

Research Report

Does sentinel lymph node biopsy in endometrial cancer surgery have an impact on the rate of adjuvant post operative pelvic radiation? An Israeli Gynecologic Oncology Group Study

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ABSTRACT

Objective: To compare the rates of post-operative radiotherapy between two methods of lymph nodes assessment during surgical staging for endometrial cancer (EC).

Methods: We conducted a comparative study of all consecutive women with endometrial cancer who underwent sentinel lymph node detection and biopsy using blue dye and isotope scan (SLNB) at Kaplan Medical Center and patients from the IGOG database, who underwent staging lymphadenectomy (PLND). The primary outcome was the rate of adjuvant and therapeutic radiation. The secondary outcome was a comparison of disease-free survival (DFS) and overall survival (OS).

Results: There were 138 patients in the SLNB group and 1022 women in the PLND group. The detection rate of SLN was 74% for unilateral detection and 54% for bilateral detection. In the PLND group 57% were high risk patients vs. 47% in SLNB group ($p = 0.03$). 43% of high-risk patients in the PLND group received adjuvant or therapeutic pelvic radiation vs. 28% of high-risk women in the SLNB arm ($p = 0.017$). No statistically significant difference in recurrence rates nor in death rates had been observed in the high-risk group patients. The 5-years survival in the high-risk PLND group was 80% and the recurrence rate was 19% vs. 75% 5-year survival and 14% recurrence in high-risk SLNB cohort, log-rank $p = 0.82$ for survival and long-rank $p = 0.25$ for recurrence.

Conclusion: Endometrial cancer patients undergoing lymph node assessment by sentinel lymph node biopsy, receive less pelvic radiotherapy.

1. Introduction

Endometrial cancer is the most common cancer of the reproductive tract in the US and other developed countries (Siegel et al., 2019).

Worldwide, it's the second most common gynecological malignancy with cervical cancer being the first (Bray et al., 2018).

Lymph node assessment is an integral part of the surgical staging of endometrial cancer. Nodal status is associated with prognosis and used

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for tailoring of adjuvant therapy (Colombo et al., 2016). There are two accepted methods for surgical evaluation of lymph nodes: sentinel lymph nodes sampling and complete systematic pelvic and para-aortic lymphadenectomy. The literature is inconsistent on the therapeutic value of full lymphadenectomy. A few retrospective analyses found a survival benefit (Mohan et al., 1998) but two large randomized clinical trials have failed to demonstrate any survival benefit for complete removal of pelvic lymph nodes (Benedetti Panici et al., 2008; Kitchener et al.). Complete lymphadenectomy is associated with significant intra and post-operative morbidity, including blood loss, nerve injury, lymphocele and lymphedema (Volpi et al., 2019; Franchi et al., 2001). Today, there is a trend to more conservative surgery in endometrial cancer.

Sentinel node sampling is a well-established procedure in the treatment of melanoma and breast cancer. In gynecology, its use is widely accepted in the staging and treatment of vulvar cancer, however in endometrial cancer, despite robust prospective and retrospective data supporting it, this technique is utilized in less than two thirds of the cases (Chambers et al., 2019; Ballester et al., 2011; Rossi et al., 2017; Daraï et al., 2015).

In a meta-analysis comparing sentinel node mapping vs. lymphadenectomy, sentinel node method was superior for detecting positive pelvic nodes and non-inferior to lymphadenectomy for assessing para-aortic lymph node involvement (Bogani et al., 2019). No statistically significant difference in recurrence rate was observed. Few studies evaluating the impact of lymph node assessment method on survival of women with endometrial cancer have been published, and found no survival benefit for any method (Buda et al., 2017; Schlappe et al., 2018; Multinu et al., 2019).

After surgical staging, some patients are referred for adjuvant treatment according to stage, grade and risk factors. Guidelines algorithms leave some room for clinical judgement regarding radiotherapy recommendations in endometrial cancer, leaving the decision to the oncologist (National Comprehensive Cancer Network, 2020). For example, in case of stage IA G3, the NCCN guidelines permit three possible options for adjuvant treatment: brachytherapy, observation and EBRT (external beam radiotherapy). In stage III and IV cases the addition of EBRT and or brachytherapy to systemic chemotherapy is optional.

