Long-term survival outcomes in high-risk endometrial cancer patients undergoing sentinel lymph node biopsy alone versus lymphadenectomy

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ABSTRACT

Objective Endometrial cancer is the most common gynecologic neoplasm. To date, international guidelines recommend sentinel lymph node biopsy for low-risk neoplasms, while systematic lymphadenectomy is still considered for high-risk cases. This study aimed to compare the long-term survival of high-risk patients who were submitted to sentinel lymph node biopsy alone versus systematic pelvic lymphadenectomy.

Methods Patients with high-risk endometrial cancer according to the 2021 European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology/European Society of Pathology risk classification were retrospectively analyzed. The primary aim of the study was to compare the long-term overall survival and disease-free survival of high-risk endometrial cancer patients undergoing sentinel lymph node biopsy versus systematic lymphadenectomy. A supplementary post-hoc survival analysis of cases with nodal metastasis was performed to compare sentinel lymph node and lymphadenectomy survival outcomes in this subset of patients.

Results The study enrolled 237 patients with histologically proven high-risk endometrial cancer. Patients were followed up for a median of 31 months (IQR 18–40). During the follow-up, 38 (16.0%) patients had a recurrence, and 19 (8.0%) patients died. Disease-free survival (85.2% vs 82.8%; p=0.74) and overall survival (91.3% vs 92.6%; p=0.62) were not different between the sentinel lymph node alone and lymphadenectomy groups. Furthermore, neither overall survival (96.1% vs 91.4%; p=0.43) nor disease-free survival (83.7% vs 76.4%; p=0.46) were different among sentinel lymph node alone and lymphadenectomy groups in patients with nodal metastasis.

Conclusions Sentinel lymph node mapping alone in high-risk endometrial cancer appears to be an oncologically safe technique over a long observational time. Systematic lymphadenectomy in this population does not offer a survival advantage.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Although several studies have reported high sensitivity and feasibility of sentinel lymph node biopsy in high-risk endometrial cancer patients, poor scientific evidence on the long-term outcomes of high-risk patients undergoing sentinel lymph node biopsy alone compared with pelvic lymphadenectomy is available in the literature.

WHAT THIS STUDY ADDS

⇒ Sentinel lymph node mapping alone in high-risk endometrial cancer patients is an oncologically safe technique over a median observational time of 31 months.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The usefulness of systematic lymphadenectomy in high-risk endometrial cancer patients should be questioned. Sentinel lymph node biopsy appears to be oncologically equivalent to full lymphadenectomy.

INTRODUCTION

Endometrial cancer is the most common gynecologic neoplasm in high-income countries countries.[1] Usually, endometrial cancer is diagnosed at an early stage and in most cases is associated with a good outcome.[2] However, based on pathological and molecular characteristics, subtypes of high-risk endometrial cancer characterized by a worse prognosis are acknowledged.[3] According to the most recent guidelines, high-grade tumor, non-endometrioid histology, myometrial infiltration, lymphovascular space invasion, advanced International Federation of Gynecology and Obstetrics (FIGO) stage, and molecular profiling define high-risk endometrial cancer patients, featured by a greater risk of recurrence and worse outcome.[4 5] High-risk endometrial cancer showed 20–30% of nodal metastasis and 13% 5-year recurrence risk; consequently, adjuvant treatment with chemo- and/or radiotherapy is recommended.[6–8]

Traditionally, endometrial cancer surgical treatment included hysterectomy, salpingo-oophorectomy, and systematic pelvic and aortic lymphadenectomy. Since the 2000s, the introduction of sentinel node

biopsy offered an alternative to systematic lymphadenectomy with a less invasive approach and less intra- and post-operative morbidity.[9 10] However, to date international guidelines recommend sentinel lymph node biopsy for low-risk endometrial cancers, while systematic pelvic and aortic lymphadenectomy is still suggested for high-risk patients.[4] The ALICE trial has been launched to clarify if sentinel lymph node biopsy can be safely offered also to high-risk endometrial cancer patients, but before its results will become available uncertainty exists around the management of such cases.[11] Some authors have prospectively assessed the sentinel lymph node appropriateness in high-risk endometrial cancer cases with promising results.[12–14]

Despite the reassuring data on sentinel lymph node sensitivity, there is poor scientific evidence on the long-term outcomes of high-risk endometrial cancer patients undergoing sentinel lymph node compared with lymphadenectomy.[15 16] Furthermore, most of the studies focused on sentinel lymph node diagnostic sensitivity and specificity rather than on the long-term outcome of high-risk endometrial cancer patients.[17] With this background, our study aimed to compare the long-term overall survival and disease-free survival of high-risk endometrial cancer patients who underwent sentinel lymph node biopsy alone versus systematic lymphadenectomy.

