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ORIGINAL ARTICLE

Paraaortic lymphadenectomy in intermediate to high risk uterine endometrioid cancer : a retrospective evaluation

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Summary

Purpose: *To investigate the impact on survival of paraaortic lymph node dissection (PALND) added to pelvic lymph node dissection (PLND) in patients with intermediate to high-risk endometrioid endometrial cancer (EC). Surgical parameters and perioperative morbidity have been explored as well.*

Methods: *We retrospectively identified all eligible patients that received LND as part of their primary treatment at a single institution from January 2000 to December 2010. Survival curves for overall (OS), disease-specific (DSS) and disease-free (DFS) survival were plotted by the Kaplan-Meier method and compared by the log-rank test. Cox proportional hazards regression was used for multivariable analysis for OS and DSS.*

Results: *93 patients underwent PLND plus PALND in their initial operation (PALND group) and 177 patients underwent PLND only (no-PALND group). Patients in the non-PALND group were older, more obese and had higher rates of comorbidities. The median number of PLN and PALN retrieved were 26 and 13 respectively. Isolated PALN metastasis was seen in 2 (2.1%) patients. PALND was associated with longer operative time, higher transfusion rate and longer hospital stay. PALND group had a benefit in OS (p=0.033), which did not persist in DSS or DFS. Furthermore, the type of LND did not significantly improve either OS or DSS according to the multivariate analysis results.*

Conclusion: *PALND had no therapeutic value per se in women with intermediate to high risk endometrioid tumors and the improvement seen in OS should rather be attributed to the better medical status of women who received PALND.*

Key words: *endometrioid, high-risk, intermediate, lymph node dissection, morbidity, paraaortic, survival*

Introduction

EC is the sixth most common malignancy in females worldwide with approximately 290,000 new cases annually [1]. As its incidence rises with obesity, physical inactivity [2] and increase in life expectancy [3], EC is more frequent in high-income countries (5.5%) compared with low-income countries (4.2%). Up to the age of 75 years the cumulative risk of EC has been estimated as high as 1.6% [4]. In Europe and North America, EC is the most common gynecologic cancer [1].

In 1988, the International Federation of Gynecology and Obstetrics (FIGO) declared EC as a surgically staged disease [5]. Although since then FIGO mandates PLND and PALND areas for staging purposes [6], controversy still exists regarding their indications, anatomic extent and therapeutic

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value in the management of EC [7]. According to current FIGO recommendations, an extrafascial total hysterectomy with bilateral salpingo-oophorectomy (TH-BSO) is the standard surgical treatment for EC. Additionally, as a minimum, any enlarged or suspicious lymph nodes should be removed in all patients and complete pelvic lymphadenectomy and resection of any enlarged paraaortic nodes should be performed in high risk patients [6]. The rationale is to identify the high risk population with positive nodes, who would benefit from chemotherapy [8].

The therapeutic value of lymphadenectomy *per se* has been largely disputed. Although large retrospective studies had associated LND with improved survival [9-13], they were contradicted by the results of two randomized trials [14,15], which examined the survival effect of PLND in clinically early stage EC patients and found no benefit. However, these randomized trials have been heavily criticized [16-18]. Among the few studies that have addressed the issue of therapeutic role of PALND the results have also been contradictory [10,19-22]. It was recently proposed that the improved survival seen with PALND is a reflection of the general health of the patient rather than a therapeutic benefit of surgery [23].

The aim of this study was to examine whether the performance of PALND compared with PLND alone improves the survival in patients with intermediate and high risk endometrioid EC. Surgical parameters and perioperative morbidity have also been explored.

Methods

We retrospectively identified all women who were treated for cancer of the uterine corpus at the Department of Obstetrics-Gynaecology of Aschaffenburg–Hospital Clinicum, of the University Würzburg in Germany from January 2000 to December 2010. Patients with uterine sarcomas or non-endometrioid endometrial tumors and those with endometrioid tumors who were not subjected to primary surgical treatment with TH-BSO for any reason were excluded. For the remaining patients, a detailed review of operative and final pathology reports was conducted. Women who did not receive LND in their initial surgery for any reason were excluded. Furthermore, we applied the ESMO-ESGO-ESTRO criteria [7]-stage I endometrioid EC, grade 1 or 2, myometrial invasion less than 50%, lymphovascular space invasion (LVSI) negative- among those who underwent LND to exclude women with low-risk endometrioid tumors. Thus, the study population consisted of women that were subjected to TH-BSO plus LND as primary treatment for intermediate to high-risk endometrioid tumors.

