

# Comparative Study Between Superficial and Deep Myometrial Invasion in Endometrial Cancer Type 1 in Relation to Regional Lymph Nodes Metastasis

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## ABSTRACT

**Background & Objective:** The present study compares between superficial and deep myometrial invasion in type 1 endometrial cancer in relation to regional lymph nodes metastasis, so we can answer the question to do or not do lymphadenectomy, this life-threatening procedure in both superficial and deep myometrial invasion with type 1, clinically and radiologically stage 1 endometrial cancer.

**Materials & Methods:** Patients were divided into 2 groups distributed as follows: group I includes 50 patients type 1 endometrial cancer with superficial myometrial invasion and group II includes 50 patients type 1 endometrial cancer with deep myometrial invasion. Total abdominal hysterectomy with bilateral salpingo-oophorectomy with pelvic and lower para-aortic lymphadenectomy to all patients included in the study from both groups. Histopathological examinations were done to all the specimen from both groups to confirm diagnosis of type 1 endometrial cancer, depth of myometrial invasion, pathological grading and metastasis to the regional lymph nodes.

**Results:** Considering regional lymph nodes metastasis in both groups, there is a statistical difference between group I and group II in relation to regional lymph nodes metastasis as group II (cases with deep myometrial invasion) are associated with more regional lymph nodes metastasis ( $P= 0.0001$ ).

**Conclusion:** Deep myometrial invasion in type 1 endometrial cancer is associated with significant increase in regional lymph nodes metastases.

**Keywords:** Endometrioid adenocarcinoma, Deep myometrial invasion, Regional lymph nodes metastases, Lymphadenectomy



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## Introduction

Endometrial cancer is the most common genital tract cancer ranking the 6th most commonly occurring cancer in female (1). Moreover, it is the fourth cause of death due to genital tract cancer in developed countries (2). Pathologically, it is divided into 2 types, type 1 includes endometrioid adenocarcinoma grade 1 and grade 2, while type 2 includes endometrioid grade 3 and non-endometrioid types like serous adenocarcinoma, clear cell adenocarcinoma, carcinosarcoma and undifferentiated types (3, 4). considering management of endometrial cancer, there is a world wide dilemma especially in the matter of to do or not to do lymphadenectomy and in many parts of the world there is no guide line that specifies the extent of surgery especially in type 1, FIGO (The International Federation of Gynecology and Obstetrics) stage 1 endometrial cancer (5). Regarding type 2 there is a general agreement that regional lymphadenectomy that includes pelvic and para-aortic lymph nodes till the level of inferior mesenteric artery at least for proper FIGO staging should be done (6). Regional lymphadenectomy in type 1, clinically and

radiologically stage 1 endometrial cancer is still matter of controversy (7). Microscopic metastasis of the regional lymph nodes can greatly affect the prognosis and the 5 years survival if not removed during primary surgery, so complete surgical staging and extensive lymphadenectomy may have therapeutic and not only diagnostic role in stage 1 type 1 endometrial cancer (8). But lymphadenectomy, especially the extensive one, may have great hazards as great vessel injuries which is a life-threatening condition or remote complications such as lymphedema, deep veins thrombosis and paralytic ileus due to autonomic nerve injuries (9). Many articles deny the benefit of regional lymphadenectomy in stage 1 type 1 endometrial cancer (10). But other studies such as Abu-Rustum *et al.*, proved the benefit of lymphadenectomy in stage 1 type 1 endometrial cancer especially in deep myometrial invasion (11). The present study compares the superficial and deep myometrial invasions in type 1 endometrial cancer in relation to regional lymph nodes metastasis, so we can answer the question whether or not to do regional lymphadenectomy, this life-

threatening procedure in both superficial and deep myometrial invasion with type 1, clinically and radiologically stage 1 endometrial cancer. The aim of the study is to compare between superficial and deep myometrial invasion in endometrial adenocarcinoma type 1 in relation to regional lymph node metastasis.

