for criticism could be the inclusion of a significant number of low-risk cases in the lymphadenectomy arm and in addition the small number of lymph nodes removed.

Given the above observations, the conclusions of both trials are that pelvic node removal has no therapeutic effect in most patients with endometrial carcinoma. However, the important questions are which subgroup of patients might possibly benefit from systematic surgical staging and whether we still perform overtreatment in patients with early endometrial cancer surgically.

Here, we present a retrospective population-based cohort study, in which we thoroughly analyzed a large patient cohort comprising exclusively type I FIGO IB EC. We applied multivariable regression analysis to exclude the influence of confounding factors on patient survival. For instance, the age of the patient is a major concern since old individuals are less likely to undergo a severe and high-risk intervention such as systematic LND (Andersen et al. 2005).

**Table 3** Hazard ratios, derived from univariable and multivariable Cox regression, for overall (OAS) and recurrence-free survival (RFS) in type I FIGO IB patients who did or did not undergo lymphadenectomy and according to extent of LND

| LND group | Total *n* | *n* of events | Univariable Cox regression | | | | Multivariable[a] Cox regression | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Hazard ratio[a] | Lower 95% CI | Upper 95% CI | Log-rank *p* | Hazard ratio[a] | Lower 95% CI | Upper 95% CI | Log-rank *p* |
| Overall survival | | | | | | | | | | |
| LND yes | 217 | 54 | 1.000 | Reference | | | 1.000 | | | |
| LND no | 82 | 36 | 1.673 | 1.096 | 2.555 | 0.017 | 1.214 | 0,771 | 1.911 | 0.402 |
| Total | 299 | 90 | | | | | | | | |
| Recurrence-free survival | | | | | | | | | | |
| LND yes | 217 | 62 | 1.000 | Reference | | | 1.000 | | | |
| LND no | 82 | 38 | 1.488 | 0.992 | 2.231 | 0.055 | 1.059 | 0.689 | 1.626 | 0.795 |
| Total | 299 | 100 | | | | | | | | |
| Overall survival | | | | | | | | | | |
| Systematic LND | 103 | 12 | 1.000 | Reference | | | 1.000 | | | |
| Elective LND | 63 | 25 | 2.653 | 1.331 | 5.288 | 0.006 | 1.699 | 0.835 | 3.460 | 0.144 |
| Unclassified LND | 51 | 17 | 1.689 | 0.799 | 3.569 | 0.170 | 1.380 | 0.649 | 2.931 | 0.403 |
| No LND | 82 | 36 | 2.872 | 1.488 | 5.545 | 0.002 | 1.764 | 0.892 | 3.487 | 0.103 |
| Total | 299 | 90 | | | | | | | | |
| Recurrence-free survival | | | | | | | | | | |
| Systematic LND | 103 | 14 | 1.000 | Reference | | | 1.000 | | | |
| Elective LND | 63 | 28 | 2.794 | 1.469 | 5.313 | 0.002 | 1.925 | 0.971 | 3.817 | 0.061 |
| Unclassified LND | 51 | 20 | 2.087 | 1.044 | 4.171 | 0.037 | 1.846 | 0.905 | 3.767 | 0.092 |
| No LND | 82 | 38 | 2.753 | 1.486 | 5.101 | 0.001 | 1.735 | 0.890 | 3.384 | 0.106 |
| Total | 299 | 100 | | | | | | | | |

[a]Adjusted for age at diagnosis, comorbidity, obesity, year of diagnosis, region of lymphadenectomy, lymph vessel invasion, vein invasion, oophorectomy, radiotherapy and chemotherapy. Model selection was performed using conditional stepwise forward selection