The number of harvested lymph nodes, ultrastaging and uterine factors all have an impact on the choice of adjuvant treatment in endometrial cancer.

Reports in the literature on the association of the lymph node assessment protocol with the adjuvant treatment plan are contradictory: Some state that patients undergoing sentinel lymph node biopsy receive more adjuvant radiotherapy (Schlappe et al., 2018) while others report the opposite (Buda et al., 2017).

The aim of our study is to evaluate whether the method of lymph node assessment has had an impact on adjuvant treatment.

2. Methods

Patients who had surgery for endometrial cancer in Kaplan medical center were identified and compared to women with endometrial cancer treated in ten other hospitals in Israel: Barzilai, Meir, Rabin, Shamir, Wolfson, Rambam, Hillel Yaffe, Ziv, Poria and Carmel medical centers, whose data was collected by the Israeli Gynecologic Oncology Group (IGOG). The data was obtained by retrospective review of electronic records and medical files. The Kaplan cohort consisted of patients treated between 2013 and 2018. The IGOG database encompassed the years 2002–2014. The Memorial Sloan Kettering Cancer Center sentinel lymph node biopsy protocol (Barlin et al., 2012) was introduced to Kaplan in 2012 and from 2013 it became the standard of care for surgical staging of endometrial cancer. Patients in the IGOG database had either no lymphadenectomy or full pelvic lymphadenectomy according to pre- and intra- surgical assessment. Para-aortic lymph node dissection was

added at the surgeon's discretion. Patients from the IGOG records, who did not undergo lymphadenectomy, were excluded from the analysis.

Women in both groups underwent hysterectomy, bilateral salpingo-oophorectomy and peritoneal washing for cytological evaluation. Mapping of sentinel lymph nodes in the SLN group was performed in two steps: A day before surgery, Tc99 was injected into the cervix and SPECT scan performed. During surgery, methylene blue was introduced through the cervix before entering the abdomen. To identify the nodes the surgeon looked for blue dye and radioactive reading from a Geiger probe. Blue and/or radiopositive nodes were removed and submitted for ultrastaging. In case of negative sentinel node mapping, a full pelvic lymphadenectomy was performed on the ipsilateral side. Any suspicious nodes were also removed as per protocol. Except two cases that were converted to laparotomy due to severe abdominal adhesions, all women in the SLN group were operated laparoscopically. Women in the IGOG database were operated by laparotomy or laparoscopy.

After discharge, patients were invited to a follow up visit one month after surgery. The decision to refer a patient to adjuvant therapy and treatment selection were made by a multidisciplinary team, based on the NCCN guidelines (National Comprehensive Cancer Network, 2020) and in accordance with disease stage, grade and other risk factors for recurrence. Women referred for adjuvant radiotherapy, received either vaginal brachytherapy alone or a combination of brachytherapy and pelvic external beam radiotherapy. Rates of external beam radiotherapy were compared between the groups because of the strong association of positive lymph nodes and pelvic radiotherapy and the potential for serious side effects from this treatment (Kong et al., 2012; Koh et al., 2014).

The primary outcome was the rate of adjuvant radiotherapy after sentinel lymph node biopsy versus full lymphadenectomy. The secondary outcome was a comparison of disease-free survival (DFS) and overall survival (OS) between the two cohorts.

After initial statistical analysis patient in each arm were sub-divided into two groups according to stage and grade of their disease – high risk and low risk. Patients with stage IA, grade 3 and patients staged IB, grade 2 or 3 were classified as 'high risk' as well as stage II+. Women with stage IA, grade 1 and 2 and stage IB, grade 1 were tagged as 'low risk' in the sub-group analysis. Cases of non-endometrioid cancers were also included in the 'high risk' arm. This classification intended to overcome the selection bias in the fact that patients in the IGOG arm directed for full pelvic lymphadenectomy may be higher risk women compared to those who had no lymphadenectomy.

Data was collected and assembled in Microsoft Excel sheets and statistically analyzed utilizing IBM SPSS software. Chi square and T-test were used for categorical and numerical variables comparison, respectively. Variables found to have a significant association with the dependent variable – adjuvant treatment, were included in a multivariable logistic regression model. Kaplan-Meier plots and the log-rank test were used to compare overall and disease-free survival.