## Methods

An analytical observational comparative cross-sectional study was managed on 100 endometrial adenocarcinoma type 1 patients recruited from the gynecology-oncology unit at Al Shatby university hospital after taking a written consent and following approval by the Alexandria medical school institutional ethics committee. Patients were divided into 2 groups distributed as follows: group I included 50 patients of type 1 endometrial cancer with superficial myometrial invasion diagnosed by vaginal ultrasound and confirmed later by histopathological examination of the hysterectomy specimen, and group II included 50 patients of type 1 endometrial cancer with deep myometrial invasion diagnosed by vaginal ultrasound and confirmed later by histopathological examination of the hysterectomy specimen. Inclusion criteria was cases with endometrial carcinoma type 1 which had endometrioid adenocarcinoma grade 1 and 2 proved on histopathological examination after endometrial biopsy sampling. Exclusion criteria were all cases unfit medically for major surgery, grade 2 and 3 obesity with body mass index more than 34 and advanced stage as stage 3b with parametrial invasion and stage 4 diagnosed clinically and radiologically. All cases from both groups were subjected to CT scan of abdomen, pelvis and chest for radiological staging to exclude advanced stage cases as stage 4B whom were excluded from the study; and MRI to exclude cases with locally advanced stages as 3B and 4A in the presence of suspicious parametrial, bladder and rectal invasion by clinical examination and vaginal ultrasound scanning. Total abdominal hysterectomy with bilateral salpingo-oophorectomy with pelvic and lower para-aortic lymphadenectomy was done to all patients included in the study from both groups. Histopathological examinations were done on all the specimens from both groups to confirm the diagnosis of type 1 endometrial cancer, pathological grading and depth of myometrial invasion and metastasis to the regional lymph nodes. Data of regional lymph node metastasis, its anatomical types in both groups, endometrial cancer grades, depth of myometrial invasion and all other data were gathered, coded, tabulated, and statistically investigated using IBM SPSS statistics (Statistical Package for Social Sciences) software (version 24.0, IBM Corp., Chicago, USA). Descriptive statistics were done for qualitative data as number and percentage.

Inferential analyses for independent variables were done using the Chi square test for differences between proportions and Fisher's exact test for variables with small, expected number.

The level of significance was taken at *P*. value < 0.05 as statistically significant, otherwise it was non-significant.

## Justification of the sample

The sample size should depend on the research context, including the researchers aim and proposed analyses.

The following formula was used to estimate the number of the sample size of cases needed in this study;

$$n = \frac{Z^2 P (1 - P)}{d^2}$$

Where *n* is the sample size, *Z* is the statistic correspondent to level of confidence, *P* is expected prevalence, and *d* is precision (corresponding to effect size). The level of confidence was 95%. By using this equation, the number of the cases in the sample size was 50 cases in each group (i.e., 100 cases in the two groups).

## Results

Regarding demographic data of group I (superficial myometrial invasion or no invasion) showed the following results: age of the cases ranged from 55 y to 75 y with a mean value of 66.82 y, body mass index ranged (BMI) from 28 to 34 with a mean value of 31.4, gravidity ranged from 1 to 5 with mean 2.48, and parity ranged from 0 to 4 with a mean value of 1.46; while in group II (deep myometrial invasion group) age ranged from 54 y to 73 with a mean value of 64.44, BMI ranged from 27 to 34 with a mean value of 32.04, gravidity ranged from 0 to 4 with a mean value of 1.86, and parity ranged from 0 to 3 with a mean value of 1.22. There was a statistical significance difference regarding age and gravidity between both groups as the mean of both parameters was higher in group I while there was no significant statistical difference regarding BMI and parity taking into consideration that BMI should not be more than 34 as one of the exclusion criteria was to be more than that ([Table 1](#)). Histopathological examination of the hysterectomy specimen of group I patients confirmed the presence of superficial myometrial invasion and showed that 37 out of 50 patients in this group were grade 1 endometrioid adenocarcinoma and 13 cases were grade 2 endometrioid adenocarcinoma. Regarding group II patients, histopathological examination confirmed the presence of deep myometrial invasion and showed that 19 out of 50 patients were grade 1 and 31 cases were grade 2. There was a statistical significance difference between grade 1 and 2 in both groups in relation to depth of myometrial invasion as grade 2 cases in both groups were associated with deep myometrial invasion than in grade 1 cases in both groups (*P*= 0.00028) ([Table 2](#)). Regarding number of lymph nodes resected in both groups, group I showed the following; the right pelvic lymph nodes ranged from 5 to 13 with mean 9.84, left pelvic ranged from 5 to 13 with mean 9.8, the

