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Oncological safety and perioperative morbidity in low-risk endometrial cancer with sentinel lymph-node dissection

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ABSTRACT

Background: and Purpose: In endometrial cancer, staging is performed surgically. Controversy about the required extent of lymph node removal is ongoing. In low-risk endometrial cancer (FIGO Stage 1, endometrioid histology, Grades 1 and 2), the risk of lymph-node involvement is 4–17%. Since the introduction of near-infrared optics and the use of indocyanine green, the role of sentinel lymph node removal is increasing and could offer an appropriate balance between the morbidity of a complete lymph-node dissection and the risk of missing lymph-node involvement.

Methods: In this retrospective comparative study on low-risk endometrial cancer, the extent of surgical lymph-node assessment (no lymphadenectomy vs removal vs lymphadenectomy) in two European institutions was compared and analyzed on the basis of perioperative data and oncological outcome.

Results: The study included 279 patients from: 103 (36.9%) had no lymphadenectomy, 118 (42.3%) underwent SLN removal and 58 (20.8%) underwent pelvic and/or para-aortic lymphadenectomy. There were significant differences among the groups in blood loss ($p = 0.000$), operation time ($p = 0.000$), and severity of postoperative complications ($p = 0.063$). In comparing only sentinel lymph-node removal vs no lymphadenectomy, there were no significant differences. No significant difference was seen between the extent of lymphadenectomy removal and the risk of recurrence. Age and Lymphovascular space invasion positivity were significant risk factors for recurrence ($p = 0.004$ and $p = 0.019$).

Conclusions: In early-stage, endometrial cancer, Grade 1 and 2, sentinel lymph node removal offers a convincing balance between oncological safety and perioperative morbidity. Especially in LVSI-positive cases, lymph-node evaluation in any form is crucial.

Introduction

Endometrial cancer (EMCA) is the most common gynecologic-oncological disease, with a good 5-year overall survival rate of between 74% and 91% [1,2]. Due to the symptom of postmenopausal bleeding, in 75% of cases the diagnosis is made in early-stage disease [3]. The staging of the extent of disease is performed surgically; controversy is ongoing about the extent of lymph-node removal that is needed. In low-risk EMCA (FIGO Stage 1, endometrioid histology, Grades 1 and 2), the risk of lymph-node involvement is 4–17% [4]. Two prospective, randomized studies showed no improvement in overall and disease-free survival by adding a pelvic lymphadenectomy (LND) in Stage I disease [5,6]. For these reasons, systematic LND in this population is not mandatory [7,8]. However, in both studies mentioned, more patients of the "no LND group" had radiation therapy. Accordingly, a considerable number of patients had unnecessary adjuvant therapy, as the lymph-node status was not known.

Over the past few years, since the introduction of near-infrared optics and indocyanine green (ICG), the role of sentinel lymph node (SLN) removal is increasing; SLN dissection could offer a balance between the known morbidity of a complete lymph-node removal and the risk of missing lymph-node involvement due to not adding

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LND. Studies on lymph-node pathways and detection rates led to the inclusion of SLN removal in the National Comprehensive Cancer Network (NCCN) and British Gynecological Cancer Society (BGCS) guidelines [7,8]. However, oncological follow-up data on patients treated with SLN removal are scarce.

In this study, we analyzed intraoperative and postoperative data from patients diagnosed with low-risk EMCA and compared the oncologic outcome among the different surgical stagings performed: no LND; SLN mapping; and pelvic lymphadenectomy (PLND) +/-para-aortic lymphadenectomy (PALND).

Materials and methods

This retrospective comparative study compares three categories of low-risk endometrial cancer surgical treatments performed in two institutions: University Hospital of Bern/University of Bern (Switzerland) and Ospedale Santa Chiara di Trento (Italy). Three different lymph-node staging approaches were compared: (1) no LND; (2) SLN mapping; and (3) pelvic (PLND) and/or para-aortic lymphadenectomy (PALND).

For this study, only patients with FIGO Stage 1, endometrioid histology, Grade 1 or 2 endometrial cancer (EMCA) at final diagnosis after surgical staging at that time were included. In the patients undergoing SLN removal and LND, the lymph nodes were by definition negative. In patients where no LND was performed, due to the decision at that time, the lymph-node status was by definition unknown.