3. Results

The electronic medical records and files of 1160 women with endometrial cancer were retrospectively reviewed after excluding patients with missing data or non-endometrial cancer pathology. The full pelvic lymphadenectomy arm (LND) contained 1022 patients, and the sentinel lymph node biopsy arm (SLN) comprised 138 women with endometrial cancer. After dividing the patients into sub-groups by risk for recurrence, 583/1022 (57%) and 65/138 (47%) women were classified as high risk in the LND and SLN arms respectively (Fig. 1).

Patient characteristics are shown in Table 1. The mean age of women in the LND and SLN groups was 65 (± 10) and 66 (± 9), respectively ($p = 0.16$). More women in the SLN cohort had diabetes mellitus – 33% vs. 25% in the LND cohort ($p = 0.05$), while the LND group included more women using HRT – 6% vs. 2% in the SLN arm ($p = 0.05$). The rates of hypertension, history of breast cancer, use of tamoxifen and median Ca-

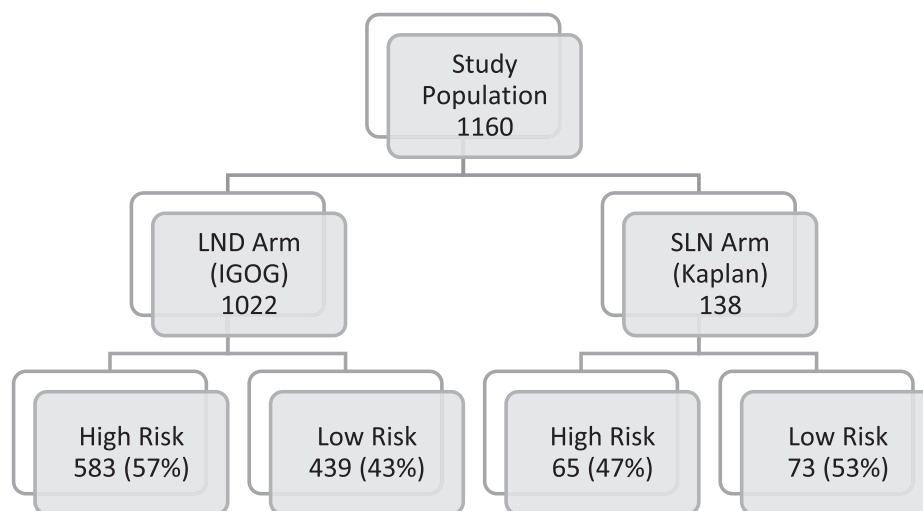


Fig. 1. Patients Classification.

Table 1
Patients Characteristics.

	LND (n = 1022)	SLN (n = 138)	p.
Age mean ± SD	65.1 ± 10.2	66.4 ± 9.7	0.16
Diabetes mellitus N(%)	255 (25%)	45 (33%)	0.05
Hypertension N(%)	562 (55%)	84 (61%)	0.14
Breast cancer N(%)	112 (11%)	18 (13%)	0.27
Colon cancer N(%)	10 (1%)	3 (2%)	0.33
Other cancer N(%)	30 (3%)	7 (5%)	0.14
Tamoxifen Tx N(%)	51 (5%)	5 (4%)	0.5
HRT N(%)	61 (6%)	3 (2%)	0.05
Ca-125 median(IQR)	17 (11,31)	16 (10,26)	0.47

HRT – hormone replacement therapy.

125 levels before the surgery were similar in the two groups. The detection rate for SLN was 74% for unilateral detection and 54% for bilateral detection.

Table 2, summarized the pathological features of endometrial tumors classified as ‘high-risk’ in the LND and SLN patient groups. Both groups included similar proportions of patients with endometrioid type endometrial cancer (52.7% of LND patients and 47.6% of SLN patients, $p = 0.47$). There was a similar distribution of non-endometrioid tumors in both groups of patients. There was no statistically significant difference in the distribution of disease stages between the groups ($p = 0.14$). More patients in the high-risk SLN arm were LVSI (lympho-vascular space invasion) positive in comparison to high-risk LND women, 42.4% vs. 28.0% ($p = 0.02$).

There was a similar proportion of stage IIIC patients in both groups of

Table 2
Pathological Characteristics of Patients Classified as High-Risk.

