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The role of sentinel lymphadenectomy in the management of Endometrial Cancer

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Abstract

Back ground: Endometrial cancer is counted to be the most common gynecological malignancy and it is usually diagnosed at the early stages of the disease .Cancer staging main target is to help clinicians in making the decision for best management of cases and to guide treatment plan. Surgical staging includes; hysterectomy, bilateral salpingo-oophorectomy, and estimation of regional LN involvement, specifically the pelvic and aortic lymph node. Some instructed that lymphadenectomy clarifies 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 with fewer traumas has considerable appeal.

The aim of this study: was to assess the accuracy of sentinel lymphadenectomy in the staging of endometrial cancer.

Methodology: 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 56ys (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). 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 shown in our study there is no statistically significant difference between both groups regarding BMI, age, clinical and family history. 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 it is usually diagnosed at the early stages of the disease**.** It is represented by irregular uterine bleeding in about 90% of patients (usually during menopause), sometimes accompanied by vaginal discharge and pyometra. About 10% of patients will have metastasis in the pelvic lymph nodes (LN) in spite of favorable tumor characteristics **[1].** the International Federation of Gynecology and Obstetrics (FIGO) surgical system had staged endometrial cancer, but accurate diagnosis of of gynecologic malignancies status is important for better treatment planning and outcome **[2].** According to a recent Classification and Regression Tree (CART) analysis, surgical staging, but not the total number of lymph nodes excised, was found to be the most important prognostic factor for overall survival in endometrial cancer **[3].**

Treatment algorithms that do not include surgical staging depend upon an increased use of external beam radiation that is linked with higher morbidity. On the other hand pathological assessment of lymph nodes is important in determining adjuvant therapies **[4].** Surgical staging of endometrial cancer include: hysterectomy, bilateral salpingo-oophorectomy, and assessment of regional LN involvement, specifically the pelvic and aortic lymph node. Some suggested that lymphadenectomy defines the recurrence risk and helps clinicians make the decision to give adjuvant treatment to high-risk patients, and some said, complete pelvic and para-aortic lymphadenectomy itself is linked with major comorbidities .The decision of LN dissection, and to what extent has been one of the most debatable areas in the management of endometrial cancer **[5]**

Sentinel lymph node is the first node that receive lymphatic drainage from the

primary tumor and pathological status of SLN should then reveal the overall status of whole lymphatic basin **[6]**

Less extensive LN excision and less surgical trauma are the benefits of the sentinel lymph node (SLN) approach, also the potential for improving the sensitivity of detecting the metastases of LN. The SLN procedure is well recognized in the surgical treatment of breast cancer and malignant melanoma. To this point
, SLN mapping in gynecological oncology has been most frequently used for vulvar cancer. However, there is a concern to develop SLN approaches in uterine cancer,specially endometrial cancer where LN mapping might be viewed only as a staging procedure that allows proper triage of patients for adjuvant therapy [**7,8].**

Aim of the study

The aim of the study was to assess the accuracy of sentinel lymphadenectomy in the staging of endometrial cancer

Patients and Methods

Written informed consent was obtained from all participants, the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University. Sample size was calculated by open EPI to be 30 cases with confidence level 95% and power of test 80%. This cross sectional study was conducted between September2018 till April 2020 in obstetrics and gynecology surgery department in Zagazig university. Egypt. **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 under gone 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 5mL 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 under gone 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 histopathological 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 ± 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** the mean age of patients was 55 years (range 45-74) for group 1 and was 56ys (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).this is shown in **Table 2**. Also table 3 showed that (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 shown in our study there is no statistically significant difference between both groups regarding BMI, age, clinical and family history.