Adoption of ICG-SLN removal at the two institutions

At the University Hospital of Bern/University of Bern (Switzerland), ICG-SLN has been performed since December 2012; data on operations were collected prospectively. We analyzed retrospectively all patients treated for low-risk EMCA since 2004 who had given consent for use of their data for research. The treatment of EMCA evolved over the time; between 2004 and 2012, a complete LND was often performed, especially in cases prior to the application of the 2009 FIGO classification showing a formally called stage IC (>50% myometrial invasion) with Grade 1 or a formally IB (<50% myometrial) Grade 2. After 2012, SLN removal was introduced; when an LND was indicated, it was always performed in both the pelvic and para-aortic lymph nodes. Currently, all low-risk EMCA are treated with SLN removal.

In the Ospedale Santa Chiara, data on low-risk EMCA patients were collected prospectively since 2011 for surgical and oncological outcomes. SLN removal was introduced in 2015 and gradually also took over as the standard for care. Before 2015, patients with low-risk EMCA had no LND performed.

All data on patient characteristics, intraoperative, postoperative, and histological findings, perioperative morbidity (operation time, blood loss, complications, hospital stay), oncologic follow up (progression-free survival (PFS), disease-specific survival (DSS), and overall survival (OS)) were collected from the hospital internal databases. Intraoperative complications were graded with the CLASSIC classification and post-operative complications with the Clavien-Dindo Classification [9,10].

The SNL removal procedures at the two institutions

The SLN technique has been described in earlier publications [11,12]. In short, following a diagnostic laparoscopy, the cervix is injected submucosal and one centimeter deep in the stroma at the four cardinal points with a total of 6–8 ml ICG. One vial of 25 mg ICG powder (Pulsion®, since November 2016 Verdye®) is suspended with 10 ml sterile water (in 20 ml before 2016). This is the procedure applied in University Hospital of Bern. In the cohort from the Ospedale Santa Chiara, the technique was comparable to this procedure; however, 4 mL of ICG (Verdye®) was diluted to 2.5 mg/mL and was injected 1 mL superficially and 1 mL deeply into the cervical stroma at 3 and 9 o'clock.

In both institutions, after injection of the tracer, the pelvic peritoneum is opened and the camera switched onto NIR mode to detect the fluorescent signal and the SLNs, which were excised and sent to permanent pathology. Non-SLNs (NSLNs) that appeared macroscopically suspicious were removed and sent for frozen section. After completion of the total laparoscopic hysterectomy (HE), the uterus is sent to frozen section; based on the identification of tumor risk factors and clinical judgment, a laparoscopic PLND and/or PALND is performed.

Statistical analysis

Statistical analysis was performed using SPSS (IBM, version 25.0). Patient and clinical-pathological analyses were conducted using basic descriptive statistics. To further compare the characteristics among the different groups (for example, no LND, SLN, LND), the Chi-Square test and ANOVA were used. For variables not meeting the assumptions of the *t*-test equivalent, a non-parametric test was used. Survival analysis was performed using Kaplan-Meier curves and the log-rank test. All tests were two sided, and p values < 0.05 were considered statistically significant.

Ethical permission was obtained by APSS Ethical Committee (RGCS-I-2016) and the Ethics Commission of the Canton of Bern (261/2015).

Results

A total of 279 patients from the two institutions with a diagnosis of Stage 1 EMCA, including Grade 1 and 2, were included in the study. They were divided into groups according to the extent of LND: 103 (36.9%) had no LND, 118 (42.3%) had SLN removal, and 58 (20.8%) a pelvic ± para-aortic LND. Patient characteristics are presented in Table 1. Comparison of patient characteristics among the groups shows only a significant difference in BMI, with patients without LND having a BMI of 31.0, patients with SLN having a BMI of 28.0, and patients with LND having a BMI of 29.9 ($p = 0.026$). All other parameters are comparable among the groups. As defined in the inclusion criteria, all patients have Stage I disease, 81.4% (227) had a FIGO IA, and 18.6% (52) had a Stage IB. All tumors had an endometrioid histology: 52.3% (146) a Grade 1 differentiation, and 47.7% (133) a Grade 2 differentiation. Lymphovascular space invasion (LVSI) was positive in 9.6% of cases (24). There were significant differences in tumor characteristics when comparing the groups (Table 1).

Perioperative data

In analyzing perioperative data, blood loss, operation time, and intraoperative complications were compared among the groups (Table 1 and Fig. 1). In summary, there was a significant difference among the groups in blood loss, operation time, and severity of postoperative complications. In comparing only SLN removal vs no LND, there were no significant differences ($p = 0.198$, $p = 0.895$, and $p = 0.799$). Detection rates of SLN showed an overall detection rate of 97.9% and a bilateral detection rate of 84%. The mean number of lymph nodes removed in the group of LND was 36.