The extent of LND performed was not used as an exclusion criterion. Retrospective studies by definition lack a standardized surgical protocol. Multiple LN samplings or systematic LND were performed according to surgeon's preference with consideration of the patients' preoperative risk for nodal disease, intraoperative findings, as well as each patients' medical comorbidities. We divided the study population in two groups, according to the type of LND performed- women that underwent PLND plus PALND (PALND group) and women that underwent only PLND (no-PALND group). The no-PALND group included all patients who underwent PLND, regardless of the number of nodes excised. Similarly, the PALND group included all patients who underwent PALND, regardless of the number of retrieved nodes.

An extensive research was made through the patients' medical records. We collected information on 130 parameters, including demographics, medical comorbidities and ASA (American Society of Anesthesiologists) status at the time of surgery, detailed surgical descriptions, pathology reports, complications, adjuvant therapy and survival data on recurrence, death and cause of death. Following final pathology review, surgical stage was redefined according to 2009 FIGO staging system [24]. An attempt was made to contact patients lost to follow up, fill in the missing information and verify their current state. When this attempt was unfruitful, the patients' status on their last follow up was taken into account.

OS was defined as the time from surgery to death from any cause. DSS was defined as the time from surgery to uterine cancer-related death or death related to treatment. DFS was defined as the time from surgery to the earliest occurrence of relapse or death from any cause.

Statistics

Survival curves were plotted by the Kaplan-Meier method and comparisons were made by using log-rank test. Cox proportional hazards regression was used for multivariate analysis (following univariate significant association of variables with survival). Qualitative parameters were compared by the Pearson's or Fisher's exact test. Continuous parameters were compared by Student's t-test or Mann-Whitney U test. All statistical tests were two-sided and the level of statistical significance was set at 0.05. Data analysis was performed using IBM SPSS Statistics for Windows, Version 20.0, Armonk, NY.

Results

From January 2002 to December 2010 425 women were treated for endometroid cancer of the uterine corpus at our institution. Patients were excluded from the study for the following reasons: uterine sarcomas (N=24), serous carcinomas (N=30), clear cell carcinomas (N=10), not a primary surgical treatment (N=10), a primary surgical treatment with no LND performed (N=66) or low-risk endometrioid tumors according to the criteria applied [7] (N=65). Two hundred and seventy women fulfilled the inclusion criteria and were included in the study. Ninety three patients (34.4%) underwent PLND plus PALND in their initial surgery (PALND group), while 177 patients (65.5%) underwent PLND only (no-PALND group).

The clinico-pathological characteristics of each group are listed in Table 1. Significant differences arose between baseline characteristics

Table 1. Clinicopathological characteristics of 270 patients with uterine endometrioid cancer of intermediate or high risk of recurrence by PALND status

Clinicopathological characteristics	*PALND (N=93) N (%)*	*No PALND (N=177) N (%)*	*p-value**
Age at diagnosis, years (range)	63 (48-81)	67 (44-82)	<0.001
BMI, kg/m^2 (range)	30.8 (17.1-40.1)	35.1 (19.7-42.2)	0.017
Comorbidities			
Hypertension	46 (49.4)	11 (64.9)	0.013
Diabetes	16 (17.2)	52 (29.3)	0.028
Coronary artery disease	3 (3.2)	16 (9.0)	0.070
Simple general disease	65 (69.8)	13 (75.7)	NS
Serious general disease	6 (6.4)	27 (15.2)	0.038
ASA score			0.038
I-II	67 (72.0)	10 (59.3)	
III-V	26 (28.0)	72 (40.7)	
Surgical approach			NS
Abdominal	70 (75.3)	14 (80.2)	
Minimally invasive	23 (24.7)	35 (19.8)	
FIGO stage (2009)			NS
IA	55 (59.1)	115 (64.9)	
IB	7 (7.5)	25 (14.1)	
II	6 (6.5)	9 (5.0)	
IIIA	2 (2.1)	3 (1.7)	
IIIB	3 (3.2)	3 (1.7)	
IIIC	18 (19.3)	18 (10.1)	
IV	2 (2.1)	4 (2.2)	
Tumor grade			NS
1	17 (18.2)	27 (15.2)	
2	56 (60.2)	97 (54.8)	
3	20 (21.5)	53 (29.9)	
Tumor size, cm (range)	4.3 (0.4-12)	3.5 (0.4- 9.0)	NS
Depth of myometrial invasion			NS
≤1/2	35 (37.7)	73 (41.2)	
>1/2	58 (62.3)	10 (58.8)	
LVSI			NS
Negative	57 (61.3)	11 (67.2)	
Positive	36 (38.7)	58 (32.8)	
Adjuvant therapy			NS
None	6 (6.4)	11 (6.2)	
Radiotherapy	62 (66.6)	13 (77.9)	
Radiotherapy and chemotherapy	25 (26.9)	28 (15.8)	

