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Evaluating long-term outcomes of three approaches to retroperitoneal staging in endometrial cancer☆

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HIGHLIGHTS

- Sentinel node mapping (SNM) allows an accurate detection of nodal involvement.
- Low volume disease accounts for about 50% of nodal disease diagnosed with SNM.
- Backup lymphadectomy does not improve oncologic outcomes in comparison to SNM alone.

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ABSTRACT

Objective. Sentinel lymph node mapping (SNM) has gained popularity in managing apparent early-stage endometrial cancer (EC). Here, we evaluated the long-term survival of three different approaches of nodal assessment.

Methods. This is a multi-institutional retrospective study evaluating long-term outcomes of EC patients having nodal assessment between 01/01/2006 and 12/31/2016. In order to reduce possible confounding factors, we applied a propensity-matched algorithm.

Results. Overall, 940 patients meeting inclusion criteria were included in the study, of which 174 (18.5%), 187 (19.9%), and 579 (61.6%) underwent SNM, SNM followed by backup lymphadenectomy (LND) and LND alone, respectively. Applying a propensity score matching algorithm (1:1:2) we selected 500 patients, including 125 SNM, 125 SNM/backup LND, and 250 LND. Baseline characteristics of the study population were similar between groups. The prevalence of nodal disease was 14%, 16%, and 12% in patients having SNM, SNM/backup LND and LND, respectively. Overall, 19 (7.6%) patients were diagnosed with low volume nodal disease. The survival

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analysis comparing the three techniques did not show statistical differences in terms of disease-free ($p = 0.750$) and overall survival ($p = 0.899$). Similarly, the type of nodal assessment did not impact survival outcomes after stratification based on uterine risk factors.

Conclusion. Our study highlighted that SNM provides similar long-term oncologic outcomes than LND.

1. Introduction

Endometrial cancer (EC) is the most common gynecological malignancy, with an estimated incidence of >65,000 new cases in the United States in 2022 [1]. The mainstay of treatment for patients with EC is hysterectomy with bilateral salpingo-oophorectomy, which allows to remove the primary tumor and to identify patients at risk of developing recurrences, thus tailoring the optimal adjuvant treatment. Several international guidelines, including the American College of Obstetricians and Gynecologists (ACOG), recommend the execution of retroperitoneal staging (i.e., pelvic and/or para-aortic lymphadenectomy (LND)), since lymphatic dissemination is considered one of the most important prognostic factors [2–6]. Notably, no level A evidence supported the therapeutic role of lymphadenectomy in EC. Benedetti Panici et al. and ASTEC study group, with two independent randomized controlled trials, have assessed the role of LND in early-stage EC, showing that pelvic LND was not associated with increased overall or recurrence-free survival [7,8]. These studies have many pitfalls ((i) the high prevalence of low risk EC, (ii) the low number of nodes retrieved in the LND arms, and (iii) adjuvant therapy administration rate) that limit interpretation of the results [7,8]. Moreover, several well designed retrospective and prospective studies highlighted the importance of performing retroperitoneal staging, thus allowing to tailor appropriate adjuvant therapy [9,10]. Hence, lymph node status evaluation has been supported by the European Society of Gynecological Oncology (ESGO), European Society for Radiotherapy & Oncology (ESTRO), and the European Society of Pathology (ESP) and National Comprehensive Cancer Network (NCCN) guidelines as part of the surgical staging in patients with apparent early-stage EC [3,6].

Over the past decade, with the intent of finding a balance between the risks and harms of no nodal staging vs systematic pelvic and para-aortic LND, sentinel lymph node mapping (SNM) has emerged as an alternatively staging approach in patients with presumed early-stage EC [11–13]. Indeed, data shows that SNM mapping has two major advantages in EC patients, compared to systematic LND. First, surgical staging with SNM is associated with a reduction in lymphatic-specific morbidity, such as lower extremity lymphedema, lymphocystis, and cellulitis derived from systematic nodal dissection. Second, ultrastaging of the sentinel nodes is superior to LND in identifying women with lymphatic dissemination because of the identification of low volume metastases which are usually not detectable by using the conventional histological examination [14–18]. For these reasons, the ESGO/ESTRO/ESP and the NCCN guidelines included SNM as an option in the treatment algorithm of EC even in high-risk disease [3,6]. However, although accumulating data showed that SNM provides similar oncologic outcomes in comparison to systematic LND [19,20], the evidence is still limited due to the inherent biases of the available studies [19–22]. In the present paper, we aim to evaluate the long-term oncologic outcomes of SNM vs. LND, comparing three different staging approaches (1) SNM, (2) SNM followed by backup LND, and (3) SNM alone.

