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## ORIGINAL ARTICLE

# Sentinel lymphadenectomy versus total lymphadenectomy in the staging of endometrial cancer

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## ABSTRACT

**Background:** The Surgical staging of endometrial cancer includes a hysterectomy, bilateral salpingo-oophorectomy, and estimation of regional LN involvement, specially the pelvic and aortic lymph node. Some advised that lymphadenectomy explains the risk of recurrence and helps clinicians make the decision to give adjuvant treatment to high-risk patients. While, some suggested that, complete pelvic and para-aortic lymphadenectomy itself is associated with major comorbidities. Sentinel lymphadenectomy has been suggested in the staging process of the diseases.

The aim of this study was to compare the role SLN mapping over total lymphadenectomy for detection of disease metastasis in cases of cancer of the endometrium.

**Method:** 30 patients that were diagnosed of having endometrial cancer based on biopsy were included in this study and were divided in to two equal groups and mapping of sentinel lymph nodes was done to 15 patients and all patients had undergone lymphadenectomy

**Results:** In this study The mean age of patients was 55 years ( range 45-74) for group 1 and was 56yrs ( range 43-75) for group2. Also the increase in weight as BMI, Median (Range) was 35 (26-45) for group 1 and for group2 was 34 (28-50)... And shown in our study there is no significant difference between both groups regarding BMI, age, clinical , family history and preoperative pathological results. we approved that proved that SLN biopsy has relatively equal values like lymphadenectomy in staging of endometrial cancer with sensitivity 80% and specificity 90%. Sentinel mapping had good sensitivity and specificity diagnostic potentials.

**Key words:** Endometrial, sentinel, mapping, methylene



## INTRODUCTION

Endometrial cancer is counted to be the most common gynecological malignancy and usually diagnosed at early stages of the disease. It is represented by abnormal uterine bleeding in about 90% of patients (usually during menopause), sometimes accompanied by vaginal discharge and pyometra. About 10% of patients will have pelvic lymph node (LN) metastasis in spite of encouraging tumor characteristics. (1). Cancer staging main target is to help clinicians in making the decision for best management of cases and to guide treatment plan. Results from different studies of systematic evaluation of surgical–pathological patterns of spread, FIGO approved in 1988 that uterine cancer have to be staged surgically . Specially, lymph node involvement and the depth of myometrial invasion (2) . Algorithms of treatment that do not include surgical staging depend upon an increased use of external beam

radiation, which is associated with higher morbidity. On the other hand pathological evaluation of lymph nodes is important in determining adjuvant therapies (3). The decision to perform a LN dissection, and to what extent has been one of the most debatable areas in the management of endometrial cancer (4). Sentinel lymph node is the first node receiving lymphatic drainage from the primary tumor and pathological status of SLN should then reflect the overall status of whole lymphatic basin (5). Less extensive LN removal and less surgical trauma are benefits of the sentinel lymph node (SLN) line of treatment, accompanied with the potential for improving the sensitivity of detecting the metastases of LN. The SLN is well recognized in the surgical treatment of breast cancer and malignant melanoma. To this point, in gynecological oncology the most frequent use of SLN mapping has been for vulvar cancer.

However, there is a growing concern to develop SLN approaches in uterine cancer, (6,7)

Aim of the study: The aim of this study was to compare the role SLN mapping over total lymphadenectomy for detection of disease metastasis in cases of cancer of the endometrium

## METHODS

Written informed consent was obtained from all participants, the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University. The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans. Sample size was calculated by open EPI to be 30 cases with confidence level 95% and power of test 80%. This comparative cross sectional study was conducted between September 2018 till April 2020 in obstetrics and gynecology surgery department in Zagazig university. Egypt. patients were divided into 2 equal groups where group 1 had no mapping while group 2 had undergone mapping of sentinel lymph nodes. Inclusion criteria Patients with abnormal vaginal bleeding who were diagnosed of having endometrial cancer based on biopsy with stage I, II, IIIA endometrial cancer.