METHODS

This multicentric retrospective study was conducted between January 2007 and December 2019. All patients with high-risk endometrial cancer treated at the Gynecology Unit of Parma, IRCCS A. Gemelli University Polyclinic Foundation of Rome, Department of Gynecologic Oncology A.R.N.A.S. Ospedali Civico Di Cristina Benfratelli of Palermo, and Department of Medicine and Health Science "V.Tiberio" University of Molise (Campobasso) were included in the study population. All patients with high-risk endometrial cancer histological and/or molecular diagnosis according to the 2021 European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology/European Society of Pathology risk classification were included in the analysis.[4]

Patients with unknown pathological data, not undergoing nodal surgical staging, <18 years old, and undergoing fertility-sparing surgery were excluded from the analysis. Patients with unilateral sentinel lymph node failure undergoing side-specific lymphadenectomy of the non-capturing hemipelvis were also excluded from the analysis. Data regarding demographic characteristics, type of surgical treatment, pathological data, surgical FIGO stage, recurrences, and cancer-related deaths were collected. Following the scientific evidence at the time of diagnosis, all patients underwent the recommended pre-operative workup, surgical treatment (hysterectomy, bilateral salpingo-oophorectomy with or without omentectomy, and nodal surgical staging), adjuvant treatments, and follow-up to detect recurrences. Patients were divided into two groups depending on the type of procedure for nodal surgical assessment (sentinel lymph node alone group or lymphadenectomy group). Sentinel lymph node mapping has been performed since 2016.

In the case of sentinel lymph node mapping, the Memorial Sloan Kettering Cancer Center algorithm was applied.[18] All patients in the lymphadenectomy group performed systematic pelvic lymphadenectomy. In selected cases, pelvic plus aortic lymphadenectomy up to the level of the left renal vein was achieved. Patients who underwent sentinel lymph node mapping and concomitant pelvic lymphadenectomy or patients with bilateral sentinel lymph node failure undergoing bilateral pelvic lymphadenectomy were allocated to the lymphadenectomy group. Intra- and post-operative complications were described. Post-operative complications were categorized according to the Clavien-Dindo classification.[19]

The primary aim of the study was to compare the long-term overall survival and disease-free survival of high-risk endometrial cancer patients undergoing sentinel lymph node biopsy alone versus systematic lymphadenectomy. The secondary objective was to identify the predictive factors for the occurrence of surgical complications in the two groups. Finally, a supplementary post-hoc survival analysis of cases with nodal metastasis was performed to compare sentinel lymph node and lymphadenectomy survival outcomes in this subset of patients.

The study was approved on April 14, 2022, by the ethics committee of the University of Parma under code 842/2021/OSS/AOUPR.

Statistical Methods

The baseline characteristics of the lymphadenectomy and sentinel lymph node patients were summarized and compared. Categorical variables are expressed as absolute numbers and relative frequencies (percentages) and were compared using the χ^2 test. Continuous variables are expressed as mean±SD and were compared using a t-test for independent samples. The set of adjusting variables for the survival endpoint analysis (age, body mass index, histologic subtype, tumor grading, FIGO stage, adjuvant treatments, and complications) was selected based on the literature and by the use of a stepwise backward selection identifying the most parsimonious multivariable model. The time to the first endpoint was analyzed for its dependence on the putative predictors using Cox proportional hazard models. The survival endpoints during the follow-up were graphically depicted using Kaplan-Meier curves. Multivariable logistic regression models were implemented to estimate the odds ratio of complications outcome. An alluvial plot was used to graphically depict the flow of patients divided by treatment group (sentinel lymph node vs lymphadenectomy), safety (complication event), and survival (cancer-related death) outcomes. All of the tests were two-sided at a significance level of 0.05. The R Statistical software version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria) was used for statistical analyses.