total pelvic ranged from 12 to 25 with mean of 19.64, and lower para aortic ranged from 3 to 8 with mean of 5.38; while group II showed the following; the right pelvic ranged from 6 to 13 with mean 10.8, the left pelvic ranged from 7 to 13 with mean 10.4, the total pelvic ranged from 17 to 24 with mean 21.2, and lower para aortic ranged from 3 to 8 with mean 5.7. There

was a significant statistical difference between both groups in relation to the number of lymph nodes resected in the right, left and total pelvic as the mean were higher in group II while there was no statistically significant difference between both groups regarding lower para-aortic lymph nodes (Table 3).

**Table 1.** Comparison between the two studied groups regarding basic demographic data

	Group I	Group II	P. value
<b>Age</b>			
Range	55-75	54-73	
Mean	66.82	63.44	0.001*
SD	5.393	4.841	
<b>BMI</b>			
Range	28-34	28-35	
Mean	31.42	32.04	0.065 N.S.
SD	1.617	1.616	
<b>Gravidity</b>			
Range	1-5	0-4	
Mean	2.48	1.86	0.011*
SD	1.054	0.881	
<b>Parity</b>			
Range	0-4	0-3	
Mean	1.46	1.22	0.098 N.S.
SD	0.930	0.910	

**Table 2.** Comparison between the two studied groups (myometrial invasion <50% or ≥50.0%) regarding the grade of endometroid adenocarcinoma.

Pathological grading	Group I		Group II	
	myometrial invasion		myometrial invasion	
	(Less than 50 %)		(Equal or more than 50%)	
	"n=50"		"n=50"	
	No.	%	No.	%
Grade 1 endometroid adenocarcinoma	37	74.0	19	38.0
Grade 2 endometroid adenocarcinoma	13	26.0	31	62.0
X <sup>2</sup>	13.14			
P value	0.00028*			

X<sup>2</sup>= Chi square test  
P was significant if ≤ 0.05  
\* Significant difference

**Table 3.** Comparison between the two studied groups regarding numbers of lymph nodes resected

	Group I	Group II	P value
<b>Right pelvic nodes</b>			
Range	5-13	6-13	
Mean	9.84	10.8	0.016*
SD	2.235	1.485	

	Group I	Group II	P value
<b>SD</b>			
<b>Left pelvic nodes</b>			
Range	5-13	7-13	
Mean	9.8	10.4	0.038*
SD	1.884	1.443	
<b>Total pelvic lymph nodes</b>			
Range	12-25	17-24	
Mean	19.64	21.2	0.011*
SD	3.13	1.69	
<b>Lower paraaortic nodes</b>			
Range	3-8	3-8	
Mean	5.38	5.7	0.114 N.S.
SD	1.398	1.233	

Considering regional lymph nodes metastasis in both groups, group I showed 7 cases with regional lymph nodes secondaries, 2 cases of them were grade 1 and 5 were grade 2 in comparison to group II that showed 28 cases with regional lymph nodes secondaries distributed as follows: 9 cases were grade 1 and 19 were grade 2. There was a statistical difference between group I and group II in relation to regional lymph nodes metastasis as group II (Cases with deep myometrial invasion) were associated with

more regional lymph nodes metastasis ( $P = 0.0001$ ) (Table 4 and Figure 1). In relation to grading in the same group and regional lymph nodes metastasis, there was a statistically significant difference between grade 1 and grade 2 cases and lymph nodes metastasis in group I patients ( $P = 0.0032$ ) while there was no statistically significant difference between grade 1 and grade 2 cases and lymph nodes metastasis in group II ( $P = 0.33$ ) (Table 5, Figure 2).