*Pearson's or Fisher's exact test for qualitative parameters, Student's t-test or Mann-Whitney U test for continuous parameters. NS: non significant. For other abbreviations see text and comorbidities of patients who received or not PALND. Namely, patients in the no-PALND group were older (p<0.001), more obese (p=0.017) and with higher rates of hypertension (p=0.013), diabetes (p=0.028) and coronary artery disease (p=0.07). Twenty seven (15.2%) patients in the no-PALND group were deemed to suffer from a serious general disease, as opposed to 6 (6.4%) patients in the PALND group (p=0.038). ASA score was selected as a general indicator of patients' performance at the time of surgery and was found to be different between the two groups, with patients in the no-PALND group doing significantly worse (p=0.038). On the other hand, tumor characteristics were not significantly different. The majority of patients in both groups had stage I tumors with intermediate or poor differentiation. Frozen section diagnosis was available in 116 (42.9%) cases and no significant differences were observed from the final pathology report. Data on tumor size were available in 101 (37.4%) cases.

Surgery details and perioperative morbidity of each group are listed in Table 2. In the PALND group a median number of 28 (range 15-59) PLN was retrieved, while in the no-PALND group the median number of PLN retrieved was 24 (range 2-46). This difference was significant (p=0.001). In both groups the majority of cases had more than 20 PLN removed (83.9 and 66.1% respectively). In 12 (6.7%) cases of the no-PALND group less than 10 PLN were retrieved. In the PALND group, the median number of PALN retrieved was 13 (range 3-51). In 48 (51.6%) cases, more than 10 PALN were removed. LN metastasis was present in 18 (10.1%) patients in the no-PALND group and in 18 (19.3%) patients in the PALND group. In this latter group, 11 (11.8%) patients had metastatic disease involving only PLN and 5 (5.3%) patients had metastatic disease involving both PLN and PALN. Isolated PALN metastasis was seen in 2 (2.1%) patients. Bulky PALN, larger than 1 cm in diameter were palpated intraoperatively in 44 patients (16.3% of the study population). All 44 patients had PALND and metastatic PALN disease was present in 7 patients (7/44, 15.9%). Notably, in the absence of bulky PALN, no metastatic PALN was found.

Operative time in the PALND group (median 180 min., range 98-250) was significantly longer (p<0.001) than in no-PALND group (median 125 min., range 20-50). Median duration of PALND was 35 min (range 20-50). We estimated that performing PALND prolonged the operative time in each patient by an average 27% (range 19-50%). Blood loss and blood transfusion rate were greater in the PALND group (p<0.001 and p= 0.046 respectively). However, no major intraoperative injuries or surgery related deaths occurred in any group. Early postoperative complications were similar in the two groups. Hospital stay was longer in the PALND group (median 10 vs 8 days, p=0.022). The rate of late postoperative complications was also similar and low in both groups. Five (2.8%) patients in the no-PALND group and 3 (3.2%) patients in the PALND group developed lymphocyst or lymphedema and 2 (1.1%) patients in the no-PALND group developed urine incontinence.

Postoperatively, adjuvant therapy was administered to patients in both arms according to the ongoing practice at our institution (Table 1). Most of them received radiotherapy (66.6% of the patients in the PALND group and 77.9% in the no-PALND group). Other treatment options were no adjuvant therapy or both radiation therapy and chemotherapy. Overall, adjuvant therapy was no different between the two groups (p=0.11).

Median follow up time was 61 months (range 7-184) and did not differ between groups (p=0.47). Fifteen (16.1%) patients died in the PALND group and 51 (28.8%) patients died in the no-PALND group (p=0.07). EC or treatment was the cause of death for 9 (9.7%) patients and 27 (15.3%) patients respectively (p=0.23). EC recurred in 27 (29.0%) patients in the PALND group and 61 (34.5%) patients in the no-PALND group (p=0.25). Median time to relapse was 27 months and 19 months respectively. Patients were managed similarly after recurrence in both groups. Thirty nine (44.3%) patients underwent a second operation and all received additional therapy (radiotherapy alone or both radiotherapy and chemotherapy).

Sites of first recurrence were similar between groups. In both groups, the vagina was the most common site of first recurrence and others included peritoneum, lung, LNs, bones and liver. The recurrence rate in LNs did not differ between groups either (p=0.77). In the PALND group, 3 (3.2%) patients recurred. Pelvic relapse occurred in 2 patients without LN metastasis at primary surgery. Paraaortic relapse occurred in 1 patient who had both pelvic and para-aortic mtastasis at surgery. In the no-PALND group, 6 (3.4%) patients recurred. Pelvic relapse occurred in 4 patients, 2 of whom had pelvic metastasis at primary surgery. Paraaortic relapse occurred in 1 patient without LN metastasis at surgery.