In accordance with the journal's guidelines, we will provide our data for independent analysis by a team selected by the Editorial Team for the purposes of additional data analysis or for the reproducibility of this study in other centers if such is requested.

RESULTS

The study evaluated 237 patients who had histologically proven high-risk endometrial cancer diagnoses. All patients underwent nodal surgical staging (sentinel lymph node biopsy alone or systematic lymphadenectomy) at the time of the index event. Table 1 shows the baseline characteristics of the overall study population and the two treatment groups. One hundred and fifteen patients

Table 1 Patients' characteristics

		Intervention group		
	Overall, n=237	**Sentinel lymph node, n=115**	**Lymphadenectomy, n=122**	**P value**
Median±SD age (years)	65±11	66±11	65±10	0.40
Median±SD BMI (kg/m^2)	28.5±6.1	28.8±6.1	28.2±6.2	0.43
BMI >30	88 (37.1%)	44 (38.3%)	44 (36.1%)	0.73
Histologic subtype				0.47
Endometrioid	123 (51.9%)	56 (48.7%)	67 (54.9%)	
Mucinous	1 (0.4%)	0 (0%)	1 (0.8%)	
Clear cells	10 (4.2%)	5 (4.3%)	5 (4.1%)	
Serous	70 (29.5%)	35 (30.4%)	35 (28.7%)	
Mixed	20 (8.4%)	9 (7.8%)	11 (9.0%)	
Undifferentiated	4 (1.7%)	3 (2.6%)	1 (0.8%)	
Carcinosarcoma	9 (3.8%)	7 (6.1%)	2 (1.6%)	
Tumor grade				0.058
G1	14 (5.9%)	11 (9.6%)	3 (2.5%)	
G2	75 (31.6%)	33 (28.7%)	42 (34.4%)	
G3	148 (62.4%)	71 (61.7%)	77 (63%)	
LVSI				0.40
0	120 (50.6%)	55 (47.8%)	65 (53.3%)	
1	117 (49.4%)	60 (52.2%)	57 (46.7%)	
FIGO stage				0.039
IA	60 (25.3%)	32 (27.8%)	28 (23.0%)	
IB	23 (9.7%)	12 (10.4%)	11 (9.0%)	
II	12 (5.1%)	7 (6.1%)	5 (4.1%)	
IIIA	14 (5.9%)	10 (8.7%)	4 (3.3%)	
IIIB	6 (2.5%)	3 (2.6%)	3 (2.5%)	
IIIC1	113 (47.8%)	51 (44.3%)	62 (50.6%)	
IIIC2	8 (3.4%)	0 (0%)	8 (6.6%)	
IVB	1 (0.4%)	0 (0%)	1 (0.8%)	
Adjuvant treatment				0.85
None	22 (9.3%)	11 (9.6%)	11 (9.0%)	
Chemotherapy	30 (12.7%)	13 (11.3%)	17 (13.9%)	
Radiotherapy	41 (17.3%)	22 (19.1%)	19 (15.6%)	
EBRT	12 (5.1%)	7 (6.1%)	5 (4.1%)	
BRT	23 (9.7%)	13 (11.3%)	10 (8.2)	
EBRT plus BRT	6 (2.5%)	2 (1.7%)	4 (3.3%)	
Chemo plus radiotherapy	144 (60.8%)	69 (60.0%)	75 (61.5%)	
Chemo plus EBRT	91 (38.4%)	44 (38.3%)	47 (38.5%)	
Chemo plus BRT	5 (2.1%)	1 (0.9%)	4 (3.3%)	
Chemo plus EBRT plus BRT	48 (20.3%)	24 (20.9%)	24 (19.7%)	
Recurrence	38 (16.0%)	17 (14.8%)	21 (17.2%)	0.61
Nodal recurrence	14 (5.9%)	4 (3.5%)	10 (8.2%)	
Pelvic lymph node	6 (2.5%)	2 (1.7%)	4 (3.3%)	
Aortic lymph node	6 (2.5%)	2 (1.7%)	4 (3.3%)	
Pelvic and aortic	2 (0.8%)	0 (0%)	2 (1.6%)	
Death	19 (8.0%)	10 (8.7%)	9 (7.4%)	0.71