**Table 4.** Comparison between the two studied groups regarding regional lymph nodes metastasis

Regional lymph node metastasis	Group I		Group II		X <sup>2</sup> P value
	Myometrial invasion (Less than 50 %)		myometrial invasion (Equal or more than 50%)		
	No.	%	No.	%	
Negative	43	86.0	22	44.0	19.4
Positive	7	14.0	28	56.0	0.0001*
<b>Total</b>	50		50		

**Table 5.** Comparison between the two studied groups (myometrial invasion <50% or ≥50.0%) regarding regional lymph nodes metastasis findings and pathological grading

Regional lymph node metastasis	Group I				Group II			
	Myometrial invasion (Less than 50 %)				myometrial invasion (Equal or more than 50%)			
	Grade 1		Grade 2		Grade 1		Grade 2	
	No.	%	No.	%	No.	%	No.	%
Negative	35	94.59	8	61.54	10	52.63	12	38.71
Positive	2	5.41	5	38.46	9	47.37	19	61.29
<b>Total</b>	37		13		19		31	
X <sup>2</sup> -1	8.73				0.926			

Regional lymph node metastasis	Group I Myometrial invasion (Less than 50 %)				Group II myometrial invasion (Equal or more than 50%)			
	Grade 1		Grade 2		Grade 1		Grade 2	
	No.	%	No.	%	No.	%	No.	%
P value	0.0032*				0.33 N.S.			
X <sup>2</sup> -2					14.00		4.02	
P value					0.00018*		0.02*	

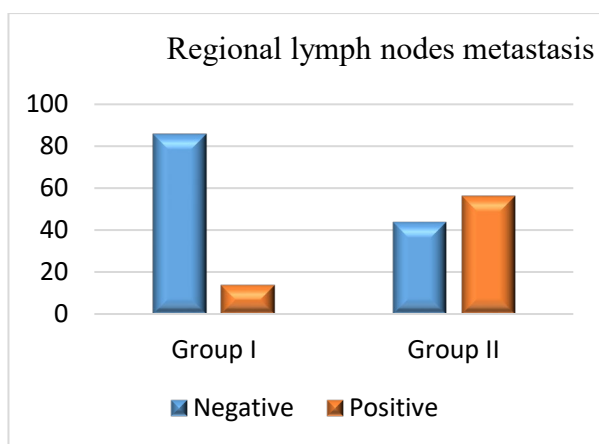
X<sup>2</sup>-1 = Chi square to compare between the grade 1 and 2 in the same group.

X<sup>2</sup>-2 = Chi square to compare between grade 1 in both groups I and II, and grade 2 in group I and II.

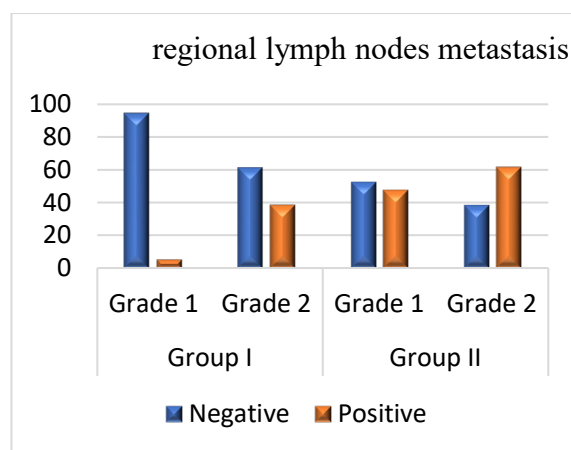
P was significant if  $\leq 0.05$

\* Significant difference

N.S. = Not significant



**Figure 1.** Comparison between the two studied groups regarding regional lymph nodes metastasis



**Figure 2.** Comparison between the two studied groups (myometrial invasion  $<50\%$  or  $\geq 50.0\%$ ) regarding regional lymph node metastasis findings and pathological grading

Comparison between the two studied groups regarding regional lymph node metastasis showed that there was a significant increase in positive cases in group II more than group I. This last finding is denoting the importance of deep myometrial invasion than pathological grading as a causative factor for regional lymph nodes metastasis. In comparison of grading in both group and regional lymph nodes metastasis, there was a significant statistical increase between grade 1 cases with regional lymph nodes metastasis in group II than in grade 1 cases with regional lymph nodes metastasis in group I ( $P = 0.00018$ ). The same finding was present between grade 2 with regional lymph nodes metastasis in both group as grade 2 is associated with more regional lymph nodes metastasis in group II than in group I ( $P = 0.02$ ) (Table 3, Figure 2). This finding again is denoting the importance of deep myometrial invasion than pathological grading as a causative factor for regional lymph nodes metastasis. In relation to type of metastatic lymph nodes whether pelvic or para-aortic and depth of myometrial invasion, group I patients showed 6 cases with pelvic lymph nodes metastasis and 1 case with positive para-aortic