Kaplan- Meier curves for OS, DSS and DFS

Table 2. Surgery details and perioperative morbidity by PALND status

	PALND (N=93) N (%)		*No PALND (N=177) N (%)*		*p value**
No. of PLN retrieved (range)	28	(12-59)	24	(2-46)	0.001
1-5	0		5	(2.8)	
6-10	0		7	(3.9)	
11-20	15	(16.1)	48	(27.1)	
>20	78	(83.9)	117	(66.1)	
No of PALN retrieved	13	(3-51)			
1-5	21	(22.6)			
6-10	24	(25.8)			
11-20	30	(32.2)			
>20	18	(19.4)			
Presence of LN metastasis	18	(19.3)	18	(10.1)	NS
No. of metastatic PLN	2	(1.7)	2	(1.3)	
No. of metastatic PALN	4	(1.11)			
PLN(-)/PALN(-)	75	(80.6)			
PLN(+)/PALN(-)	11	(11.8)			
PLN(+)/PALN(+)	5	(5.3)			
PLN(-)/PALN(+)	2	(2.1)			
Presence of palpable PALN >1 cm	44	(47.3)	0		
No. of palpable PALN >1 cm	4	(1.14)			
PALN (+) in presence of palpable PALN	7	(15.9)			
PALN (+) in absence of palpable PALN	0				
Operative time, min (range)	180	(98-250)	125	(45-280)	<0.001
Operative time for PALND, min (range)	35	(20-50)			
Blood loss, ml (range)	400	(100-1200)	200	(100-1500)	<0.001
Blood loss >1000ml	6	(6.4)	2	(1.1)	0.022
Blood transfusion	10	(10.7)	5	(5.3)	0.011
Intraoperative complications	5	(5.3)	5	(2.8)	NS
Ureter injury	3	(3.2)	2	(1.1)	
Vesical injury	1	(1)	1	(0.5)	
Vascular injury	1	(1)	1	(0.5)	
Bowel injury	0		1	(0.5)	
Early postoperative complications	15	(16.1)	28	(15.8)	NS
Wound infection	2	(2.1)	4	(2.2)	
Urinary infection	5	(5.3)	7	(3.9)	
Pneumonia	0		2	(1.1)	
Isolated fever >38°C	3	(3.2)	4	(2.2)	
Ureter dilatation	2	(2.1)	1	(0.5)	
Ileus	1	(1)	4	(2.2)	
Deep vein thrombosis	1	(1)	3	(1.6)	
Wound dehiscence	1	(1)	3	(1.6)	
Hospital stay (days, range)	8	(5-80)	6	(4-50)	0.022
Late postoperative complications	3	(3.2)	7	(3.9)	NS
Lymphocyst/ Lymphedema	3	(3.2)	5	(2.8)	
Urine incontinence	0		2	(1.1)	

*Pearson's or Fisher's exact test for qualitative parameters, Student's t-test or Mann-Whitney U test for continuous parameters. NS: non significant. For other abbreviations see text are presented in Figure 1. Five-year OS was 90.3% for patients in the PALND group and 80.2% for patients in the no-PALND group. The difference in OS was statistically significant (p=0.033, log-rank test). However, neither DSS, nor DFS differed significantly between the two groups. Five-year DSS was 92.4% for patients in the PALND group and 87.0% for patients in the no-PALND group (p=0.203, log-rank test), while 5-year DFS was 78.4 and 75.1 % respectively (p=0.27, log-rank test). An additional analysis was performed to partly compensate for the heterogeneity of surgical procedures. The exclusion from no-PALND group of patients (N=60) with low nodal count (<20 PLN) combined with the exclusion from PALND group of patients (N=21) with low nodal count (<5 PALN), did not change the pattern of results on survival analysis (data not shown).

Multivariate Cox proportional hazards analyses for OS and DSS are presented in Table 3 and Table 4 respectively. The type of LND performed and the number of removed PALN did not significantly improve either OS or DSS, after including in the model covariates, such as FIGO stage, tumor grade, age, body mass index (BMI) and ASA score at the time of surgery. For OS, the independent poor prognostic factors were FIGO stage III-IV (HR 3.49, 95% CI 2.76 – 4.39; p=0.007), tumor grade 3 (HR 2.34, 95% CI 1.32 – 4.12; p=0.008), age >65 years (2.01, 95% CI 1.10 – 3.32, p=0.005), BMI >30 kg/m^2 (HR 1.97, 95% CI 1.05 – 3.70, p= 0.035) and ASA score (HR 2.22, 95% CI 1.12 – 4.39, p=0.010). For DSS, the independent factors associated with poor prognosis were only FIGO stage III-IV (HR 3.50, 95% CI 2.08 – 5.88; p <0.001), tumor grade 3 (HR 2.22, 95% CI 1.29 – 3.55; p=0.01) and age >65 years (2.49, 95% CI 1.52 – 4.05, p<0.001).