Continued

Table 1 Continued

	Overall, n=237	Intervention group		P value
		Sentinel lymph node, n=115	Lymphadenectomy, n=122	
Surgical approach				0.19
Robotic	4 (1.7%)	0 (0%)	4 (3.3%)	
Laparoscopy	176 (74.3%)	86 (74.8%)	90 (73.8%)	
Laparotomy	57 (24.1%)	29 (25.2%)	28 (23.0%)	
Median±SD EBL (mL)	110±153	87±114	133±181	0.019

BMI, body mass index; BRT, brachytherapy; EBL, estimated blood loss; EBRT, external beam radiation therapy; FIGO, International Federation of Gynecology and Obstetrics; LVSI, lymphovascular space invasion.

(48.5%) were staged by sentinel lymph node mapping alone. The median age was 65 years (SD±11) with no difference between the two groups (p=0.40). Compared with the lymphadenectomy group, the sentinel lymph node alone group was more commonly early stage (44% vs 59%; p=0.039). Besides, sentinel lymph node alone patients had lower estimated blood loss (87 vs 133 mL; p=0.019). In the lymphadenectomy group, a median of 14 pelvic lymph nodes (range 8–36) and 15 aortic lymph nodes (range 5–42) were excised. In the sentinel lymph node alone group a median of 2.1 (range 2–4) lymph nodes were excised including both hemipelves.

Regarding the primary endpoint, patients were followed for a median of 31 months (IQR 18–40). During the follow-up, 20 (8.4%) patients had at least one complication, 38 (16.0%) patients experienced a recurrence, and 19 (8.0%) women died. Disease-free survival was not statistically different between the sentinel lymph node alone and lymphadenectomy groups during the follow-up period (85.2% vs 82.8%; adjusted HR 1.12, 95% CI 0.58 to 2.13, p=0.74) (Figure 1A, Table 2). Furthermore, tumor grade and FIGO stage were independently associated with the risk of recurrence (adjusted HR 2.43, 95% CI 1.19 to 4.98, p=0.015; and adjusted HR 1.50, 95% CI 1.01 to 2.24, p=0.045, respectively). Also, overall survival did not show a statistically significant difference among sentinel lymph node alone and lymphadenectomy groups during the study period (91.3% vs 92.6%; adjusted HR 0.79, 95% CI 0.32 to 1.96, p=0.62) (Figure 1B, Table 2). Tumor grade and age were both independent risk factors for cancer-related death (HR 4.35, 95% CI 1.06 to 17.9, p=0.042; and HR 1.06, 95% CI 1.01 to 1.12, p=0.013, respectively).

Twenty complications in total occurred, seven in the sentinel lymph node alone group and 13 in the lymphadenectomy group. In the sentinel lymph node alone group, three intra-operative complications (one vaginal laceration during surgical specimens extraction and two bleedings requiring blood transfusion) and four post-operative complications (two hyperpyrexia, one ileal perforation, and one vaginal cuff dehiscence) were encountered. Two complications were grade II, one grade IIIA, and one grade IIIB according to the Clavien-Dindo classification. In the lymphadenectomy group, four intra-operative complications (one ureteral injury with ureterovesical reimplantation, one superficial sigma injury, one bladder injury, and one bleeding requiring blood transfusion) and nine post-operative complications (one deep vein thrombosis, two lower limb lymphedema, two obturator nerve deficits, one lymphocele, one anemia, one laparotomy suture diastasis, and one bowel perforation) occurred. Two complications were grade I, five grade II, and two grade IIIB according to the Clavien-Dindo classification.