Table (1): Demographic 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)

**** Mann Whitney U test, P < 0.05 is significant, NS: Not significant.***

Table (2): Clinical data of the studied groups

Item	*Group 1 (N=15)*	*Group 2 (N=15)*	*P- value*
BMI			
Mean ± SD	***33.4± 7.973***	***32.8 ± 6.8***	***0.541***
Median (Range)	***35 (26-45)***	***34 (28-50)***	***(NS)***
Parity			
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.***

Table 3: Comparison between the two studied groups according to clinical history among studied patients:

Item	group 1		group 2		Total		$\chi 2$	pvalue
	No	%	No	%	No	%		
			Medical History					
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%		
			Family History for breast or endometrial cancer					
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%		

X2: chi-square test, P-value > 0.05 is non-significant

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. 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 group1 and 6 for group 2) on the other hand Myometrial invasion was more that 50% in about 7 patients (3 for group 1 and 4 for group 2). While Postoperative pathological report is shown in **Table 4 and 5.**

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 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.

Table 4: Comparison between the two studied groups according to pre and post-operative pathology grading.

Grading	**Group1**				**Goup2**				**p-value**	**p-value**
	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.

Table 5: Comparison between the two studied groups according to Myometrial invasion and tumor size

Item	Group 1		Group 2		χ^2	p-value
	No	%	No	%		
Myometrial invasion						
No	8	53.3%	8	53.3%		
Superficial	4	26.7%	3	20.0%	0.28	0.866
Deep	3	20.0%	4	26.7%		
Tumor size						
>2 cm	5	33.3%	6	40.0%	0.14	0.704
<2cm	10	66.7%	9	60.0%		

X2: chi-square test p-value > 0.05 is non-significant

50 sentinel lymph nodes were mapped, from theses 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%).This is shown in **Tables 6.**

Regarding our study intra and post-operative complications in the studied groups were found as: Lymphocyst in one case in group 1 and in only one case in group 2. Fever more than 38°C was documented in two cases in group 1 and in one case in group 2. two cases of postoperative hip pain and limitation of movement in group 1 and this was attributed to faulty or prolonged positioning during operation

and 2 cases in each group developed lower limb numbness . Blood transfusion was needed for only 1 case in group 1 due to preoperative anemia and for 1 case in group 2. About 3 cases needed to be admitted to ICU (2cases in group 1 and 1 case in group 2) **Table 7.**

Table 6: 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

Table7: Intra and post-operative complications among both groups

Complications	Group 1	Group 2	p- value	Sig.
Intraoperative				
Bowel injury	0 (0.0%)	0 (0.0%)	---	
Bladder injury	0 (0.0%)	0(0.0%)	----	
Vascular injury	0 (0.0%)	0 (0.0%)	----	
Transfusion	1 (6.7%)	1 (6.7%)	1.000	NS
Postoperative				
ICU admission	2 (13.4)	1 (6.7)	0.542	NS
Haemorrhage	0(0.0%)	0(0.0%)	----	
Fever	2 (13.4%)	1 (6.7%)	0.542	NS
Lymphocyst	1(6.7%)	1 (6.7%)	1.000	NS
Locomotor (hip pain)	2 (13.4%)	1 (6.7%)	0.542	NS
Lower limb numbness	2 (13.4)	2 (13.4)	1.00	NS

X2: chi-square test, p-value > 0.05 is non-significant

Table 8 shows that the time of operation it was ranging from (90 to 160) minute in group 1 with a mean of about (116.6 min).while, In group 2 the time of operation was ranging from (85-160 min) giving a mean of about (112.6min). The time needed for lymphadenectomy was ranging from (30-75 min) while in group 1 it was ranging from (30-80 min) showing that there is no significant difference between the two studied groups. Despite that, there is a significant different between the time used for sentinel and total lymphadenectomy to the studied group 2 which is more cost effective.