**Exclusion criteria** Inoperable late stage endometrial cancer cases and patients that were recognized of having gross extra-uterine disease at surgery time and patients who had a history of any hepatic impairment .

**Operative design:** All cases that had harmony to the inclusion criteria had been subjected to the following: Full history was taken from patients including personal, medical, surgical, menstrual and obstetric history. The patient was examined generally, abdominally and locally. Patients were admitted and investigations were done in the form of: Pelvic ultrasonography, MRI or CT scanning,

Pre-operative lab investigations were done (CBC, kidney function test, liver function test & coagulation profile).

**Intraoperative steps:** Patients were divided into 2 equal groups where the second group had undergone mapping of sentinel lymph nodes at the beginning of the surgery.

**Injection and mapping Technique:** General anesthesia was applied.

Sterilization of the urethra, vulva and perineum region. Injection of methylene blue dye was done by expert gynecological surgeon. The cervix was injected by a standardized dose of 0.5 mg/mL done by diluting 1 mL of methylene blue dye (2.5 mg/mL) into 5 mL of saline and (4 mL) was injected at 3 and 9 o'clock positions respectively at a depth of (1–2 cm) superficially using a spinal needle.

-Good exploration of the nodes that had taken the dye was done .

All patients had undergone total abdominal hysterectomy, bilateral salpingo-oophorectomy and peritoneal cytology.

-Any suspicious lymph nodes per surgeon's assessment were removed and had been separately labeled and sent as non-sentinel lymph nodes .

-Sentinel lymph nodes had been determined to at least one hemi pelvis all cases had undergone lymphadenectomy and in some cases it was hard to elect para aortic lymph nodes so they were not been removed . Both SLNs and non-SLNs had been sent for histo-pathological assessment

## STATISTICAL ANALYSIS

Data collected throughout history, basic clinical examination, laboratory investigations and outcome measures coded, entered and analyzed using Microsoft Excel software. Data were then imported into Statistical Package for the Social Sciences (SPSS version 20.0) (Statistical Package for the Social Sciences) software for analysis. According to the type of data qualitative represent as number and percentage quantitative continues group represent by mean  $\pm$  SD , The other continuous variables and ordinal variables were presented by the median and 25th and 75th percentiles. Number and percentage were reported for categorical variables. the following tests were used to test differences for significance; difference and association of qualitative variable by Chi square test ( $X^2$ ) . Differences between quantitative independent groups by t test, multiple by ANOVA, correlation by Pearson's correlation agreement by Kappa . P value was set at <0.05 for significant results & <0.001 for high significant result.

## RESULTS

As shown in tables (1,2) The mean age of patients was 55 years ( range 45-74) for group 1 and was 56 years ( range 43-75) for group 2. Also the increase in weight as BMI, Median was 35 **kg/m<sup>2</sup>** with a Range of (26-45) for group 1 and for group 2 was 34 **kg/m<sup>2</sup>** with a Range of (28-50). Also 6 patients are diabetic and 5 patients are both diabetic and hypertensive beside that 6 patients have positive family history as 2 patients have positive family history for endometrial cancer and 4 patients have positive family history for breast cancer. Also 5 patients are of null parity. And as shown in our study there is no statistically significant difference between both groups regarding BMI, age, clinical and family history. The preoperative pathological tissue grading resulted that about (73.3%) of patients are of grade 1 and about (20%) of patients were of grade 2 while about (6.7%) of patients were of grade 3 for both groups . The postoperative results had shown some changes as about (60%) of patients were of grade 1 and about (33.3%) of patients were of grade 2 and about (6.7%) of patients were of grade 3 as shown in table 3 this was

for group 1 while for group 2 about (66.7%) of patients were of grade 1 and about (20%) of patients were of grade 2 while about (13.3%) of patients were of grade 3 as shown in tables (3). The pathological results also resulted that lymphatic affection in group 1 was about (13.3%) and about (33.3%) for group 2 as shown in table 4. About (26.7%) of patients of group 1 and 2 showed superficial Myometrial invasion and about (20%) showed deep Myometrial invasion. Also the tumor size for patients in group 1 was about (33.3%) were more than 2 cm in diameter and (66.7%) were less than 2cm in diameter. And for group 2