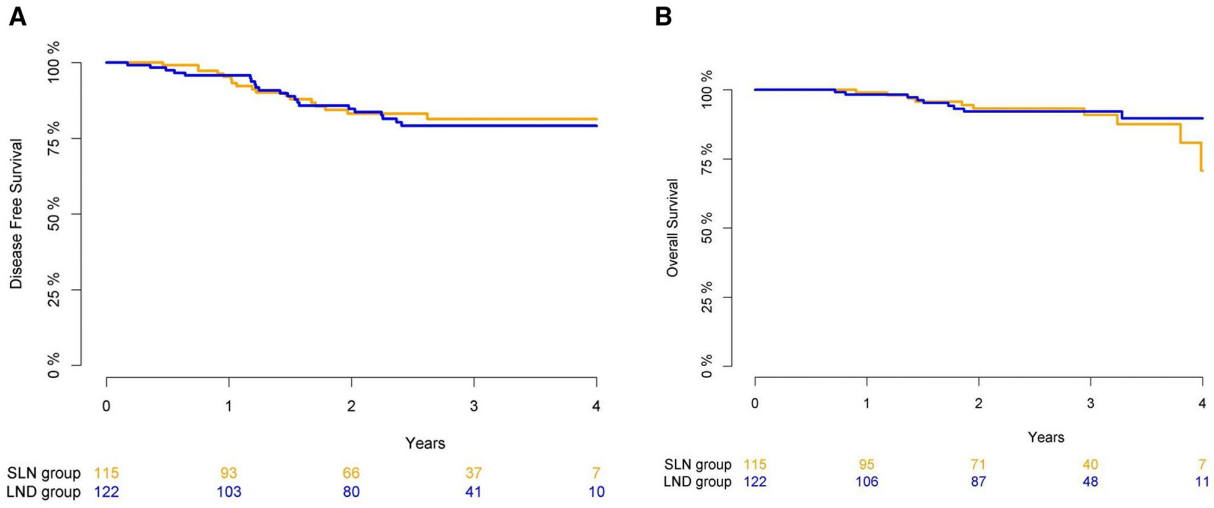

Figure 1 Kaplan-Meier curves for disease-free survival (A) and overall survival (B) between sentinel lymph node alone (SLN) and lymphadenectomy (LND) groups.

Table 2 Univariable(u) and multivariable(m) analysis for disease-free survival and overall survival

Disease-free survival	HR^u	95% CI^u	P value	HR^m	95% CI^m	P value
Lymphadenectomy	1.11	0.59 to 2.11	0.742	1.12	0.58 to 2.13	0.738
Median age	1.04	1.01 to 1.08	**0.010**	1.03	1.00 to 1.07	**0.070**
Median BMI	0.99	0.94 to 1.05	0.804			
Histology	1.48	0.78 to 2.80	0.230			
Tumor grade	2.09	1.08 to 4.05	**0.029**	2.43	1.19 to 4.98	**0.015**
FIGO stage	1.16	0.81 to 1.66	0.409	1.50	1.01 to 2.24	**0.045**
Adjuvant treatment	0.85	0.63 to 1.15	0.293	0.80	0.58 to 1.11	0.185
Complications	1.24	0.44 to 3.49	0.685			
Overall survival	**HR^u**	**95% CI^u**	**P value**	**HR^m**	**95% CI^m**	**P value**
Lymphadenectomy	0.75	0.30 to 1.85	0.530	0.79	0.32 to 1.96	0.616
Median age	1.08	1.03 to 1.13	0.002	1.06	1.01 to 1.12	**0.013**
Median BMI	1.00	0.93 to 1.07	0.971			
Histology	2.11	0.83 to 5.35	0.117			
Tumor grade	5.55	1.34 to 22.9	0.018	4.35	1.06 to 17.9	**0.042**
FIGO stage	0.85	0.53 to 1.36	0.505			
Adjuvant treatment	1.21	0.73 to 2.01	0.461			
Complications	0.00	0.00 to Inf	0.998			
Complications	**OR^u**	**95% CI^u**	**P value**	**OR^m**	**95% CI^m**	**P value**
Lymphadenectomy	1.84	0.72 to 5.06	0.211	2.62	0.96 to 7.88	0.070
Median age	1.00	0.95 to 1.04	0.878			
Median BMI	1.12	1.04 to 1.21	0.002	1.13	1.05 to 1.23	<0.001
Histology	1.38	0.55 to 3.55	0.495	3.75	0.85 to 20.9	0.103
Tumor grade	0.73	0.37 to 1.53	0.374	0.34	0.10 to 1.07	0.071
FIGO stage	1.00	0.62 to 1.67	0.996			
Adjuvant treatment	0.82	0.55 to 1.29	0.368	0.75	0.47 to 1.23	0.235

BMI, body mass index; FIGO, International Federation of Gynecology and Obstetrics.