2. Materials and methods

This is a multi-institutional retrospective study collecting data from endometrial cancer patients treated in referral oncological centers in Italy and Switzerland. Data of consecutive women undergoing surgery with newly diagnosed endometrial cancer between 01/01/2006 and 12/31/2016 were collected. The institutions included were reported in Supplemental material 1. Institutional Review Board (IRB) approval was obtained by all the centers (IRB#140/20; date of approval June 30, 2020). The inclusion criteria were the following: (1) age ≥ 18 years old, (2) execution of surgical staging with hysterectomy +/− bilateral salpingo-oophorectomy and nodal evaluation with one of the following approaches: (i) systematic pelvic +/− para-aortic LND, (ii) SNM followed by backup pelvic +/− para-aortic LND, and (iii) SNM, (3) at least 3-year of follow-up for patients who did not experience a recurrence. Exclusion criteria were the following: (i) consent withdrawal, (ii) preoperative suspicious or intra-operative finding of bulky nodes, (iii) presence of peritoneal dissemination (i.e., stage IV EC), (iv) personal history of other solid tumors (within 5 years). All women included in the study signed informed consent for data collection for research purposes. Computerized databases were created, maintained, and updated on regular basis by trained residents and nurses. Data on surgical procedures, peri-operative care, adjuvant therapy as well as follow-up d were collected.

Patients were staged according to the International Federation of Obstetrics and Gynecologists (FIGO) staging system. Histological classification and the degree of glandular differentiation were performed according to the World Health Organization (WHO) and FIGO classification systems [23].

Patients were classified into three (low, intermediate, and high) risk classes according to the stratification system proposed by the ESGO/ESTRO/ESP consensus (Supplemental material 2) [6]. Previous publications of our group included part of the study population of the present paper [19,20]. Details of surgical technique and pathological evaluation were previously described [19,20]. Briefly, all patients underwent surgical treatment including hysterectomy, with or without bilateral salpingo-oophorectomy. At the beginning of the study period, the standard of care was LND (pelvic with or without para-aortic nodal dissection), but over the study period there was an increase in SNM adoption in all EC patients (regardless of the classes of risk) with a progressive implementation in the use of SNM with or without backup LND [19,20].

All the lymph nodes removed were placed in formalin and subsequently included in paraffin. The sentinel nodes underwent ultrastaging following institutional protocols. The non-sentinel lymph nodes underwent traditional evaluation with hematoxylin and eosin. According to the American Joint Committee on Cancer (AJCC) classification, macrometastasis, micrometastasis, and isolated tumor cells are defined by the presence of cluster of neoplastic cells >2 mm, between 0.2 and 2 mm, and <0.2 mm [24]. The Clavien-Dindo severity system was used to classify severe complications and the Martin criteria to improve quality of complications' reporting [19,20]. Criteria regarding adjuvant therapy administration and detailed descriptions of follow-up protocols are reported elsewhere [19,20]. Adjuvant therapy Adjuvant therapy was administered per recommended institutional guidelines and according to each patient's values and preferences. In case of low-risk disease the adjuvant therapy was not indicated. In case of intermediate-risk disease, vaginal brachytherapy, or external beam radiotherapy (EBRT) were considered the standard of care [19,20]. The high-risk patients received radiotherapy and/or chemotherapy. External beam radiotherapy (EBRT) was administered using 3-dimensional conformal or intensity-

modulated radiotherapy to deliver standard pelvic doses of 45–50.4 Gy and para-aortic doses of 45 Gy. Platinum-based combination, usually in combination with paclitaxel or doxorubicin (or both), was adopted as chemotherapy treatment. When chemotherapy was not associated with EBRT in the adjuvant treatment, 4 to 6 cycles (more commonly 6) were delivered in standard doses. Follow-up data were registered prospectively in electronic institutional databases.