about (40%) more than 2cm and about (60%) were less than 2cm in diameter as shown in table 5. Table 6 shows that 50 sentinel lymph nodes were mapped, from these 50 specimens about 23 lymph nodes were removed from the left side and 27 were removed from the right side. Where About 20 external iliac LN, 15 obturator LN, 10 Para aortic LN and 5 common iliac and internal iliac lymph nodes were removed. Table 7 shows that sensitivity of sentinel mapping in diagnosis of metastasis is (80%) means that mapping have the ability to diagnose metastasis truly in 80% of cases, sentinel mapping have good sensitivity and specificity diagnostic potentials

**Table (1):** Demographic and clinical data of the studied groups

Demographic data		Group 1 (N=15)	Group 2 (N=15)	P- value
Age (years)				
Mean ± SD		58.6 ± 8.973	59.6 ± 8.5	0.402
Median (Range)		55 (45-74)	56 (43-75)	(NS)
Item	Group 1 (N=15)	Group 2 (N=15)	P- value	
<b>BMI</b>				
Mean ± SD	33.4 ± 7.973	32.8 ± 6.8	0.541	
Median (Range)	35 (26-45)	34 (28-50)	(NS)	
<b>Parity</b>				
Mean ± SD	4.2 ± 2.6	4 ± 1.5	0.798	
Median (Range)	4 (0-9)	4(1-10)	(NS)	

\* Mann Whitney U test.

P < 0.05 is significant.

NS: Not significant.

This table shows that there is no statistically significant difference between both groups regarding BMI and parity and age.

**Table 2:** Comparison between the two studied groups according to clinical history among studied patients:

Item	group 1		group 2		Total		χ <sup>2</sup>	p-value
	No	%	No	%	No	%		
<b>Medical History</b>								
Hypertension	5	33.3%	3	20.0%	8	26.7%	1.5182	0.67
DM only	3	20.0%	3	20.0%	6	20%		
Both	3	20.0%	2	13.3%	5	16.7%		
Free	4	26.7%	7	46.7%	11	36.6%		
Total	15	100.0%	15	100.0%	30	100.0%		
<b>Family History for breast or endometrial cancer</b>								
Negative	12	80.0%	12	80.0%	24	80.0%	0.000	1.000
Positive	3	20.0%	3	20.0%	6	20.0%		
Total	15	100.0%	15	100.0%	30	100.0%		

X<sup>2</sup>: chi-square test

p-value > 0.05 is non-significant

This table shows that there is no significant difference between both groups regarding medical history and family history,

**Table 3:** Comparison between the two studied groups according to pre and post-operative pathology grading.

Grading	Group1				Goup2				p-value G1	p-value G2
	Pre-operative		Post-operative		pre-operative		Post-operative			
G1	11	73.3%	9	60.0%	11	73.3%	10	66.7%	0.751	0.683
G2	3	20.0%	5	33.3%	3	20.0%	3	20.0%	0.563	1.000
G3	1	6.7%	1	6.7%	1	6.7%	2	13.3%	1.000	0.479

Mc nemar test for comparison between paired data

P-value >0.05 in non significant

This table shows that there no difference among either group 1 or group 2 according to pre and post-operative pathology grading.

**Table 4:** Comparison between the two studied groups according to Lymphatic affection of the whole cases

lymph affection	Group 1		Group 2		χ <sup>2</sup>	p-value
	No	%	No	%		
No	7	46.7%	8	53.3%	3.35	0.187
Hyperplasia	6	40.0%	2	13.3%		
+ ve spread	2	13.3%	5	33.3%		

X<sup>2</sup>: chi-square test

p-value > 0.05 is non-significant

This table shows that there is no significant difference between both groups regarding lymph affection

**Table 5:** Successful mapped nodes (all cases )

successful mapped nodes (N=50)	Right side	Number of positive sentinel	Left side	Number of positive sentinel
Ext.iliac	11	2	9	1
Obturator	8	1	7	0
Para aoric	6	1	4	0
Common and internal iliac	2	0	3	0