The alluvial plot (Figure 2) shows the pattern in percentage of the two groups among the occurrence of the survival endpoints and complications. The flow reports the equivalence hypothesis in terms of survival endpoints among the two groups except for complication rate in favor of the sentinel lymph node group (6.1% vs 10.7%; adjusted OR 2.62, 95% CI 0.96 to 7.88, p=0.07). Body mass index was the only significant risk factor associated with complications occurrence (adjusted OR 1.13, 95% CI 1.05 to 1.23, p<0.001). Finally, of the 38 total recurrences, 14 nodal recurrences were found: four (3.5%) in the sentinel lymph node alone and 10 (8.2%) in the lymphadenectomy group. The nodal recurrence sites are summarized in Table 1.

The post-hoc subgroup analysis including only patients with nodal metastasis (FIGO stage IIIC1 and IIIC2) showed neither overall survival (96.1% vs 91.4%; HR 1.91, 95% CI 0.38 to 9.46, p=0.43) nor disease-free survival (83.7% vs 76.4%; HR 1.404, 95% CI 0.57 to 3.48, p=0.46) differences among the sentinel lymph node alone and lymphadenectomy groups during the study period (Figure 3). Furthermore, there was no difference in recurrence in the lymphadenectomy patients compared with the sentinel lymph node alone group (OR 1.41, 95% CI 0.80 to 1.76, p=0.078).

DISCUSSION

Summary of Main Results

Our study showed no significant difference in overall and disease-free survival among high-risk endometrial cancer patients undergoing sentinel lymph node mapping alone compared with systematic lymphadenectomy. Furthermore, patients with histologically proven nodal metastasis had overlapping survivals and disease-free survival in the sentinel lymph node alone and lymphadenectomy groups. Tumor grade, advanced FIGO stage, and age were independent factors worsening patients' prognosis. The body mass index was the only independent risk factor for surgical complications.

Results in the Context of Published Literature

Over the years, doubts have arisen about the impact of lymphadenectomy on endometrial cancer patient survival. Benedetti Panici et al and the ASTEC study group evaluated in 2008 and 2009 the role of lymphadenectomy in early-stage endometrial cancer.[20] Then, international