2.1. Statistical methods

We performed a propensity-score matching analysis with the aim of reducing possible inherent selection biases of a retrospective study. We made a multivariable logistic regression model to perform this analysis, including the following variable: age (years), body mass index (BMI, kg/mq), histology type (endometrioid vs. nonendometrioid), deep of myometrial invasion (<50% vs. >50%), lympho-vascular space invasion (LVSI, yes vs. no). We performed a 1:1:2 matching (for every patient who had SNM we select a patient who had SNM/backup LND and two patients who had LND). The description of the statistical methods adopted to perform the propensity-score matching are reported elsewhere [23].Basic descriptive statistics were used. Normality testing (D'Agostino and Pearson test) and Kruskal-Wallis test were used to compare the three groups, according to the parametric and nonparametric distribution, respectively. The Chi-square test was used to analyze proportions. Ninety-five percent confidence intervals (95%CI) were calculated for each comparison. When indicated, odds ratio (OR) and 95% confidence intervals (95%CI) were calculated. The Kaplan-Meier model was used to evaluate survival outcomes (disease-free and overall survivals). The risk of developing recurrence and the risk of death between the two groups over time were compared using the log-rank test. *P* values <0.05 were considered statistically significant. Statistical analysis was developed with GraphPad Prism version 6.0 (GraphPad Software, San Diego CA) and IBM-Microsoft SPSS version 20.0 (SPSS Statistics. International Business Machines Corporation IBM 2013 Armonk, USA) for Mac.

3. Results

Overall, 940 patients were included in the study, of which 174 (18.5%), 187 (19.9%), and 579 (61.6%) underwent SNM, SNM/backup LND and LND, respectively. Applying a propensity-score matching (1:1:2) we identified 500 patients: 125 SNM vs. 125 SNM/backup LND vs. 250 LND. Fig. 1 shows the flow of patients into the study design. The propensity-score matching resulted in the baseline patients' characteristics being similar between the groups. Baseline patients' characteristics are shown in Table 1. The mean (SD) patients' age was 62 (±12) years. The median body mass index was 27.3 (8.8) kg/m2. At the final histological evaluation, the study population included 53 (10.5%) patients with nonendometrioid histology. This latter group of patients had LND ($n = 26$), SNM/backup LND ($n = 14$), and SNM alone ($n = 13$).

3.1. Prevalence and type of lymph node metastasis

Overall, 68 out of 500 patients (13.6%) were diagnosed with positive nodes. The prevalence of nodal disease was 14% (18/125), 16% (20/125), and 12% (30/250) in patients having SNM, SNM/backup LND and LND, respectively. We calculated the detection rate of stage IIIC disease, and this was similar comparing the three groups ($p = 0.540$). Among SNM groups (with or without backup LND), 19 (7.6%) patients were diagnosed with low volume metastasis, including 7 (2.8%) with micrometastasis and 12