		LND (n = 583)	SLN (n = 65)	p.
Grade	1	26 (4.5%)	1 (1.5%)	0.47
	2	144 (24.8%)	19 (29.2%)	
	3	136 (23.4%)	11 (16.9%)	
Stage	IA	141 (25.7%)	23 (35.4%)	0.14
	IB	178 (32.5%)	23 (35.4%)	
	II	55 (10.0%)	7 (10.8%)	
	IIIA + IIIB	43 (7.8%)	1 (1.5%)	
	IIIC	110 (20.1%)	11 (16.9%)	0.55
LVSI		163 (28.0%)	27 (42.4%)	0.02
Histology	Endometrioid	306 (52.7%)	31 (47.7%)	0.47
	Serous papillary	183 (31.5%)	28 (43.1%)	
	Clear cell	35 (6.0%)	3 (4.6%)	
	Carcinosarcoma	51 (8.8%)	3 (4.6%)	

lymph nodes assessment – 20.1% in full pelvic lymphadenectomy vs. 16.9% in sentinel lymph node biopsy method, $p = 0.55$. All nodes harvested by the SLN protocol were ultra-staged for micro metastases (>0.2 mm and ≤ 2 mm), however in every patient, in our data, with positive nodes at least one macro metastasis (>2 mm) was present.

Fewer patients in the SLN group received adjuvant pelvic radiotherapy compared to patients in the LND arm – 14% (19/138) vs. 27% (279/1022) respectively, $p < 0.001$.

Patients cases were subdivided into high-risk and low-risk groups. There was no statistically significant difference in pelvic radiotherapy rates among low-risk patients – 1.4% (1/73) of low-risk women in the SLN group received pelvic radiotherapy vs. 5% (22/439) of low-risk LND patients, $p = 0.228$. However, fewer women in the high-risk SLN group, received pelvic radiotherapy – 28% (18/65) in comparison to high-risk LND cases – 43% (251/583), $p = 0.017$.

The proportion of high-risk patients without adjuvant treatment was similar in both study arms (Table 3). No statistically significant differences were found, between complete lymphadenectomy and sentinel lymph node dissection, in the number of women that were referred to chemotherapy only, as well as among those who were treated by a combination of chemotherapy and external beam radiotherapy, 14% vs. 8% ($p = 0.121$) and 18% vs. 23% ($p = 0.397$), respectively. More cases had brachytherapy only and brachytherapy with chemotherapy after SLN protocol.

A logistic regression model was built to control for potential confounders and identify the factors most strongly associated with referral to adjuvant radiotherapy. The association between radiotherapy and the following variables was tested: age, Ca-125, diabetes mellitus, hypertension, breast cancer, colon cancer, other cancer, tamoxifen, HRT, risk group, LVSI, peritoneal washing and lymph nodes metastases. Factors significantly associated with referral to external beam radiotherapy (EBRT) on univariable analysis were included in a multivariable model

Table 3
Adjuvant Treatment of High-Risk Patients.

	LND (n = 583)	SLN (n = 65)	p.
No Adjuvant Treatment	100 (17%)	7 (11%)	0.145
Brachytherapy Only	66 (11%)	17 (26%)	0.001
Ebrt +/- Brachytherapy	135 (23%)	3 (5%)	$p < 0.001$
Chemotherapy Only	82 (14%)	5 (8%)	0.121
Chemotherapy And Brachytherapy	69 (12%)	18 (28%)	0.001
Chemotherapy And Ebrt +/- Brachytherapy	104 (18%)	15 (23%)	0.397

EBRT – External Beam Radiotherapy.

Table 4
Factors Associated with Adjuvant Radiotherapy – Multivariable Logistic Regression Analysis.

	Adjusted OR	95% C.I. for OR	Significance
LVSI positive (ref: negative)	1.624	1.152–2.287	p = 0.006
High-risk subgroup (ref: low risk)	13.213	8.371–20.856	p < 0.001
Positive peritoneal cytology (ref: negative)	0.856	0.47–1.56	p = 0.613
Full lymphadenectomy (ref: SLN sampling)	2.090	1.188–3.678	p = 0.011

(Table 4). The variable most strongly associated with EBRT treatment is patient’s risk group – OR = 13.2 (95% CI 8.37–20.86; p < 0.001). The surgical protocol for lymph node dissection is also associated with adjuvant treatment – the OR for EBRT is 2.09 (95% CI 1.19–3.68; p = 0.01) after full lymphadenectomy compared to SLN. Positive peritoneal cytology has no association with referral to adjuvant treatment – OR = 0.86 (95% CI 0.47–1.56; p = 0.613).