Discussion

Since FIGO's revision of the EC staging and shift to surgical staging in 1988, the percentage of patients undergoing LND has increased significantly [13,25]. Yet, older women are less likely to be surgically staged [13], and so are obese women [26,27]. Moreover, women undergoing LND are more likely to receive adjuvant therapy [13]. Considering that the extent of LND performed corresponds with patients' age, BMI and underlying health status, we sought to investigate the survival effect of extended LND comprising the paraaortic areas taking into account these parameters.

At the time of surgery, our study population in both groups was rather old (55.6% of women were above 65 years) and obese (62.2% of women

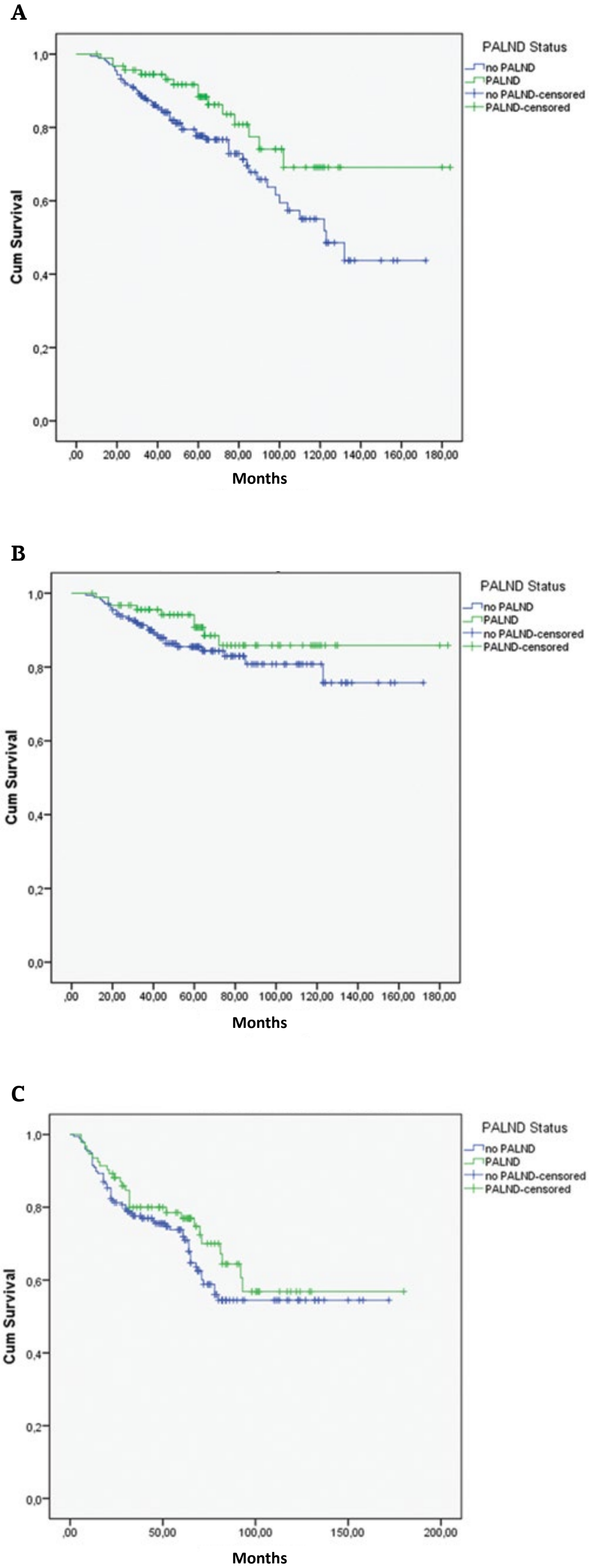

Figure 1. Kaplan- Meier survival analysis in patients with uterine endometrioid cancer of intermediate or high risk of recurrence by PALND status. **A:** Overall survival (p=0.03, log-rank test); **B:** Disease specific survival (p=0.20, log-rank test); **C:** disease free survival (p=0.27, log-rank test).