lymph node metastasis, while group II showed 21 cases with pelvic lymph nodes metastasis and 7 case with positive para-aortic lymph node metastasis. There was a significant statistical difference between both groups in relation to lower paraaortic lymph nodes metastasis as group II is associated with lower paraaortic lymph nodes metastasis than group I ( $P=0.027$ ) while in relation to pelvic lymph nodes metastasis, there was a significant increase in group II ( $P = 0.007$ ) (Table 6, Figure 3). Considering grading and types of lymph node metastasis, there was no significant statistical difference between grade 1 and grade 2 in group I and types of lymph nodes metastasis ( $P = 0.981$ ). Again, there was no significant statistical difference between grade 1 and grade 2 in group II and types of lymph nodes metastasis ( $P = 0.825$ ) (Table 5, Figure 4). As regards grading in both groups and types of regional lymph nodes metastasis, there was no significant difference between grade 1 in both groups and grade 2 in both groups and types of regional lymph nodes metastasis whether pelvic or para-aortic ( $P=0.425$ ,  $P=0.882$  respectively) (Table 7, Figure 4).

**Table 6.** Comparison between the two studied groups in relation to the site of positive regional lymph nodes metastasis

Site of lymph node	Group I Myometrial invasion (Less than 50 %)		Group II myometrial invasion (Equal or more than 50%)		X <sup>2</sup> P value
	No.	%	No.	%	
	Pelvic lymph nodes	6	12.0	21	
Lower paraaortic nodes	1	2.0	7	14.0	4.82 0.027*
<b>Total</b>	50		50		

**Table 7.** Comparison between positive cases regional lymph nodes metastasis in the two studied groups regarding to their position

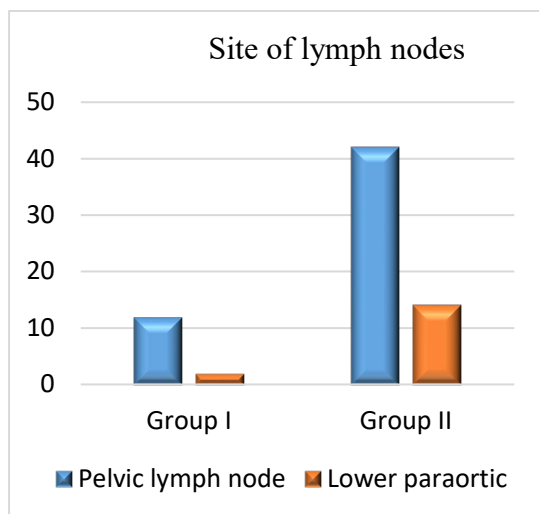
Positive regional lymph node metastasis	Group I myometrial invasion (Less than 50 %)				Group II myometrial invasion (Equal or more than 50%)			
	Grade 1		Grade 2		Grade 1		Grade 2	
	No.	%	No.	%	No.	%	No.	%
Pelvic lymph nodes	2	100.0	4	80.0	7	77.8	14	73.68
Lower paraaortic nodes	0	0.0	1	20.0	2	22.2	5	26.32
<b>Total</b>		2		5		9		19
<b>Fisher exact test-1</b>								
P value	0.981 N.S.				0.825 N.S.			
<b>Fisher exact test-2</b>								
P value					0.425 N.S.		0.882 N.S.	

Fisher exact test -1 = compare between the grade 1 and 2 in the same group.

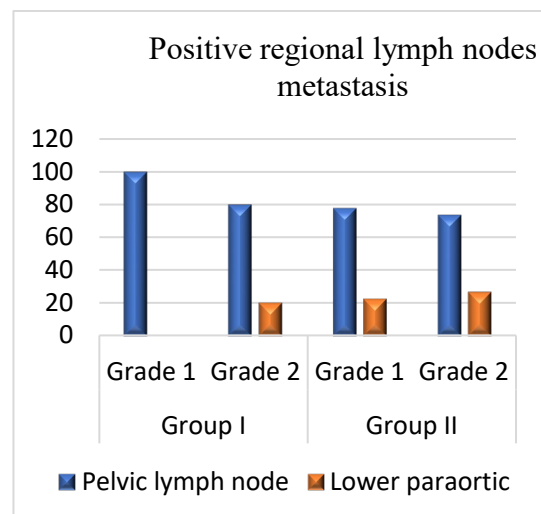
Fisher exact test-2 = compare between grade 1 in both groups I and II, and grade 2 in group I and II.