The 5-year survival rate in complete lymphadenectomy group was 80%. Patients operated by sentinel lymph node protocol had 5-year survival rate of 75%. This difference was not statistically significant, Log-rank p = 0.82 (Fig. 2). Recurrence rates were also similar between the groups. 19% of LND patients had disease recurrence over 5 years of follow-up versus 14% of SLN cases, Log-rank p = 0.25 (Fig. 3).

4. Discussion

The ideal method of lymph nodes assessment in oncologic surgery would provide accurate staging and prognosis, identify candidates for adjuvant treatment, avoid over and under treatment, reduce surgical side-effects and operative room time and optimize the work of the

pathologist.

While the optimal method of lymph node assessment in endometrial cancer is still under study and the issue of adjuvant radiotherapy in early stage endometrial cancer is controversial, our retrospective study evaluating 138 SLN procedures and comparing them to 1022 complete lymphadenectomy cases shows that sentinel lymph node protocol is a reliable staging method, associated with lower rates of adjuvant radiotherapy without compromising the patient’s outcome.

Reports in the literature about lymph node assessment method and adjuvant treatment are contradicting. In a study conducted by Schlappe et al. comparing oncological outcomes in patients with deeply invasive endometrial cancer, 28% women in the SLN cohort vs. 17% in the LND arm received EBRT (Schlappe et al., 2018). The authors found no difference in oncologic outcomes between the methods. In other report from Buda et al., analyzing survival in apparent early stage endometrial cancer patients undergoing sentinel lymph node mapping versus selective lymphadenectomy, 15% of SLN patients had EBRT compared to 20.5% of women after selective lymphadenectomy (Buda et al., 2017). No survival difference was found.

In our study, complete lymphadenectomy was associated with a significantly higher rate of adjuvant radiotherapy. The guidelines for adjuvant treatment of endometrial cancer are not conclusive, allowing some freedom for the oncologist (National Comprehensive Cancer Network, 2020). One may assume that assessing nodal status by sentinel lymph node algorithm is associated with a higher rate of adjuvant treatment due to fear of under-staging by this method, but our data implies the opposite. There was no statistically significant difference in the proportion of patients with lymph nodes involvement between the methods, thus other factors influenced the decision to refer a patient for adjuvant radiotherapy. The higher rates of EBRT among patients undergoing lymphadenectomy persisted even when considering only those with high-risk tumors. A study by Martell et al. surveying adjuvant radiotherapy practice in endometrial cancer, identified variability in