Table (8): Operative details in the study groups:

	Group A (n =15)		**Group B (n=15)**		**P-value**	**significance**
	Mean ±SD	**Range**	**Mean ±SD**	**Range**		
Time Operation	116.6 ± 20.7	(90-160)	112.6 ± 32	(85-160)	0.688	**NS**
Time of lymphadenectomy (min)	46.6 ± 12.4	(30-75)	49 ± 12.5	(30-80)	0.228	**NS**
Time needed for SLN biopsy	--	---	31± 7.6	(20-40)	---	**--**
Total Bl.loss (ml)	178.6 ± 38.1	(100-250)	190.6 ± 46.5	(150-300)	0.446	**NS**
Bl. Loss for lymphadenectomy (ml)	84.6 ± 51.2	(20-150)	72 ± 42.7	(50-150)	0.469	**NS**

	Time of lymphad-enectomy (min) (n =15)		**Time needed for SLN biopsy (n=15)**		**P-value**	**Significance**
	Mean ±SD	**Range**	**Mean ±SD**	**Range**		
Group B	49 ± 12.5	(25-80)	31 ± 7.6	(20-40)	0.01	**HS**

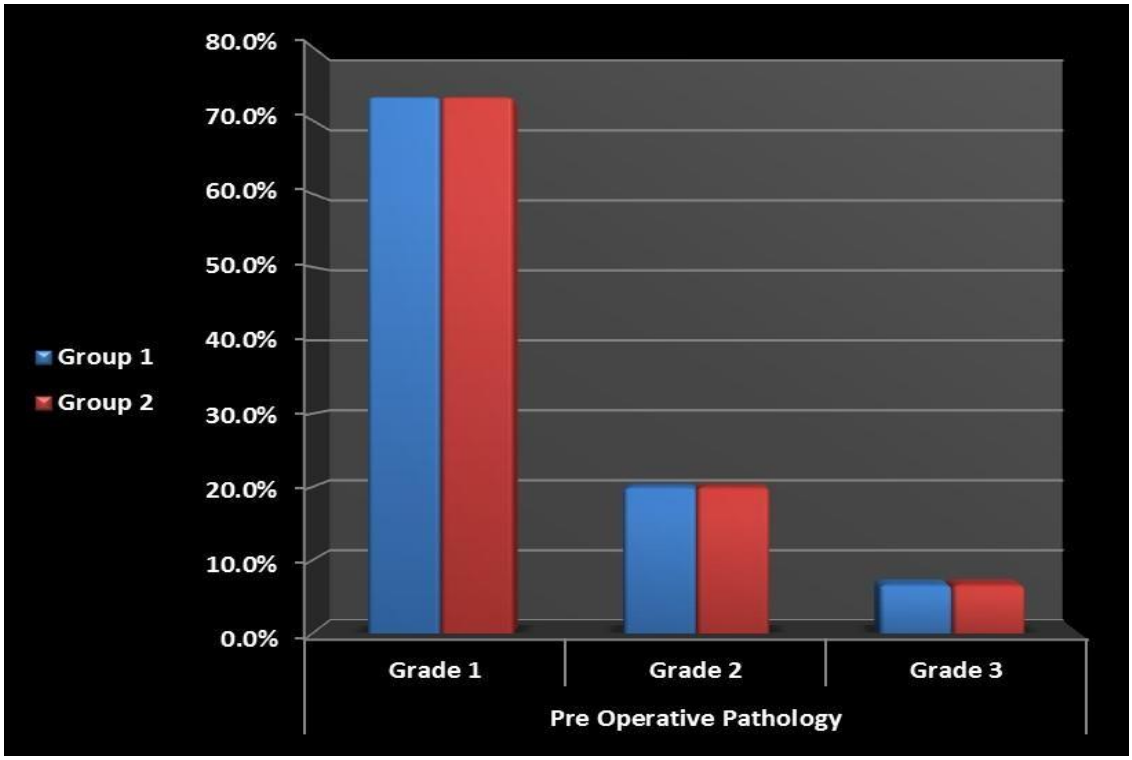

Figure 1: Comparison between the two studied groups according to pre-operative of Pathology