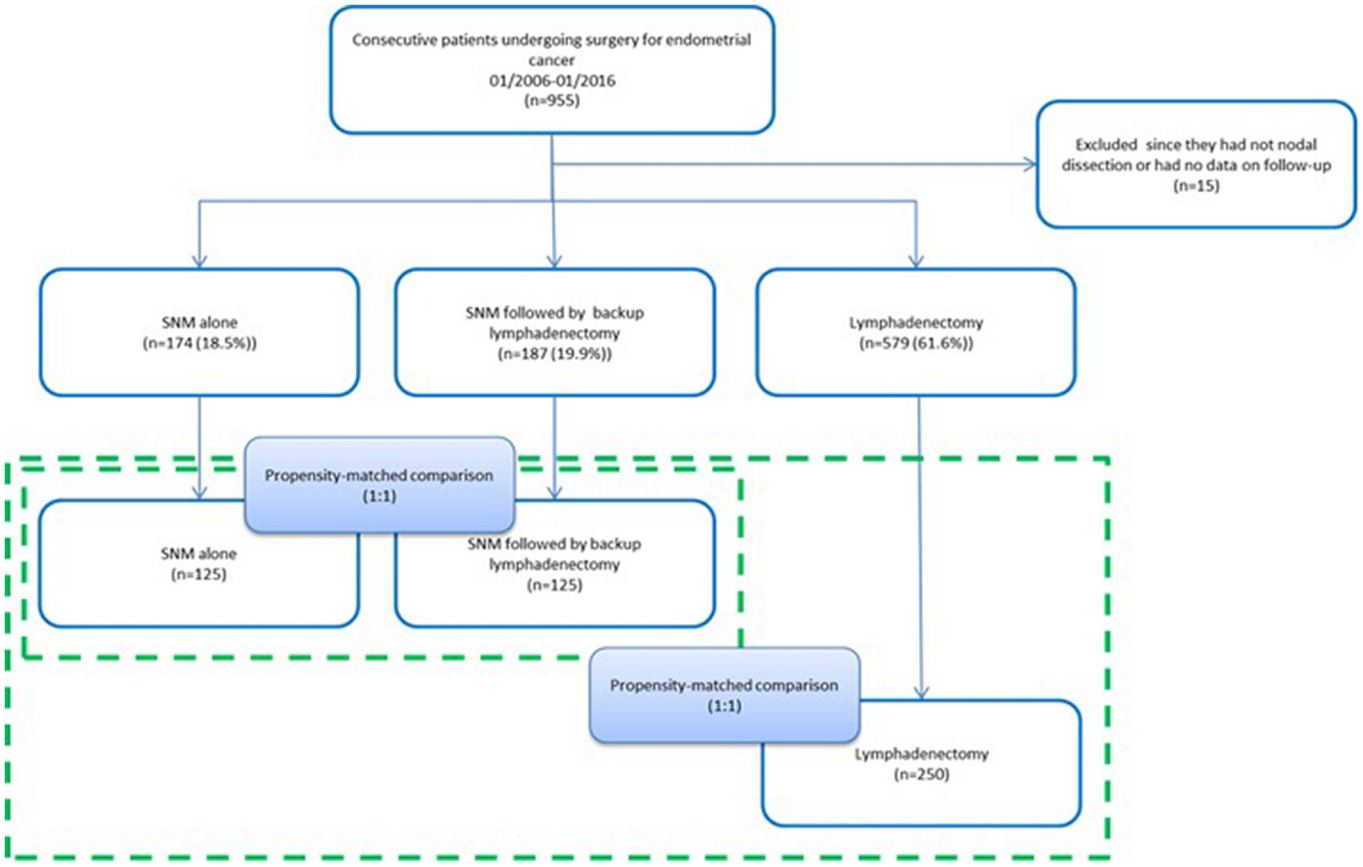

Fig. 1. Flow of patients through the study design.
Legend: Abbreviation: SNM, sentinel node mapping.

Table 1
Baseline patients 'characteristics.

	SLN ($n = 125$)	SLN plus backup lymphadenectomy (n = 125)	Lymphadenectomy ($n = 250$)	P value
Age, yrs	62.9 (11.0)	62.4 (10.1)	62.9 (8.8)	0.771
BMI, Kg/mq	27.4 (4.1)	27.1 (6.7)	27.8 (4.7)	0.642
Histology				
Endometrioid	112 (89.6%)	111 (88.8%)	224 (89.6%)	0.968
Non-endometrioid	13 (10.4%)	14 (11.2%)	26 (10.4%)	
FIGO grade				
Grade 1-2	99 (79.2%)	98 (78.4%)	197 (78.8%)	0.988
Grade 3	26 (20.8%)	27 (21.6%)	53 (21.2%)	
Myometrial invasion				
Inner half	100 (80%)	101 (80.8%)	201 (80.4%)	0.978
>50%	25 (20%)	24 (19.2%)	49 (19.6%)	
LVSI				0.991
No	83 (66.4%)	82 (65.6)	165 (66%)	
Yes	42 (33.6%)	43 (34.4%)	85 (34%)	
Cervical involvement				0.658
No	123 (98.4%)	121 (94%)	245 (98%)	
Yes	2 (1.6%)	4 (6%)	5 (2%)	
Adnexal/serosal involvement				0.772
No	122 (97.6%)	120 (96%)	242 (96.8%)	
Yes	3 (2.4%)	5 (4%)	8 (3%)	
Type of surgical approach				0.005
Laparoscopy	115 (92%)	97 (77.6%)	202 (80.8%)	
Open surgery	10 (8%)	28 (22.4%)	48 (19.2%)	
Adjuvant therapy				
Chemotherapy	10 (8%)	8 (6.4%)	30 (12%)	0.173
Radiotherapy	4 (3.2%)	6 (4.8%)	21 (8.4%)	0.108
Chemoradiotherapy	13 (10.4%)	12 (9.6%)	14 (5.6%)	0.180
Vaginal brachytherapy	19 (15.2%)	12 (9.6%)	37 (14.8%)	0.319
Follow-up, mo	62.1 (10.3)	67.7 (11.6)	60.8 (16.2)	0.680

Data are reported as mean (SD) or number (%). Abbreviations: SLN, sentinel node mapping; BMI, body mass index; FIGO, International Federation of Obstetrics and Gynecologist; LVSI, lymph vascular space invasion; yrs., years; mo, months.