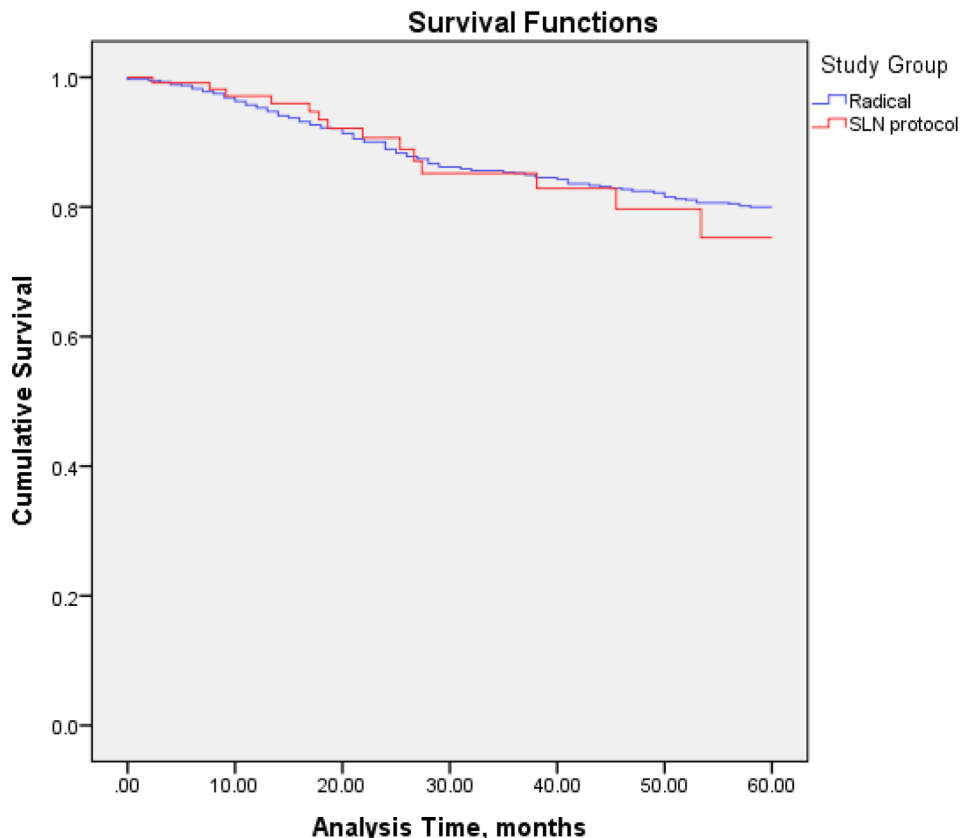


Fig. 2. Kaplan Meier Overall Survival Estimates.

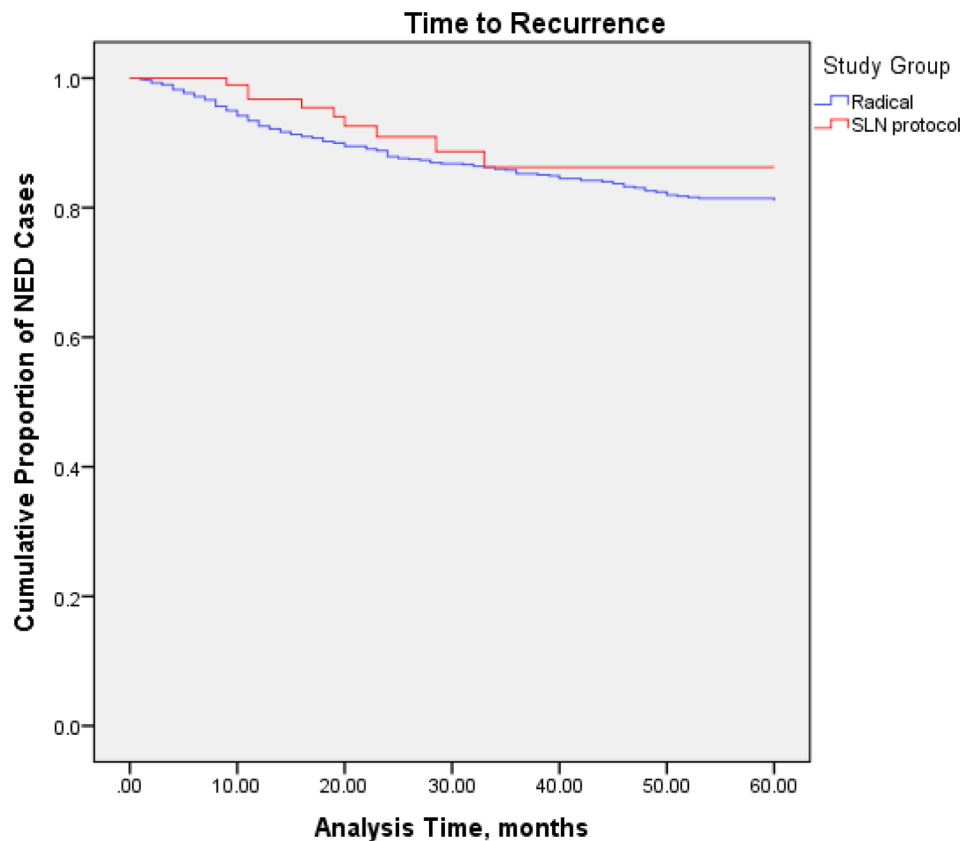


Fig. 3. Kaplan Meier Time to Recurrence Estimates.

treatment recommendations (Martell et al., 2019) but didn't stratified data by lymph node assessment method.