Table 3. Multivariate Cox proportional hazards analysis for overall survival in patients with uterine endometrioid cancer of intermediate or high risk of recurrence

	Hazard ratio	*95% CI*	*p value*
Type of LND			
PLND	1 (referent)		
PLND+PALND	0.70	0.42 – 1.16	NS
No of PALN removed			
PLND only	1 (referent)		
<5 PALN	1.09	0.65 – 1.84	NS
>5 PALN	0.71	0.40 – 1.29	NS
FIGO stage (2009)			
I-II	1 (referent)		
III-IV	3.49	(2.76 – 4.39)	0.007
Tumor grade			
1-2	1 (referent)		
3	2.34	(1.32 – 4.12)	0.008
Age, years			
≤65	1 (referent)		
>65	2.01	(1.10 – 3.32)	0.005
BMI			
≤30	1 (referent)		
>30	1.97	(1.05 – 3.70)	0.035
ASA score (at surgery)			
I-II	1 (referent)		
III-IV	2.22	(1.12 – 4.39)	0.010

NS: non significant. For other abbreviations see text

had BMI >30 kg/m^2, 40.4% of women had BMI >35 kg/m^2). However, women not receiving PALND were significantly older, more obese and more frequently medically compromised. OS was higher in the PALND group. The difference in OS implies a survival benefit for women treated with PALND, compared to women treated with PLND only. Yet, this benefit does not persist for the DFS endpoint, nor for the DFS endpoint. In multivariate Cox regression analysis age, BMI and ASA score at the time of surgery emerged as independent prognostic factors for OS, together with FIGO stage and tumor grade. The type of LND performed and the number of PALN removed were found to be non-significant in the prediction of OS and DSS. Based on our results, we conclude that PALND *per se* did not improve survival in women with intermediate to high risk endometrioid tumors and the improvement seen in OS should rather be attributed to the better medical status of women who received PALND. This conclusion is consistent with other studies [23].

Age >65 years emerged as a strong independent poor prognostic factor for both OS and DSS in multivariate Cox regression analysis, adjusted for presence of comorbidities in the form of ASA score. Moreover, our study focused on endometrioid histology only. These results imply that the effect of older age in the survival of EC patients is not related to the underlying medical status, nor to histologic subtypes with worse prognosis (serous, clear cell) more often encountered in old patients. While not in accordance with other studies [28], a recent study has also stated that age >65 years as an independent poor prognostic factor that worsens by about 10% survival expectation of older patients in comparison to younger women [29]. The impact of BMI on OS found in our study is not to be neglected either. Obesity (BMI >30 kg/m^2) has been independently correlated with worse OS and DFS in old patients (age >65) with early stage EC [29] and severe obesity (BMI ≥35 kg/m^2) has been independently correlated with poorer DFS in high-risk EC patients [26]. Concluding, it seems that among patients with EC, older age and higher BMI carry *per se* a poor prognosis, which is independent of the extent of the primary surgery.

With the exception of greater blood loss and increased transfusion rate among patients undergoing PALND, the addition of PALND generally

Table 4. Multivariate Cox proportional hazards analysis for disease-specific survival in patients with uterine endometrioid cancer of intermediate or high risk of recurrence

	Hazard ratio	*95% CI*	*p value*
Type of LND			
PL ND	1 (referent)		
PL ND+PALND	0.95	0.52 – 1.71	NS
No of PALN removed			
PLND only	1 (referent)		
<5 PALN	1.18	0.70 – 1.96	NS
>5 PALN	0.90	0.77 – 1.06	NS
FIGO stage (2009)			
I-II	1 (referent)		
III-IV	3.50	2.08 – 5.88	<0.001
Tumor grade			
1-2	1 (referent)		
3	2.22	1.29 – 3.55	0.010
Age, years			
≤65	1 (referent)		
>65	2.49	1.52 – 4.05	<0.001
BMI			
≤30	1 (referent)		
>30	1.38	0.75 – 2.53	NS
ASA score (at surgery)			
I-II	1 (referent)		
III-IV	1.25	0.62 – 2.51	NS

NS: non significant. For other abbreviations see text

did not increase intraoperative complications, nor perioperative morbidity in our series. However, it did lengthen operative time significantly by an average 27% for each patient. Although we were unable to relate the fact to specific complications, hospital stay was also longer in the PALND group, maybe reflecting just the surgeons' greater cautiousness towards a more extended procedure. We did not perform a cost analysis, but under these circumstances it is highly possible that the performance of PALND would lead to increased cost. In our study population LN metastasis was present in 13.3% of the patients. In the presence of pelvic nodal disease, metastatic PALN were also found in 31.2% of the patients, while isolated PALN were found in 2.1% of the patients. Both rates are comparable with previous large studies [30,31]. In our series, in the absence of bulky PALN intraoperatively, no metastatic PALN was found.