(4.8%) with isolated tumor cells. Table 2 shows the prevalence and the type of metastasis (macrometastasis, micrometastasis, isolated tumor cells) according to the three different methods of nodal assessment. Interestingly, in the group undergoing SNM/backup LND, SNM identified 19 of the 20 cases (95%), with one case (5%, 1/20) of false negative sentinel node identified on a high-risk patient.

3.2. Surgery-related morbidity

We observed 17 (3.4%) events of surgical-related complications within 90-day severe (grade 3 or worse according to the Clavien-Dindo classification [25]), of which 0 (0%), 5 (4%), and 12 (4.8%) occurred after SNM, SNM/backup LND, and LND, respectively. Severe complications included lymphatic complications ($n = 7$), hemorrhagic events ($n = 5$), vaginal cuff complication ($n = 3$) and bowel obstruction ($n = 2$). Table 3 shows the univariate and multivariate analysis of factors associated with the risk of developing surgical-related morbidity. The adoption of the laparoscopic approach ($p < 0.001$, log-rank test) and SNM ($p < 0.001$, log-rank test) correlated with a lower risk of developing surgery-related events, over the first 90 postoperative days. Fig. 2 shows the risk of developing surgical-related complications within 90-day. When evaluating lymphatic-specific complications, 7 (1.4%) severe events were observed, with the totality of them occurring in patients who underwent LND (5 in the LND group and 2 in the SNM/ back-up LND group). The adoption of laparoscopic approach ($p < 0.001$) and SNM ($p = 0.038$) correlated with a lower risk of developing lymphatic-specific surgery-related events over the 90-day postoperative course. Supplemental material 3 shows the risk of developing lymphatic complications over the 90-day postoperative course.

Table 2
Characteristics of lymphatic disease according to the three different nodal assessment methods.

	SLN (n = 125)	SLN plus backup lymphadenectomy (n = 125)	Lymphadenectomy (n = 250)
Patients with positive nodes	18 (14.4%)	20 (16%)	30 (12%)
Identified by lymphadenectomy	NE	1 (0.8%)	30 (12%)
Identified by SLN	18 (14.4%)	19* (15.2%)	NE
Details of nodal involvement in sentinel nodes			
Isolated tumor cells	6 (4.8%)	6 (4.8%)	0
Micrometastatis	3 (2.4%)	4 (3.2%)	0
Macrometastasis	9 (7.2%)	10 (8%)	0
Location of positive nodes			
Positive nodes in the pelvic area	14 (11.2%)	12 (9.6%)	21 (8.4%)
Positive nodes in the pelvic and para-aortic area	4 (3.2%)	7 (5.6%)	8 (3.2%)
Positive nodes in the para-aortic area only	0	1 (0.8%)	1 (0.4%)

Data are reported as number (%). Abbreviations: SLN, sentinel node mapping; NE, not executed; * one patient was diagnosed with both macrometastasis and isolated tumor cells in two different sentinel nodes.

Table 3
Predictors of 90-day surgery-related morbidity.

	Univariate		Multivariate	
	OR (95%CI)	P value	OR (95%CI)	P value
Age, years *	1.09 (1.01, 1.16)	0.142	–	–
BMI, kg/mq *	1.15 (1.01, 1.34)	0.036	1.03 (1.001, 1.14)	0.049
Year of surgery *	0.67 (0.56, 1.12)	0.450		
FIGO grade		0.540		
Grade 1&2	Reference			
Grade 3	1.49 (0.98, 2. 30)			
Histology		0.345		–
Endometrioid	Reference		–	
Non-endometrioid	2. 30 (0.56, 6.20)		–	
Stage of disease		0.254		–
Stage I	Reference		–	
Stage II or more	1.53 (0.88, 3.98)		–	
Type of nodal assessment		0.205		–
Sentinel node mapping	Reference		–	
Lymphadenectomy (with or without sentinel node mapping)	2.01 (0.61, 5. 30)		–	
Surgical approach		0.001		0.010
Laparoscopy	Reference		Reference	
Open surgery	3.94 (1.80, 7.52)		2.05 (1.01, 4.52)	
Adjuvant therapy		0.909		–
No	Reference		–	
Yes	1.18 (0.81, 8.21)		–	

Abbreviation: OR, Odds ratio; CI; confidence interval; SLN, sentinel node mapping; BMI, body mass inde; FIGO, International Federation of Obstetrics and Gynecology.
* Odds ratio per 1-year increase in age, 5- unit increase in BMI, and 1-year increase in study period.