Oncological outcome

Follow-up time was a mean of 33 months (2–86 months).

Table 1
Patient characteristics and Operation data.

	No LND N = 103	SLN N = 118	LND N = 58	p-value
Age (median, range)	62.8 (37–92)	62.9 (32–92)	64.8 (38–86)	0.481
BMI (median, range)	31.0 (18–60)	28.0 (18–52)	29.9 (17–48)	**0.026**
Parity				
Nullipara	23 (22.3%)	29 (25.7%)	11 (19.0%)	
>1para	80 (77.7%)	84 (74.3%)	47 (81.0%)	0.603
Menopausal status				
Post-	88 (85.4%)	101 (87.8%)	53 (91.4%)	
Pre-	10 (9.7%)	7 (6.1%)	4 (6.9%)	
Peri-	5 (4.9%)	7 (6.1%)	1 (1.7%)	0.609
FIGO IA	99 (96.1%)	105 (89%)	31 (53.4%)	
FIGO IB	4 (3,9%)	13 (11%)	27 (46,6%)	**0,000**
Grade 1	71 (68,9%)	53 (44,9%)	22 (37,9%)	
Grade 2	32 (31,1%)	65 (55,1%)	36 (62,1%)	**0,000**
LVSI	11 (10,8%)	3 (2,6%)	10 (18,2%)	**0,030**
Tumor size	2,6 cm	2,0 cm	2,6 cm	0.601
Operation data				
Blood loss; ml mean (range)	75 ml (10–700)	94 ml (10–400)	240 ml (50–1000)	**0,000**
Operation time (min, median, range)	140min (50–540)	140min (80–480)	244min (110–510)	**0,000**
Complications intraoperative	4	0	3	0,063
CLASSIC 3 and 4	2	0	1	
Complications postoperative	8	10	11	0,134
Clavien Dindo 3 and 4	1	0	3	**0,01**

Missing data: Parity: 5; Menopausal status: 3. BMI: 2. LVSI: 8.

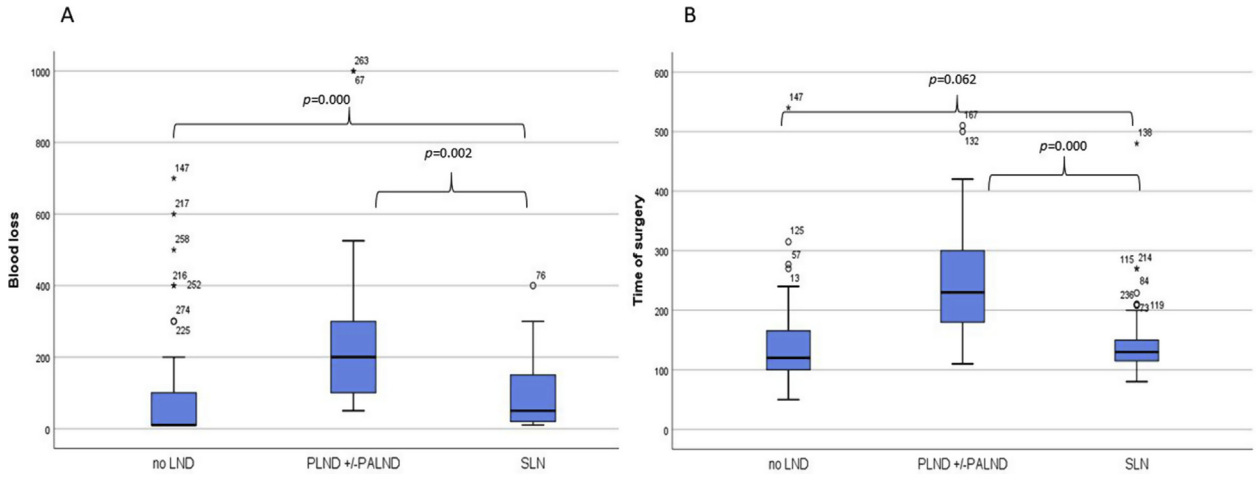

Figure 1. A: Blood loss in ml compared between the three groups of no LND, SLN and LND
B: operation time in minutes compared between the three groups of no LND, SLN and LND.