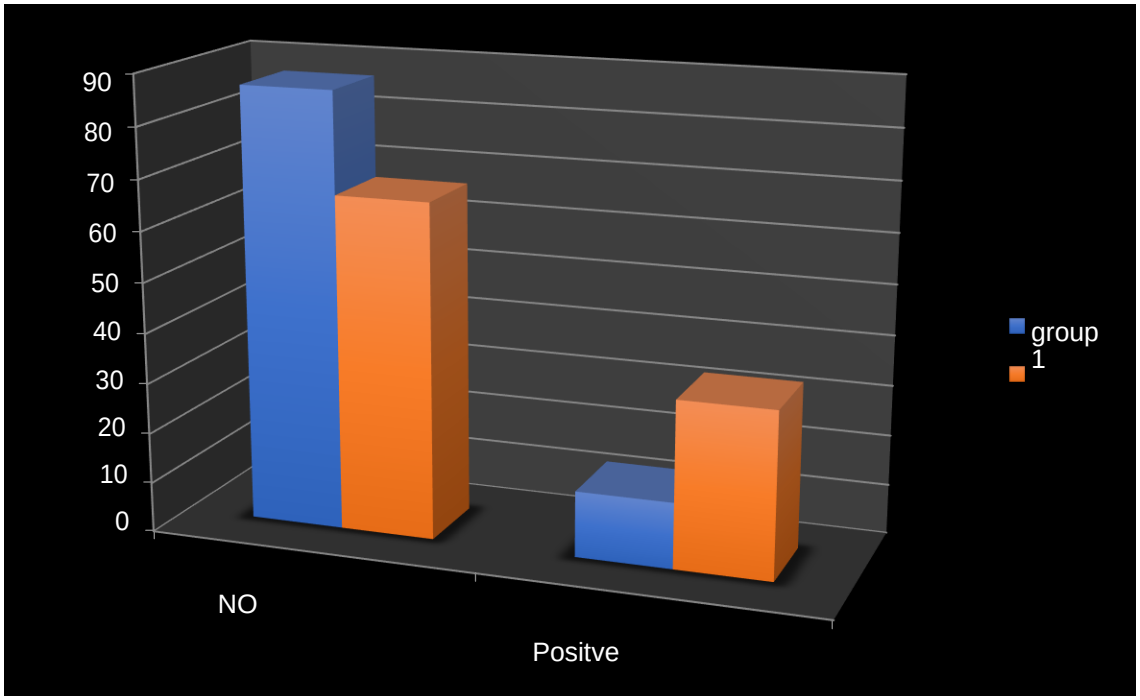

Figure (2): Comparison between the two studied groups according to nodal involvement

Discussion

This study included 30 patients who attended to Zagazig university hospital and had been diagnosed with endometrial cancer, and patients were divided in to 2 equal groups (15 patients for each group) where group1 had no mapping of nodes while group2 had undergone mapping of lymph node.

the patients had several risk factors that led them to develop endometrial cancer as the mean age of patients was 55 years (range 45-74) for group 1 and was 56ys (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). 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 shown in our study there is no statistically significant difference between both groups regarding BMI, age, clinical and family history.

This was compatible with a study Rossi et al between Aug 1, 2012, and Oct 20, 2015, 385 patients were enrolled shows the interventions for all patients. The median age of patients was 63 years (range 29–83). The mean body-mass index of patients was 33·4 kg/m2 (SD 7·9; range 17·8–60·5**.**

Also in 2010 Dossus et al. concluded that reproductive factors associated with higher exposure to estrogens not opposed by progesterone, such as null parity, low parity and longer (OC use-free) menstrual life span, are related with an increased risk of endometrial cancer.

As shown in our study 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 group1 and 6 for group 2 on the other hand Myometrial invasion was more that 50% in about 7 patients (3 for group 1 and 4 for group 2).

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 sensitivity of the sentinel lymph node technique to identify nodal metastatic disease was 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.