Using a logistic regression model, key factors associated with adjuvant radiotherapy were identified. The odds ratio for EBRT after full pelvic lymph node dissection is 2.09 (1.19–3.68) compared to SLN. Lymphovascular space invasion (LVSI) is also associated with increased odds of adjuvant radiotherapy in our data. PORTEC 1 and 2 demonstrated that LVSI is a strong predictor for pelvic recurrence, distant metastases and overall survival and the authors recommended adjuvant EBRT for stage I endometrial cancer with substantial LVSI (Bosse et al., 2015). However, a more recent publication from Boothe et al., found no difference in overall survival between EBRT versus vaginal brachytherapy in LVSI-positive patients (Boothe et al., 2019). More patients in the SLN arm were LVSI positive (42% vs. 28%, $p = 0.02$). Thus, the higher rates of EBRT in the LND arm are not explained by LVSI or other pathological findings.

Our data also shows that peritoneal washing status does not affect the treatment protocol.

The total number of removed lymph nodes has no impact on prognosis in early stage and locally advanced endometrial cancer (Polterauer et al., 2012; Huang et al., 2010) and sentinel lymph node biopsy has been shown to be a reliable staging method with 97.2% sensitivity and 99.6% negative predictive value (Ballester et al., 2011; Rossi et al., 2017; Darai et al., 2015).

External beam radiotherapy causes significant toxicity (Kong et al., 2012; Koh et al., 2014) and that added to the well-studied side effects of full pelvic lymphadenectomy such as lymphocele and lymphedema (Volpi et al., 2019; Frost et al., 2017) tips the scales in favor of sentinel lymph node dissection as the preferred method for nodal assessment.

Recently a study from Kogan et al. found that adding SLN to LND improves EC patients clinical outcomes and complements the decision on adjuvant therapy (Kogan et al., 2020). Whether SLN alone or SLN combined with LND is the optimal method for staging and treating

endometrial cancer remains to be verified, but data in favor of SLN is accumulating and this method must be considered in every endometrial cancer surgery.

In addition, although underpowered, our study found no difference in overall survival and recurrence rates between the two methods of nodal assessment.

The detection rate of sentinel lymph nodes was relatively low in our study due to the mapping method we used – Tc99 and Methylene blue. Recently, after switching to ICG for sentinel lymph node mapping, the detection rate approaches 100%.

The strengths of this study are: a large sample size; minimal selection bias due to comparison of SLN method practiced exclusively in one medical center to LND method in other unrelated hospitals; cohorts were well balanced with respect to most variables (Table 2).

Study limitations: The main limitation of the study is the possibility that the results were biased due to a comparison of groups in different time periods. The patients were treated during different time frames and changes in practice may have occurred that impacted adjuvant treatment paradigms. Also, the research was underpowered for survival analysis. Other limitations are retrospective analysis and short follow up interval.

5. Conclusions

Patients with endometrial cancer having surgical staging with the SLN protocol receive less adjuvant radiation treatment than patients having a full lymphadenectomy.

The weight of the accumulated evidence suggests that sentinel node biopsy is effective and safe, and may be the preferred method of nodal assessment in endometrial cancer.

A prospective randomized study, such as the ongoing ALICE study in Brazil, is needed to evaluate the impact of this method on survival and disease recurrence.

6. Authors' contribution

- Yoav Brezinov and Alon Ben-Arie – conceived of the presented idea and designed the study.
- Tamar Katzir, Ofer Gemer, Limor Helpman, Ram Eitan, Zvi Vaknin, Tally Levy, Amnon Amit, Ilan Bruchim, Inbar Ben Shachar, Ilan Atlas and Ofer Lavie – collected and organized data from their medical centers and were the study representatives and supervisors in their corresponding medical center.
- Ofer Gemer was responsible for data integration and final database creation.
- Yoav Brezinov – was responsible for writing the manuscript.
- Alon Ben-Arie, Yoav Brezinov and Tamar Katzir – conducted results analysis and their interpretation.
- Alon Ben-Arie, Ofer Gemer and Helpman Limor – reviewed the manuscript before its release to publication and helped in the formulation of discussion section.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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