The study presents several limitations. First, based on an accurate depiction of everyday practice, we have compared survival in groups with different baseline characteristics. However, the anticipated difference in survival due to this bias would have favored the PALND group. Retrospective studies are limited by their nature to adequately control for comorbidities. Single-institution studies like ours, have an advantage in exposing this selection bias due to available data, compared with very large retrospective studies based on national registries or databases. Second, uniform surgical procedures were not implemented. Nodal count has been frequently used as a criterion for adequate LND. Using cut-offs previously described [19,32], LND in our study is considered adequate in most of the cases for both groups. Furthermore, an additional analysis which excluded cases with low nodal counts from both groups did not change the pattern of results on survival analysis. Third, we were unable to adequately control for adjuvant therapy, which was also administered according to the ongoing practice at our institution. Adjuvant therapy was not different between the two groups in our study. However, there is an inherent difficulty to control for adjuvant therapy in all studies that examine the survival effect of LND *per se* regardless of their design.

A previous study that addressed the likelihood of confounding taking place in retrospective trials, came to question their validity. Interestingly, the dissection of >11 LN in EC patients was found to improve EC-non-specific survival and cardiac-specific survival by a relative 23% and 18% respectively. In that way, the potential biases and shortcomings in using non-randomized retrospective data were demonstrated [13]. In fact, only randomized-controlled trials can effectively control for potential confounders, as comorbidities, pretreatment performance status, socioeconomic factors or BMI. Thus, therapeutic strategies for EC should prove their value through randomized trials with survival and quality of life endpoints.

As a conclusion, there seems to be no therapeutic value of PALND *per se* in intermediate and high risk uterine endometrioid carcinoma, when compared with PLND alone, as pointed out in ours and other studies [10,22,23]. The addition of PALND was not found to increase perioperative morbidity, though it was associated with longer operative time, higher transfusion rate and longer hospital stay. The survival benefit of full staging through guidance of adjuvant therapy was not addressed in our study. An international trial of the role of lymphadenectomy to direct adjuvant therapy for high-risk endometrial cancer (STATEC) has been announced. The ongoing ENGOT-EN2-DGCG/EORCT 55102 trial will contribute in answering the same question. Following the publication of randomized trials [14,15,33-35], an agreement seems to have been reached regarding the criteria and the management of low risk EC, with TH-BSO as the standard surgical procedure and no need for adjuvant therapy. Respectively, the criteria as to what constitutes an intermediate or high risk EC patient population have been adequately described. The future goal should be to reach a consensus regarding the indications and anatomic extent of LND in the surgical management of intermediate and high risk EC. This consensus should take seriously into account issues of cost-effectiveness, as well as the indisputable reality of gynecologists with various backgrounds performing surgical procedures for uterine cancer worldwide.

Conflict of interests

The authors declare no confict of interests.

References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011;61:69-90.
2. Friedenreich CM, Neilson HK, Lynch BM. State of the epidemiological evidence on physical activity and cancer prevention. Eur J Cancer 2010;46:2593-2604.
3. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer 2013;49:1374-1403.
4. Siegel RI, Miller Kd, Jemal A. Cancer statistics , 2015 . CA Cancer J Clin 2015;65:21254. doi:10.3322/caac.21254.
5. Creasman WT, Morrow CP, Bundy BN, Homesley HD, Graham JE, Heller PB. Surgical pathologic spread patterns of endometrial cancer. A Gynecologic Oncology Group Study. Cancer 1987;60 (8 Suppl): 2035-2041.
6. Amant F, Mirza MR, Koskas M, Creutzberg CL. Cancer of the corpus uteri. Int J Gynaecol Obstet 2015;131 (Suppl):S96-S104.
7. Colombo N, Creutzberg C, Amant F et al. ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer: diagnosis, treatment and follow-up. Ann Oncol 2015;117:mdv484.
8. Randall ME, Filiaci VL, Muss H et al. Randomized Phase III Trial of Whole-Abdominal Irradiation Versus Doxorubicin and Cisplatin Chemotherapy in Advanced Endometrial Carcinoma : A Gynecologic Oncology Group Study. J Clin Oncol 2006;24:36-44.
9. Kilgore LC, Partridge EE, Alvarez RD et al. Adenocarcinoma of the endometrium: survival comparisons of patients with and without pelvic node sampling. Gynecol Oncol 1995;56:29-33.
10. Cragun JM. Retrospective Analysis of Selective Lymphadenectomy in Apparent Early-Stage Endometrial Cancer. J Clin Oncol 2005;23:3668-3675.
11. Lutman C V, Havrilesky LJ, Cragun JM et al. Pelvic lymph node count is an important prognostic variable for FIGO stage I and II endometrial carcinoma with high-risk histology. Gynecol Oncol 2006;102:92-97.
12. Chan JK, Wu H, Cheung MK, Shin JY, Osann K, Kapp DS. The outcomes of 27,063 women with unstaged endometrioid uterine cancer. Gynecol Oncol 2007;106:282-288.
13. Smith DC, Macdonald OK, Lee CM, Gaffney DK. Survival impact of lymph node dissection in endometrial adenocarcinoma: a surveillance, epidemiology, and end results analysis. Int J Gynecol Cancer

2008;18:255-261.