**Table 6:** Comparison between the two studied groups according to Myometrial invasion and tumor size

Item	Group 1		Group 2		χ <sup>2</sup>	p-value
	No	%	No	%		
<b>Myometrial invasion</b>						
No	8	53.3%	8	53.3%	0.285	0.866
Superficial	4	26.7%	3	20.0%		
Deep	3	20.0%	4	26.7%		
<b>Tumor size</b>						
>2 cm	5	33.3%	6	40.0%	0.143	0.704
<2cm	10	66.7%	9	60.0%		

X<sup>2</sup>: chi-square test

p-value > 0.05 is non-significant

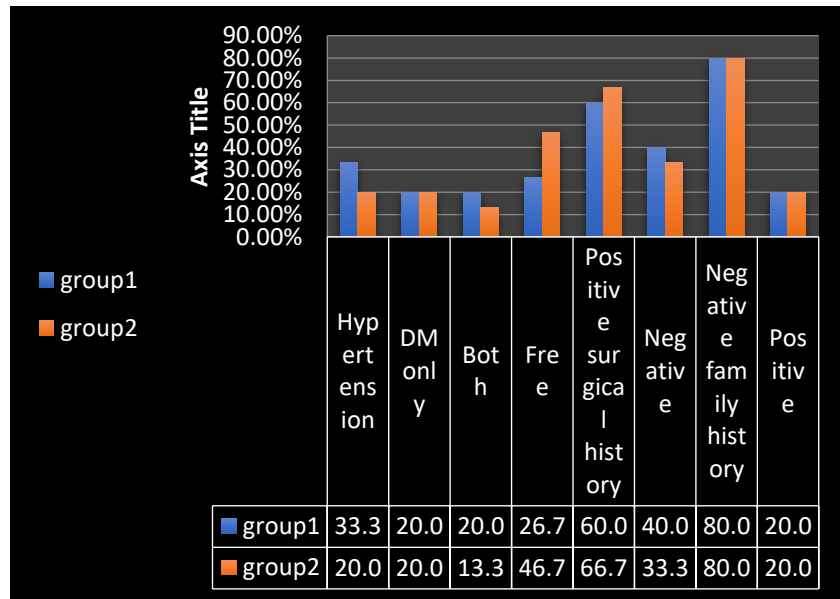
This table shows that there is no significant difference between both groups regarding Myometrial invasion and tumor size.

**Table 7:** Sensitivity, Specificity, Positive Predictive Value, and Negative Predictive Value of Sentinel

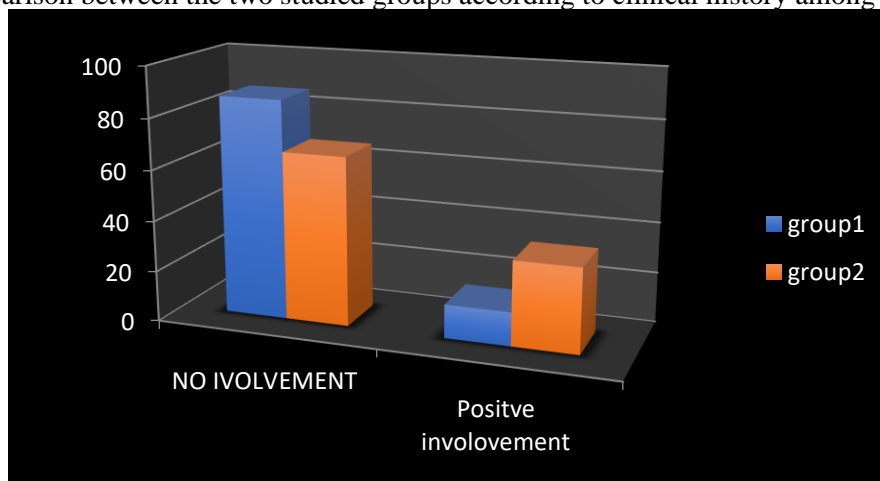
Mapping	Post-Operative Pathology Metastasis					
	Positive		Negative		Total	
	No	%	No	%	No	%
Positive	4	67%	1	4%	5	17%
Negative	1	17%	9	36%	10	33%
Total	5	83%	10	40%	15	50%