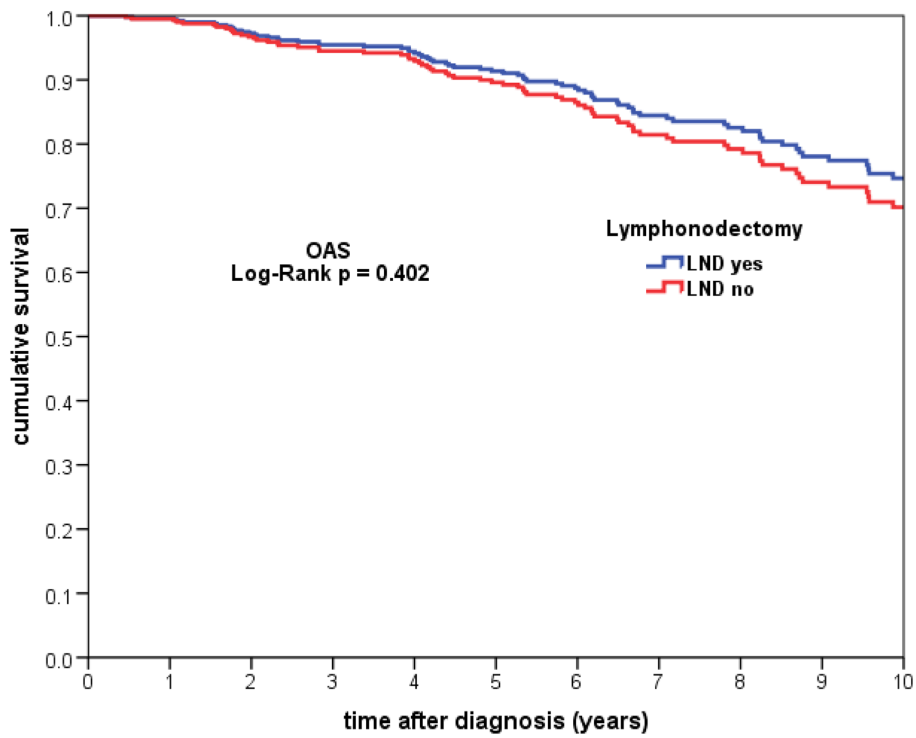


**Fig. 2** Overall survival of patients who did (blue) or did not (red) undergo lymphadenectomy. Overall survival was estimated by multivariable Cox regression with adjustment for age at diagnosis, comorbidity, obesity, year of diagnosis, region of lymphadenectomy, lymph vessel invasion, vein invasion, oophorectomy, radiotherapy and chemotherapy

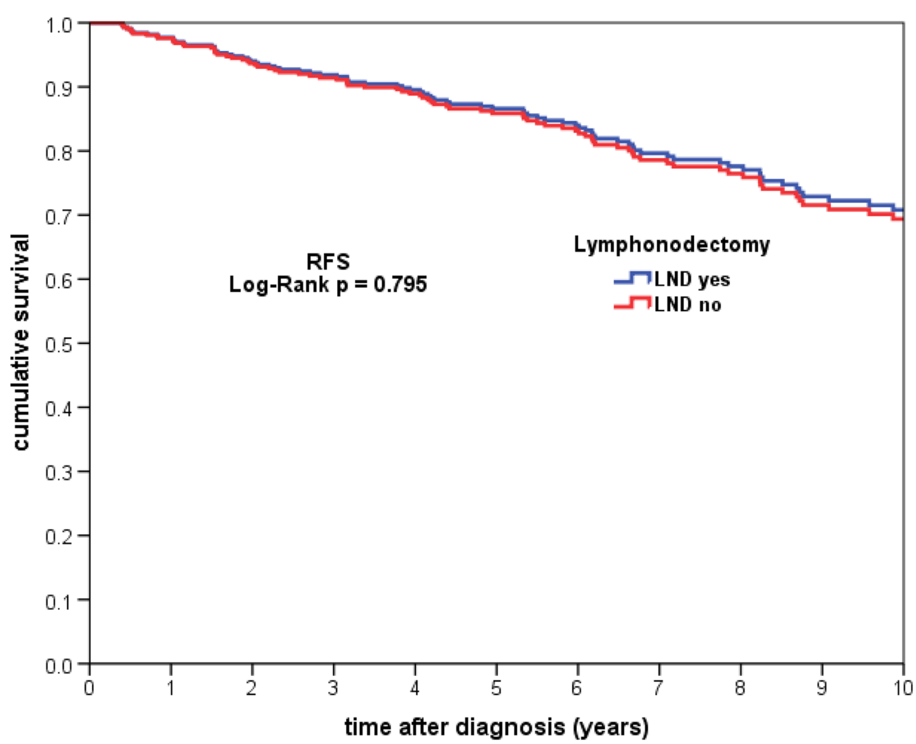


**Fig. 3** Recurrence-free survival of patients who did (blue) or did not (red) undergo lymphadenectomy. Overall survival was estimated by multivariable Cox regression with adjustment for age at diagnosis, comorbidity, obesity, year of diagnosis, region of lymphadenectomy, lymph vessel invasion, vein invasion, oophorectomy, radiotherapy and chemotherapy

Our study confirms the preliminary observation that LND as a therapeutic intervention for type I FIGO IB EC provides no statistically significant benefit for OAS and RFS. Consequently, our data raise the question whether systematic LND should further be recommended for this type of EC.

It is plausible that selection of patients manifesting the earliest indication for LND could have influenced the results obtained. We cannot rule out that LND improves the prognosis for the patient with more advanced disease. Previous reports show the benefit of systematic LND for high-grade

EC (Papathemelis 2017; Todo et al. 2010), which might suggest that a more radical therapeutic approach is beneficial at a higher stage or in case of high-risk EC.

The very recently launched ECLAT study will address this concern and provide the necessary data to ease the current doubt regarding the benefit of systematic LND for type I FIGO IB EC (ECLAT 2018); however, it will take a considerable amount of time until the first results will be available. Our study presents valid indication for the limitation of this therapeutic intervention, and will contribute to improved patient care in the future.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Human and animal rights** This article does not contain any studies with human participants or animals performed by any of the authors.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

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