Kaplan-Meier curves on progression-free survival (PFS), disease-specific survival (DSS), and overall survival (OS) are presented in Fig. 2. No significant difference is seen among the three groups concerning recurrence or survival (log rank test $p = 0.164$ and $p = 0.986$). However, in absolute numbers and as shown in the Kaplan-Meier curves, the SLN data show the lowest rate of recurrence (no LND: 10 (10.2%); SLN removal: 1 (0.9%); LND: 3 (5.7%)) and of death due to disease (no LND: 4 (4%); SLN removal: 0 (0%); and LND: 2 (3.4%)).

For the analysis of risk of recurrence, all parameters were tested using Cox regression. The most interesting parameters are presented in Table 2. No significant difference was seen between the extent of LND removal and the risk of recurrence. Age and LVSI positivity are significant risk factors for recurrence, shown also in multivariable analysis. Since LVSI is a known risk factor for recurrence, the analysis for outcome was performed comparing the LVSI status (Fig. 3). In LVSI-negative patients (N = 247), the recurrence outcome is equal for all three groups; in LVSI-positive patients (N = 24), the outcome for no LND is worse, although not significantly.

With regard to adjuvant treatment, 83.3% of the patients had no adjuvant treatment, 15.6% had a brachytherapy, 0.7% a combined radio-chemotherapy, and 0.4% a brachytherapy with chemotherapy. To analyze the effect of the adjuvant treatment on the outcome, we compared the adjuvant treatments given to the three different groups (Table 2). Comparison of the three groups results in a significant difference, due to a greater number of patients in the group with LND receiving treatment. However, comparing SLN removal to no LND, no difference is seen in whether adjuvant treatment took place or not: the recurrence rate was 5.1% with adjuvant treatment vs 5.0% without.

Discussion

This study provides evidence that adding SLN removal to HE and bilateral salpingo-oophorectomy (BSO) in EMCA treatment rather

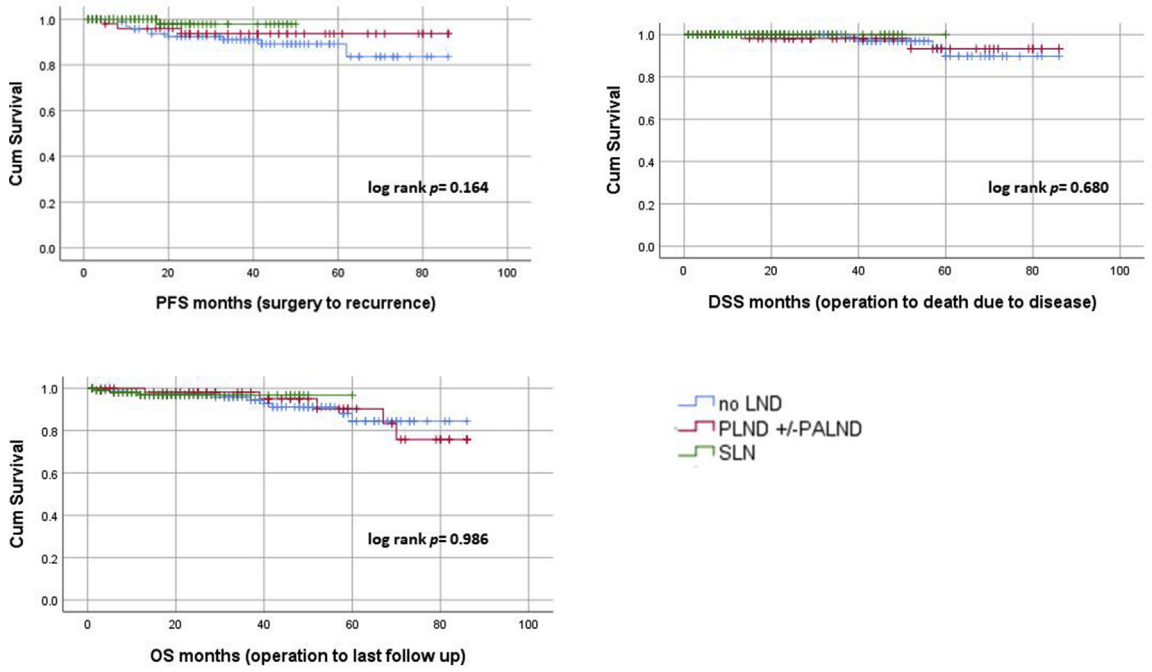

Fig. 2. Kaplan Meier curves for the three groups of no LND (blue), SLN (green) and LND (red) PFS, DSS,OS.
PFS: progression free survival, surgery to recurrence in months.
DSS: Disease specific survival, surgery to death due to disease in months.
OS: overall survival, surgery to death in months.