Sens.	Spec.	PVP	PVN
80%	90%	80%	90%

This table shows that sensitivity of sentinel mapping in diagnosis of metastasis is 80% means that mapping have the ability to diagnose metastasis truly in 80% of cases, sentinel mapping have good sensitivity and specificity diagnostic potentials



**Figure 1:** Comparison between the two studied groups according to clinical history among studied patients



**Figure (2):** Comparison between the two studied groups according to nodal involvement



### DISCUSSION

This study included 30 patients who attended to Zagazig university hospital and had been diagnosed with endometrial cancer, and patients were divided into 2 equal groups (15 patients for each group) where group 1 had no mapping of lymph node while group 2 had undergone mapping of lymph node. As shown in our study there is no statistically significant difference between both groups regarding BMI, age, clinical and family history and the mean age of patients was 55 years (range 45-74) for group 1 and was 56 years (range 43-75) for group 2. Also the increase in weight as BMI, Median was 35 kg/m<sup>2</sup> with a range of (26-45) for group 1 and for group 2 was 34 kg/m<sup>2</sup> with a range of (28-50). And this was compatible with a study by Khoury-Collado et al., 2011 where 266 patients with endometrial cancer underwent lymphatic mapping. The demographic and clinico-

pathologic data collected the median patient age was 60 years (range 33–85). The median BMI was 28.7 kg/m<sup>2</sup> (range 15.7–61) (4). Another study by Rossi et al between Aug, 2012, and Oct, 2015, 385 patients were included in it and the interventions for all patients was illustrated. The median age of patients was 63 years (range 29–83). The mean body-mass index of patients was 33.4 kg/m<sup>2</sup> (SD 7.9; range 17.8–60.5). As shown in our study and according to pre-operative biopsy results (73.3%) of patients were of grade 1 tumor 20% were of grade 2 tumor and about (6.7%) were of grade 3. We had followed the algorithm that had been proposed by Rossi et al in 2017 that suggested that selection of patients for the process of staging based on high risk chances for node metastasis include (high grade, large tumor size, deeply invasive tumors). Patients with lymphatic metastasis have at least one risk factor for that as

tumor size was more than 2 cm in 11 patients (5 for group 1 and 6 for group 2) on the other hand Myometrial invasion was more than 50% in about 7 patients (3 for group 1 and 4 for group 2). As shown in our study we had achieved successful mapping to the whole selected group (15 patients) 13 cases had bilaterally identified pelvic lymph nodes, while 2 cases had showed hemi pelvis mapping results. All suspicious lymph nodes by surgeon's assessment were removed. All cases had undergone total abdominal hysterectomy and bilateral salpingo oophorectomy. All cases had undergone bilateral pelvic lymphadenectomy (30) cases while 17 cases had para aortic lymphadenectomy. With ten lymph nodes or more were adequately removed from each patient. Mapping identified at least one sentinel lymph node in 15 patients. This agreed with the findings of Rossi et al in a study of the surgical staging outcomes and sentinel-lymph-node mapping outcomes for the 340 patients in 2017 where all patients had total pelvic lymphadenectomy. Para-aortic lymph node removal was done in 74 (74%) of 100 patients with high-grade tumors. Adequate lymphadenectomy was done by removing ten or more LN in 285 (84%) of 340 patients. One sentinel lymph node at least was identified by mapping in 293 (86%) of 340 patients. (3) In our study 50 sentinel lymph nodes were mapped, from these 50 specimens about 23 lymph nodes were removed from the left side and 27 were removed from the right side. About 20 external iliac lymph nodes were removed (40%), 15 obturator lymph nodes were removed (30%), about 10 Para aortic lymph nodes were removed (10%) and about 5 common iliac and internal iliac lymph nodes were removed (5%). Rossi, et al. Also concluded that 888 sentinel lymph nodes were mapped and about 415 sentinel lymph node specimens were removed from the left side and 472 from the right side. 1098 sentinel lymph nodes were identified within these 888 specimens by pathology. Surgeons identified sentinel lymph node in the following locations in order : external iliac (335 [38%] of 888, obturator (218 [25%]), inframesenteric para-aortic (128 [14%]), common iliac (68 [8%]), internal iliac (92 [10%]), presacral (26 [3%]), infrarenal para-aortic (11 [1%]), and other (including parametrium (10 [1%])). (3) Brügger et al. found in 2018 that SLN detection rate was 61% bilaterally and 86% on at least hemi pelvis, and they secure 26 pelvic and para aortic lymph nodes using SLN dissection. Brügger et al. concluded that the SLN reduced the radical lymphadenectomy by 50% in patients with "higher than low risk" endometrial cancer. (8) In 2011 a study by Khoury-Colladoa, et al verified that after mapping of SLN by cervical injection, metastatic LNs detection rate increased by three