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 Russi et al 2017 in a study of the surgical staging outcomes and sentinellymph-node mapping outcomes for the 340 assessable patients in 2017 were Pelvic lymphadenectomy was done in all patients. Para-aortic dissection was done in 74 (74%) of 100 patients with high-grade tumors. Removal of ten or more lymph nodes (adequate lymphadenectomy) was done in 285 (84%) of 340 patients. Mapping identified at least one sentinel lymph node in 293 (86%) of 340 patients. Two of three patients with a mapped isolated para-aortic sentinel lymph node had metastatic disease identified in this lymph node but were otherwise pelvic node negative.

In our study 50 sentinel lymph nodes were mapped, from theses 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%).

Brugger et al. found in 2018 that the detection rate of the SLN was 61% bilaterally and 86% on at least hemi pelvis, and they spared 26 pelvic and para aortic lymph nodes using SLN dissection. Brugger et al. concluded that the SLN reduced the radical lymphadenectomy by 50% in patients with "higher than low risk" endometrial cancer**.**

This was compatible with the results of two trials by Abu-Rustum. et al in 2008 and Barlin et al.in 2012 in which the removal of 10 or more nodes appeared to assign patients to the correct surgical stage and influence survival in the selected patients**.)**

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 procedure 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.

Regarding our study intra and post-operative complications in the studied groups were found as: Lymphocyst in one case in group 1 and in only one case in group 2. Fever more than 38°C was documented in two cases in group 1 and in one case in group 2. two cases of postoperative hip pain and limitation of movement in group 1 and this was attributed to faulty or prolonged positioning during operation and 2 cases in each group developed lower limb numbness . Blood transfusion was needed for only 1 case in group 1 due to preoperative anemia and for 1 case in group 2. About 3 cases needed to be admitted to ICU (2cases in group 1 and 1 case in group 2).

This agreed with Ma et al who founded in 2018 that infected lymphocysts were more frequently in patients with combined pelvic and para-aortic lymphadenectomy and higher number of resected pelvic lymph nodes. **.**

A prospective study in 2018 was conducted by Geppert et al., evaluating the lymphatic complications in women with EC undergoing SLN biopsy versus full

lymphadenectomy. They concluded that the absence of intraoperative complications and the low risk of lymphatic complications support implementing SLN biopsy in low risk EC patients.

Regarding time of operation it was ranging from (90 to 160) minute in group 1 with a mean of about (116.6 min).while, In group 2 the time of operation was ranging from (85-160 min) giving a mean of about (112.6min). The time needed for lymphadenectomy was ranging from (30-75 min) while in group 1 it was ranging from (30-80 min) showing that there is no significant difference between the two studied groups. Despite that, there is a significant different between the time used for sentinel and total lymphadenectomy to the studied group 2 which is more cost effective.

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.

Our Study showed that Sentinel lymphadenectomy decrease the number of lymph nodes needed to be removed thus decreasing the patient's morbidities caused by total lymphadenectomy. This came in harmony with the recommendations of the Society of Gynecologic Oncology that recommended SLN mapping into the surgical staging of ECs to reduce the morbidities associated with systemic lymphadenectomy.

In 2019 Abdelazim et al reviewed an article and concluded that the SLNs mapping is an accurate alternative to systemic lymphadenectomy for determining the nodal spread in early stage ECs and its cost‑effective strategy in the management of low risk EC.

SLN mapping allows upstaging in low or intermediate risk ECs in whom adjuvant therapy could be omitted. Women with ECs staged with SLNs were more likely to receive adjuvant treatment compared with women staged with systemic lymphadenectomy. Decreased lymphatic complications and operative time strongly

motivate the SLN biopsy concept in high risk ECs.

Conclusion

SLN mapping plays a role in the staging of cases of early stages of endometrial cancer. The technique is a minimal invasive one that plays a potential role in decreasing 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 weakness 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 available 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.

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