Table 2
Cox regression analysis for risk of recurrence.

Variable	p-value	HR	95% CI	Multivariable analysis
SLN vs LND (Ref LND)	0.267	0.272	0.027–2.703	
SLN vs no LND (Ref no LND)	0.122	5.168	0.645–41.401	
LVSI yes/no (Ref no LVSI)	**0.004**	5.136	1.709–15.436	**0.004**
Age at diagnosis	**0.020**	1.067	1.010–1.126	**0.019**
BMI	0.701	0.987	0.923–1.055	
Grading (Ref Grade 1)	0.504	0.689	0.230–2.057	
pT1a vs pT1b	0.442	0.450	0.059–3.442	
Ref pT1a				
Adjuvant treatment yes/no	0.844	0.860	0.190–3.888	
Ref no				

than no LND does not lead to higher morbidity. Looking at the oncological safety, this data suggest that lymph node evaluation is needed to optimize the oncological outcome.

In Stage I, Grades 1 and 2 EMCA, the risk of lymph-node involvement is 6%. This is low. However, the impact of lymph-node involvement is important, since adjuvant treatment is then indicated, and the survival outcome is impaired. In this retrospective analysis, patients were included with a final diagnosis of Stage I disease after the surgical treatment chosen at that time. In the cohort of patients without LND, it is possible that lymph nodes were affected but not diagnosed. (It was not the objective of this study to analyze which patients were suspected to be Stage I preoperative and then were upstaged through positive lymph nodes in SLN or LND.)

The result of selective lymph-node mapping for EMCA (with isosulfan blue dye injected in the myometrium during laparotomy) was first published in 1996 by Burke et al. [13]. Later, the first pilot studies published were based on the use of a radionuclide marker Tc 99 with or without patent blue dye [14–18]. However, it was only after the introduction of near-infrared optics and the application of ICG that the technique became more popular; it was included in the NCCN guidelines in 2014 as a possible treatment option [7,19–26]. Following the publication of the Memorial Sloan-Kettering Cancer Center algorithm in 2012, a clear mapping system could be implemented [27]. The FIRES study, the first multicenter prospective study, confirmed the diagnostic accuracy of the SLN technique with ICG with overall detection rates of 86% and the sensitivity to detect node-positive disease of 97.2% [28]. A recent meta-analysis of laparoscopic SLN in EMCA presents increasing detection rates: 96% overall detection and 73% bilateral detection [29].

In both cohorts in our study, the overall detection rate (97.9%) and the bilateral detection rate (84%) via SLN removal are even higher than other feasibility studies; this underlines the conclusion that SLN removal in EMCA with ICG presents excellent feasibility to ensure detection while reducing intraoperative morbidity and reducing complications in comparison to LND.

In this study, the intraoperative morbidity of no LND, SLN removal and LND was compared; the results show that there is no difference between SLN and no LND and there is a significant difference in blood loss, operation time, and complications in SLN compared to LND. The latter result is not surprising, since the morbidity of a complete LND is well known, with longer operation