3.3. Survival outcomes

The mean (SD) follow-up time was 62 (±11) months. The survival analysis comparing the three techniques did not show statistical differences in terms of disease-free ($p = 0.750$, log-rank test) and overall survival ($p = 0.899$, log-rank test). Subsequently, we stratified the results according to the ESGO/ESTRO/ESP criteria with the aim to determine whether the type of nodal assessment impacted survival outcomes. Overall, 36.6%, 41.6%, and 21.8% of patients were included in the low-, intermediate, and high-risk groups, respectively, with survival analysis showing that the type of nodal assessment did not impact these outcomes. Looking at patients with positive sentinel lymph nodes, we observed that the execution of backup LND did not impact disease-free ($p = 0.655$, log-rank test) and overall ($p = 0.930$, log-rank test) survivals of those patients. Likewise, surgical approach (laparoscopy vs. open surgery) did not impact on disease-free ($p = 0.870$, log-rank test) and overall ($p = 0.962$, log-rank test) survivals.

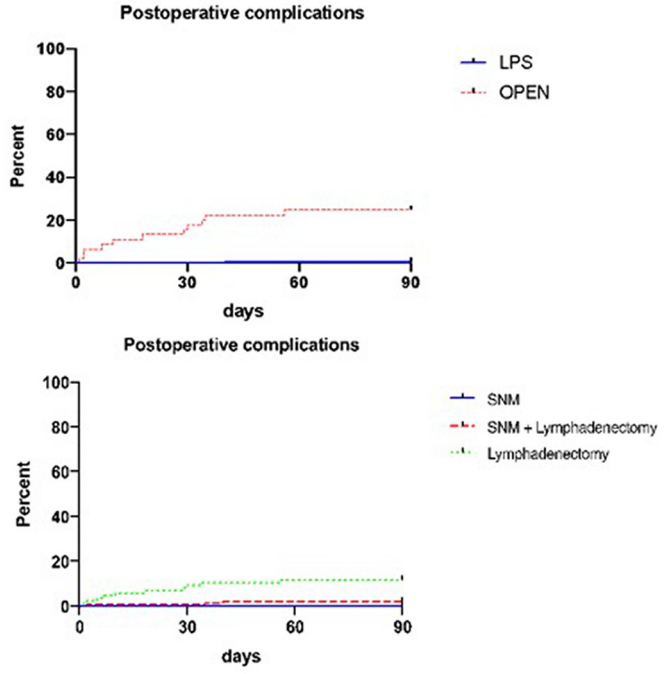

Fig. 2. Risk of developing 90-day postoperative severe complications.
Legend: Abbreviation: SNM, sentinel node mapping; LPS, laparoscopy. Severe complications included grade 3 or worse complications according to the Clavien-Dindo classification [25].

4. Discussion

The present study investigated three different modalities of nodal dissection in EC. We observed that: (i) our results highlights the safety of minimally invasive SNM in EC; (ii) type of lymph node dissection does not impact on oncologic outcomes; (iii) patients having SNM (alone or followed by LND) have an increased 5-10% possibility to be detected with low volume disease, likely not detectable with conventional histopathological examination performed in case of LND; (iv) the execution of LND does not improve survival outcomes in comparison to SNM, even in node positive patients; (v) finally, the results of the present study highlighted that the adoption of both minimally invasive surgery and SNM reduces the risk of developing post-operative morbidity, including lymphatic complications.

Previous published data showed that SNM is a safe and effective method for staging purposes in apparent early-stage EC [14–19]. For example, the FIRES and the FILM trials reported a high sensitivity, specificity, and accuracy of SNM in EC patients [26,27]. Additionally, well designed retrospective comparison observed that patients having SNM experienced similar oncologic outcomes compared to patients having LND for the treatment of low- and high-risk EC [20,21]. Looking both at the general population of EC and at the subgroup at high-risk EC other authors observed the non-inferiority of SNM in comparison to standard pelvic (and para-aortic) LND [11–15]. This evidence is confirmed by the pooled results of a recent meta-analysis on this issue [28], demonstrating that SNM and systematic LND are comparable in terms of detection of para-aortic nodal involvement and recurrence rates (any site and nodal recurrence). More interestingly, SNM (thanks to the adoption of ultrastaging) is superior to LND in identifying positive pelvic nodes. According to the data of the present paper and the data in the literature, we know that patients having SNM are more likely to be diagnosed with stage IIIC disease and they are more likely to receive