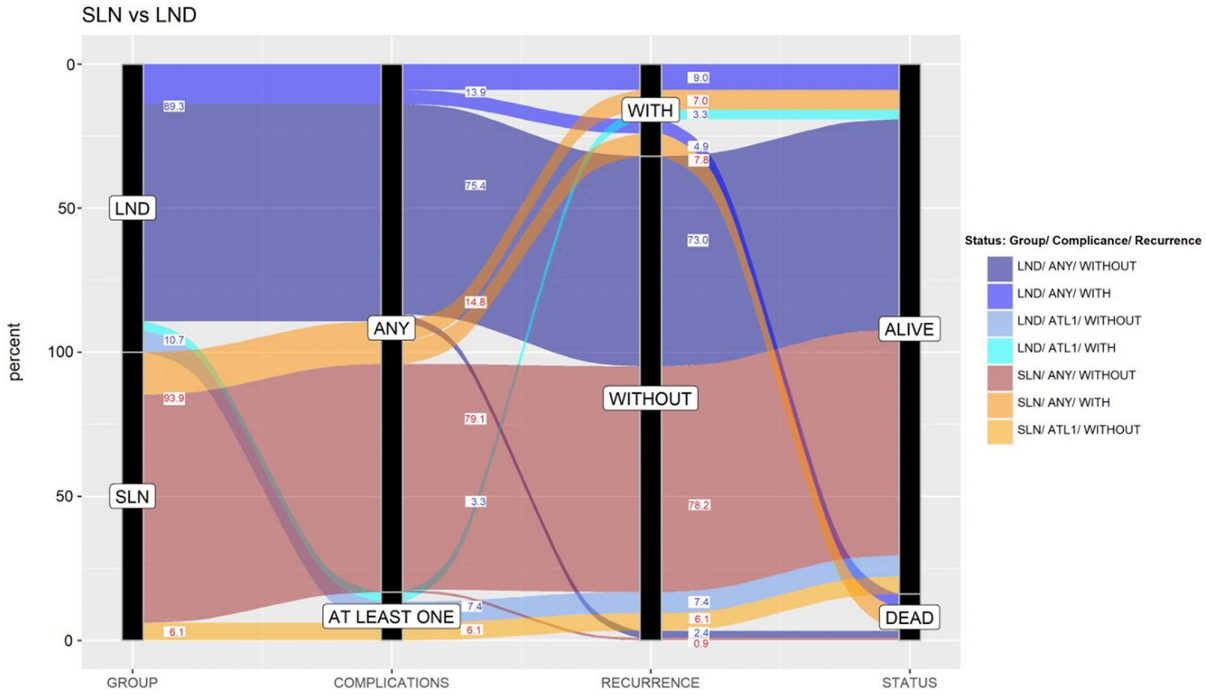

Figure 2 Alluvial plot. Reading from left to right of the alluvial plot, the blue and orange flows (lymphadenectomy (LND) and sentinel lymph node (SLN) groups, respectively) show the ramifications in terms of percentages of patients in the two study groups which, in the first step, were divided in 'any or at least one' complication experienced during the intra- and post-operative phase. Then, the patients split into 'with and without' recurrence of the disease. Finally, patients were divided into dead or still alive at the end of the follow-up.

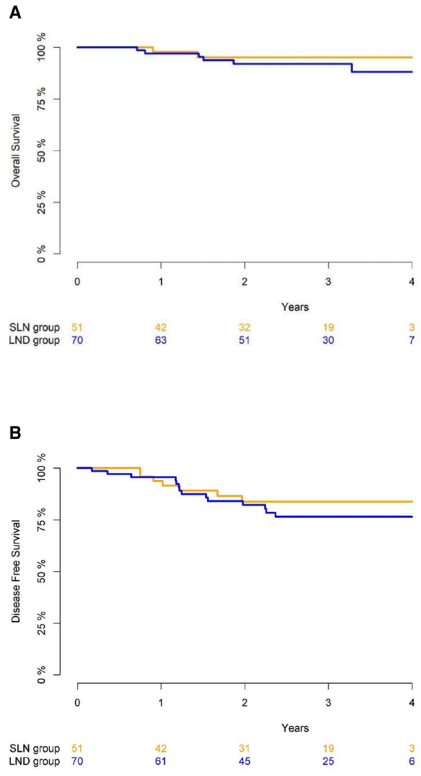

Figure 3 Kaplan-Meier curves for overall survival (A) and disease-free survival (B) in IIIC1 and IIIC2 FIGO stage patients. FIGO, International Federation of Gynecology and Obstetrics; LND, lymphadenectomy; SLN, sentinel lymph node.

guidelines subsequently recommended exclusive sentinel lymph node mapping for nodal surgical staging in low-risk endometrial cancers. Afterward, several authors tested sentinel lymph node safety in patients at high risk of nodal metastasis with encouraging results. Initially reported by Soliman et al in a prospective surgical trial including 101 high-risk endometrial cancer patients, sentinel lymph node mapping was found to be a viable alternative to systematic lymphadenectomy with a sentinel lymph node sensitivity of 95% (19/20), a false negative rate of 5% (1/20), and a false negative predictive value of 1.4% (1/71).[12]

Later, the prospective, multicenter cohort study (Sentinel Lymph Node Biopsy vs Lymphadenectomy for Intermediate- and High-Grade Endometrial Cancer Staging) SENTOR study, confirmed these results by reporting a sentinel lymph node sensitivity of 96%, a false-negative rate of 4%, and a negative predictive value of 99%.[13] Once sentinel lymph node diagnostic reliability was established, other authors analyzed sentinel lymph node oncological safety in high-risk endometrial cancer patients with serous histology and carcinosarcoma. Basaran et al and Schiavone et al reported 2-year overall survival of 89.1% and 83.9% (p=0.90) and a 2-year progression-free survival of 23 vs 23.2 months (p=0.70) in the sentinel lymph node and lymphadenectomy groups, respectively.[21 22] Unfortunately, both studies reported a small number of cases with a mean follow-up of fewer than 2 years.