14. Barton DPJ, Naik R, Herod J. Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC Trial): A Randomized Study. Int J Gynecol Cancer 2009;19:125-136.
15. Panici PB, Basile S, Maneschi F et al. Systematic Pelvic Lymphadenectomy vs No Lymphadenectomy in Early-Stage Endometrial Carcinoma: Randomized Clinical Trial. J Natl Cancer Inst 2008;100:1707-1716.
16. Uccella S, Podratz KC, Aletti GD, Mariani A. Systematic pelvic lymphadenectomy vs no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial. J Natl Cancer Inst 2009;101:897-898; author reply 898-899.
17. Höckel M, Dornhöfer N. Treatment of early endometrial carcinoma: is less more? Lancet 2009;373:97-99.
18. Creasman WT, Mutch DE, Herzog TJ. ASTEC lymphadenectomy and radiation therapy studies: are conclusions valid? Gynecol Oncol 2010;116:293-294.
19. Mariani A, Webb MJ, Galli L, Podratz KC. Potential Therapeutic Role of Para-aortic Lymphadenectomy in Node-Positive Endometrial Cancer. Gynecol Oncol 2000;76:348-356.
20. Fujimoto T, Nanjyo H, Nakamura A et al. Para-aortic lymphadenectomy may improve disease-related survival in patients with multipositive pelvic lymph node stage IIIc endometrial cancer. Gynecol Oncol. 2007;107:253-259.
21. Todo Y, Kato H, Kaneuchi M, Watari H, Takeda M, Sakuragi N. Survival effect of para-aortic lymphadenectomy in endometrial cancer (SEPAL study): a retrospective cohort analysis. Lancet 2010;375:1165-1172.
22. Wang Z-Q, Wang J-L, Shen D-H, Li X-P, Wei L-H. Should all endometrioid uterine cancer patients undergo systemic lymphadenectomy? Eur J Surg Oncol 2013;39:344-349.
23. Courtney-Brooks M, Scalici JM, Tellawi AR, Cantrell LA, Duska LR. Para-aortic Lymph Node Dissection for Women With Endometrial Adenocarcinoma and Intermediate- to High-Risk Tumors. Int J Gynecol Cancer 2014;24:91-96.
24. Creasman W. Revised FIGO staging for carcinoma of the endometrium. Int J Gynaecol Obstet 2009;105:109.
25. Chan JK, Cheung MK, Huh WK, Osann K, Husain A, Teng NN. Therapeutic Role of Lymph Node Resection in Endometrioid Corpus. Cancer 2006;107:1823-1830.
26. Canlorbe G, Bendifallah S, Raimond E et al. Severe Obesity Impacts Recurrence-Free Survival of Women with High-Risk Endometrial Cancer: Results of a French Multicenter Study. Ann Surg Oncol 2015;22:2714-2721.
27. Todo Y, Okamoto K, Minobe S, Kato H. Clinical significance of surgical staging for obese women with endometrial cancer: a retrospective analysis in a Japanese cohort. Jpn J Clin Oncol 2014;44:903-909.
28. Fleming ND, Lentz SE, Cass I, Li AJ, Karlan BY, Walsh CS. Is older age a poor prognostic factor in stage I and II endometrioid endometrial adenocarcinoma? Gynecol Oncol 2011;120:189-192.
29. Quinn MJ. Secondary analyses from a randomized clinical trial: Age as the key prognostic factor in endometrial carcinoma. Am J Obstet Gynecol 2014;210:363.e1-363.e10.
30. Mariani A, Dowdy SC, Cliby WA et al. Prospective assessment of lymphatic dissemination in endometrial cancer : A paradigm shift in surgical staging. Gynecol Oncol 2008;109:11-18.
31. Mariani A, Keeney GL, Aletti G, Webb MJ, Haddock MG, Podratz KC. Endometrial carcinoma: paraaortic dissemination. Gynecol Oncol 2004;92:833-838.
32. Chan JK, Urban R, Cheung MK et al. Lymphadenectomy in endometrioid uterine cancer staging: how many lymph nodes are enough? A study of 11,443 patients. Cancer 2007;109:2454-2460.
33. Creutzberg CL, van Putten WL, Koper PC et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. Lancet 2000;355:1404-1411.
34. Keys HM, Roberts JA, Brunetto VL et al. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: A Gynecologic Oncology Group study. Gynecol Oncol 2004;92:744-751.
35. Astec T, Study EN. Adjuvant external beam radiotherapy in the treatment of endometrial cancer (MRC ASTEC and NCIC CTG EN.5 randomised trials): pooled trial results, systematic review, and meta-analysis. Lancet 2009;373:137-146.