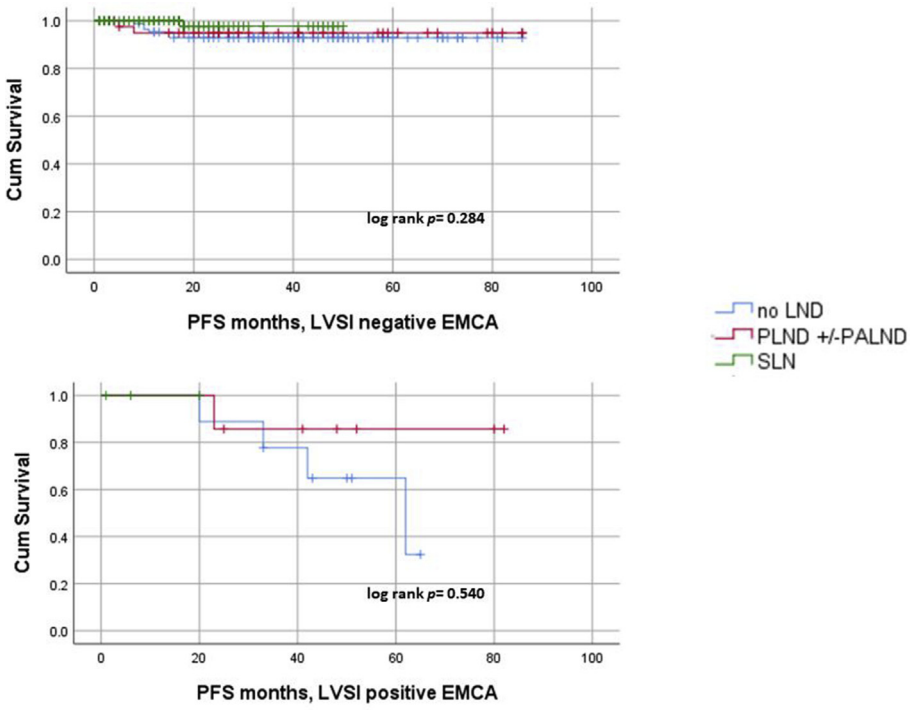

Fig. 3. Kaplan Meier curves for PFS for the three groups of no LND (blue), SLN (green) and LND (red) patients with LVSI negative tumors (above) and LVSI positive tumors (bellow). PFS: progression free survival, surgery to recurrence in months.

times and greater blood loss, as well as higher rates of complication. Persson et al. demonstrated significantly lower lymphatic complication rates with the SLN technique versus a complete LND [30]. The fact that adding the SLN to HE and BSO does not significantly increase the operation time, blood loss, and, most importantly, complication rates constitutes important evidence contributing to the discussion of over- and under-treatment of Stage I EMCA.

The most important point in the discussion of the extent of LND is the oncological outcome. Up to date, little long-term data on the oncological safety of the SLN technique in EMCA were available [31]. What is notable in this study is that there is no significant difference among the recurrence rates. Since both centers introduced SLN in 2012 and 2015, we are able to present follow-up data with a mean of 33 months. Most recurrences were diagnosed within 24 months [32, 33]. An important observation from the Kaplan-Meier curves is that SLN removal indicates a trend to better outcome and that patients without LND tend towards having a worse outcome. This result is not significant, so these findings have to be interpreted with caution. A possible explanation is that a metastatic lymph node was missed due to the absence of staging of the lymph nodes in the group with no LND. It is known to occur in 4–10% of cases. Also by performing ultra-staging in SLN more micro metastasis and isolated tumor cells can be detected. Consequently, the patients would have not received the usual adjuvant therapy that was actually needed, and this could be the reason for recurrence. The difference in outcome between LND and SLN could be explained by the significant higher-risk collective within Stage I disease (more Stage IB, Grade 2) and also by LVSI positivity. This is confirmed by the Cox regression analysis showing that LVSI and age are significant risk factors for recurrence.

LVSI is a recognized risk factor for recurrence and was included in the risk classification by the ESMO-ESG0-ESTRO recommendations in 2014 [34,35]. In our cohort, when excluding LVSI-positive patients, the outcomes are more similar. In a recent study by Creasman et al., LVSI with negative lymph node was not seen as an independent risk factor [36]. This puts emphasis on the importance of having a lymph-node assessment in LVSI-positive patients. Also, LVSI is often not known from preoperative diagnostics (biopsy or D&C). Histology and grading can be sufficiently diagnosed preoperatively and often Stage I is also suspected by preoperative imaging or diagnosed by intraoperative frozen section [37,38]. LVSI, however, is diagnosed only in the definitive pathological evaluation of the uterus, and therefore it is too late for LVSI to contribute to the decision regarding the extent of surgical staging.

Age is a significant risk factor for recurrence; this has been seen also in larger cohorts and seems to be independent of lymph-node involvement [39]. Therefore, age should be integrated in the risk analysis for decisions on treatment and extent of surgery.

In examining the effect of the adjuvant treatment on the outcome using Cox regression analysis, no significant difference is seen when comparing the adjuvant treatments, nor is there a difference in the number of recurrences between the groups with adjuvant treatment and without any form of adjuvant treatment. This suggests that the outcome effect is not due to the effect adjuvant treatment alone.

The strength of this study is the length of follow-up, with a mean of 33 months, and the availability of complete perioperative data providing evidence of outcomes and morbidities from three different degrees of LND. Weaknesses in the study are the retrospective nature and the slight difference in tumor characteristics among the groups within this or else well-defined low risk cohort.

Conclusion

In early-stage, endometrioid EMCA, Grades 1 and 2, SLN removal is a treatment option that offers a convincing balance between oncological safety and perioperative morbidity. Especially in LVSI-positive cases, lymph-node evaluation in any form is crucial.

Conflict of interest

All authors have no conflict of interest.

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