In line with our results, Nasioudis[23] et al and Bogani[16] et al reported no different survival in high-risk endometrial cancer patients who underwent sentinel lymph node biopsy alone versus systematic lymphadenectomy (p=0.27 and p=0.94, respectively). However, the former authors included only IIIC FIGO stage patients with nodal metastases excluding the remaining population, and the latter included a limited number of cases with 1.5 years of median follow-up in the survival analysis. Furthermore, Buda *et al*[24] also reported superimposable disease-free

survival (HR 0.82, 95% CI 0.53 to 1.28, p=0.390) in high-risk endometrial cancer patients undergoing sentinel lymph node alone compared with sentinel lymph node plus lymphadenectomy. Nevertheless, the authors included sentinel lymph node mapping in the lymphadenectomy group, and this aspect could affect their results.

Strengths and Weaknesses

The present study reports a large case series of high-risk endometrial cancer patients treated in oncology referral centers, and the most up-to-date guidelines at the time of primary treatment were followed during the study period. For the primary endpoint, a median follow-up of more than 2.5 years ensured a long time interval to test sentinel lymph node cancer safety, especially in the first 2 years after primary treatment when the most recurrences occurred. On the other hand, the main limitation of the study is its retrospective nature. Besides, an imbalance of the advanced FIGO stage in the lymphadenectomy group was reported. However, the sentinel lymph node technique could only be performed in the absence of nodal metastasis at pre-operative investigations. FIGO stage imbalance between the two groups could pose doubts about the results of the present study. However, this FIGO stage imbalance (especially in stage IIIC2) is justified by the aortic lymphadenectomy performed only in selected patients in the lymphadenectomy group and not in the sentinel lymph node group. Furthermore, following the sentinel lymph node algorithm, all patients with suspected nodal involvement were excluded from sentinel lymph node mapping. These aspects reflected also the higher rate of nodal recurrence found in the lymphadenectomy group. To overcome this issue, the subanalysis of patients with nodal metastasis showed no difference in the patients' prognoses in terms of both overall and disease-free survival. Besides, the alluvial plot showed overlapping survival and recurrences in sentinel lymph node and lymphadenectomy patients with a higher complication rate in the lymphadenectomy group. Consequently, the importance of sentinel lymph node mapping is still emphasized, even given the more than doubled operative morbidity in the group of patients undergoing systematic lymphadenectomy.

Implications for Practice and Future Research

Our study raises further concerns about the therapeutic role of systematic pelvic lymphadenectomy in endometrial cancer patients at high risk of nodal metastasis during a long observation time. Indeed, lymphadenectomy in high-risk endometrial cancer patients, as well as low-risk patients, would only be useful to identify an advanced FIGO stage needed for adjuvant treatment. Therefore, the complete removal of the pelvic lymph node bundles would not appear to be more radical than the removal of the single sentinel lymph node.

Pending prospective studies and randomized clinical trials, sentinel lymph node mapping even in high-risk endometrial cancers would appear not to worsen the patient's prognosis. Moreover, lymphadenectomy-related morbidity could be reduced by applying the sentinel lymph node algorithm even in patients at high risk of nodal metastasis. Likewise, pathological and clinical patient characteristics are still crucial factors in guiding the choice of adjuvant treatments. Certainly, molecular profiles may assist the choice of adjuvant treatment, but pathological data still prove decisive in predicting the risk of endometrial cancer recurrence.

CONCLUSIONS

The role of systematic lymphadenectomy in high-risk endometrial cancer patients should be questioned. Sentinel lymph node mapping alone in high-risk patients appears to be an oncologically safe technique. Even in histologically confirmed nodal metastasis, sentinel lymph nodes alone showed superimposable disease-free survival and overall survival compared with systematic lymphadenectomy. Tumor grade, advanced FIGO stage, and age were independent factors worsening prognosis.

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