times that without it, so they recommended the SLN approach (4)

This was compatible with the results of two trials by Abu-Rustum. et al in 2008 and Barlin et al. in 2012 where the removal of 10 or more nodes appeared to help in the accurate staging of the disease and impact survival in the selected patients. (9,10) And this agreed with a study in 2018 by Geppert et al that found that SLN-mapped cases had a higher frequency of lymph node metastasis that included both pelvic only (p b 0.001) and pelvic and aortic metastasis (p = 0.062). In total, 36 (30.3%) of SLN-mapped cases had at least one lymph node metastasis compared to 97 (14.7%) of non-mapped cases (p b 0.001). The SLN approach correctly identified metastasis in 35 (97.2%) of 36 node-positive cases and failed to identify one node-positive case (sensitivity=97.2%). The false negative rate for SLN detection of metastasis was 1/36 (2.8%). The one false negative SLN resulted from bisecting a fusiform (3 × 1 cm) lymph node and including only the portion with dye uptake as "sentinel" in a patient whose mapping was successful bilaterally. (11) Suidan et al compared in 2018 the three lymphadenectomy strategies in women undergoing minimally invasive surgery for low risk EC, and they found that the selective lymphadenectomy was less costly and more effective than routine lymphadenectomy. In addition, they concluded that the SLN mapping has the highest quality adjusted survival and lowest cost making it the most cost effective strategy in the management of low risk EC. (12) Our results prove that SLN biopsy has relatively equal values like lymphadenectomy in staging of endometrial cancer with sensitivity 80% and specificity 90%. Sentinel mapping had good sensitivity and specificity diagnostic potentials. In 2017 Rossi et al found that the sentinel lymph node technique to identify nodal metastatic disease was sensitive by 97.2% (95% CI 85.0–100; McNemar's p=1). Among the 258 patients with negative sentinel lymph node results, 257 had truly negative non-sentinel lymph nodes, resulting in a negative predictive value of 99.6% (95% CI 97.9–100). In a post-hoc analysis, pathologically identified sentinel lymph node specimens were significantly more likely to contain metastatic disease than non-sentinel lymph node specimens (58 [5%] of 1098 vs 63 [1%] of 5416, p=0.0001. (3) The weak point of our study is that the use of methylene blue is associated with reduced accuracy compared to other markers that been used as (isotopic detection or indocyanine green) but they are not accessible in our medical corporation and they are too costly in our country. Also, the sample size of each group is small, which is another weak point

## CONCLUSION

The procedure is a minimal invasive technique that plays a potential role in improving the quality of life and the possibility to decrease the surgical complication to patients. Using the methylene blue for the procedure represents a good simple with a low cost option that could be a benefit in our country but it also has a less detection rate.

The algorithm that had been used for SLN mapping should be followed to achieve the adequate results through increasing sensitivity and the detection rate of metastasis. SLN mapping plays a role in the staging of cases of early stages of endometrial cancer.

**Conflict of Interest: No**

**Financial Disclosure: No**

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