adjuvant therapy [18–22]. Therefore, we can assume that about 5-10% of patients included in the LND group might have had undetected low volume lymphatic disease [18–22,29,30]. Despite these patients being classified as node-negative and therefore did not receive adjuvant therapy, survival outcomes were similar between groups. However, we have to take in consideration that: (i) the role of low volume disease is controversial; (ii) the high prevalence of patients without nodal involvement is driving the cumulative survival results; (iii) an optimal treatment for managing node-positive patients is not still available. The inherent biases of the retrospective study design are the main weaknesses of the present study. However, this is one of the larger investigations on this issue. We have to take into account that one of the main strength of the present paper is to evaluate perioperative and long-term outcomes of patients undergoing three different approach for nodal staging. Moreover, although the adoption of a propensity-matched algorithm might not replace the quality of a randomized controlled study, we reduced the possible effect of allocation and selection biases in our study.

5. Conclusions

In the present study, we observed that the type of nodal assessment does not have an impact on the oncologic outcomes of patients with early-stage EC. The execution of systematic LND, SNM/backup LND, or SNM alone is linked with similar disease-free and overall survival in EC patients. Moreover, patients with SNM are more likely to be detected with a stage IIIC EC, since SNM is able to recognize low volume lymphatic disease. Further randomized controlled trials comparing LND vs. SNM alone in intermediate- and high-risk patients are warranted to clarify the role of nodal assessment and the value of low volume disease in those patients. More interestingly, an additional adoption of molecular/genomic profiling would explain the role of low volume disease in EC.

Data availability

The datasets generated during and analyzed during the current study are available from the corresponding author on reasonable request.

CRediT authorship contribution statement

Giorgio Bogani: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Violante Di Donato:** Methodology, Writing – original draft, Writing – review & editing. **Andrea Papadia:** Methodology, Writing – original draft, Writing – review & editing. **Alessandro Buda:** Methodology, Writing – original draft, Writing – review & editing. **Jvan Casarin:** Methodology, Writing – original draft, Writing – review & editing. **Francesco Multinu:** Methodology, Writing – original draft, Writing – review & editing. **Francesco Plotti:** Methodology, Writing – original draft, Writing – review & editing. **Ilaria Cuccu:** Methodology, Writing – original draft, Writing – review & editing. **Tullio Golia D'Auge:** Methodology, Writing – original draft, Writing – review & editing. **Maria Luisa Gasparri:** Methodology, Writing – original draft, Writing – review & editing. **Ciro Pinelli:** Methodology, Writing – original draft, Writing – review & editing. **Anna Myriam Perrone:** Methodology, Writing – original draft, Writing – review & editing. **Fabio Barra:** Methodology, Writing – original draft, Writing – review & editing. **Flavia Sorbi:** Methodology, Writing – original draft, Writing – review & editing. **Antonella Cromi:** Methodology, Writing – original draft, Writing – review & editing. **Giampaolo Di Martino:** Methodology, Writing – original draft, Writing – review & editing. **Innocenza Palaia:** Methodology, Writing – original draft, Writing – review & editing. **Giorgia Perniola:** Methodology, Writing – original draft, Writing – review & editing. **Simone Ferrero:** Methodology, Writing – original draft, Writing – review & editing. **Pierandrea De Iaco:** Methodology, Writing – original draft, Writing – review & editing. **Chiara Perrone:** Methodology, Writing – original draft, Writing – review & editing. **Roberto Angioli:** Methodology, Writing – original draft, Writing – review & editing. **Daniela Luvero:** Methodology, Writing – original draft, Writing – review & editing. **Ludovico Muzii:** Methodology, Writing – original draft, Writing – review & editing. **Fabio Ghezzi:** Methodology, Supervision, Writing – original draft, Writing – review & editing. **Fabio Landoni:** Methodology, Supervision, Writing – original draft, Writing – review & editing. **Michael D. Mueller:** Methodology, Supervision, Writing – original draft, Writing – review & editing. **Pierluigi Benedetti Panici:** Methodology, Writing – original draft, Writing – review & editing. **Francesco Raspagliesi:** Conceptualization, Project administration, Supervision, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare no conflicts of interest. No funding sources supported this investigation.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2022.06.007.

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