P was significant if ≤ 0.05

N.S. = Not significant



**Figure 3.** Comparison between the two studied groups in relation to the site of positive regional lymph nodes metastasis



**Figure 4.** Comparison between positive cases regional lymph nodes metastasis in the two studied groups regarding to their position



## Discussion

Endometrial cancer is the most common genital tract malignancy and its type 1 which includes endometrioid adenocarcinoma grade 1 and 2, is the most frequent type (12). The extent of surgery in type 1, clinically and radiologically stage 1A endometrial cancer varies in different countries in relation to regional lymphadenectomy (13). This controversy is to prevent life-threatening complications of lymphadenectomy as great vessels injuries (14). But on the other hand, leaving a metastatic regional lymph node may greatly affect the prognosis and the 5 years survival of the case (15). So to answer the question to do or not to do regional lymphadenectomy type 1, clinically and radiologically stage 1A endometrial cancer, the present study compared between superficial and deep myometrial invasion in endometrial cancer type 1 in relation to regional lymph node metastasis and showed that there is a statistical difference between group I and group II in relation to regional lymph nodes metastasis as group II (cases with deep myometrial invasion) are associated with more regional lymph nodes metastasis ( $P=0.0001$ ). In agreement with the present study, Euscher *et al.*, concluded that deep myometrial invasion in type 1 endometrial cancer showed a significant increase in metastatic regional lymph node than in superficial lymph node metastasis (16). Other study by Essmat *et al.* which studied the relation between the depth of myometrial invasion of endometrial cancer and the rate of lymph node metastasis, found that deep myometrial invasion is significantly associated with pelvic lymph node metastasis than in superficial myometrial invasion (17). Considering comparison of pathological grading in both groups in relation to regional lymph node involvement, the present study showed that there is a significant statistical increase between grade 1 cases with regional lymph nodes metastasis in group II than in grade 1 cases with regional lymph nodes metastasis in group I ( $P=0.00018$ ). The same finding is present between grade 2 with regional lymph nodes metastasis in both groups, as grade 2 is associated with more regional lymph nodes metastasis in group II than in group I ( $P=0.02$ ). This finding is denoting the importance of deep myometrial invasion than pathological grading as a causative factor for regional lymph nodes metastasis. Bandala-Jacques, *et al.*, studied the diagnostic accuracy of intraoperative assessment in grade 2 endometrioid endometrial carcinoma and found that grade 2 endometrioid adenocarcinoma is associated with pelvic and para-aortic lymph nodes metastasis and deep myometrial invasion provides the highest overall diagnostic accuracy (18). The last study agrees with the present study result and confirms the importance of myometrial invasion than pathological grading of endometrioid cancer in relation to regional lymph nodes metastasis. Considering grading and types of lymph node metastasis, the present study proved that there is no significant statistical difference between

grade 1 and grade 2 in group I and types of lymph nodes metastasis ( $P=0.981$ ). Again, there is no significant statistical difference between grade 1 and grade 2 in group B and types of lymph nodes metastasis ( $P=0.825$ ). As regards grading in both groups, and types of regional lymph nodes metastasis, there are no significant difference between grade 1 in both groups and grade 2 in both groups and types of regional lymph nodes metastasis whether pelvic or para-aortic ( $P=0.425$ ,  $P=0.882$  respectively). According to the last finding, pathological grading has no value in determining types of regional lymph nodes metastasis whether pelvic or para-aortic. In agreement with the last finding, Turan *et al.*, study concluded that there is no significant statistical difference between grade 1 and grade 2 endometrioid adenocarcinoma of uterine body in relation to para-aortic lymph nodes group metastasis (19). Considering types of regional lymph nodes metastases in relation to depth of myometrial invasion in type 1 endometrial cancer, the present study showed that cases with deep myometrial invasion is associated with more pelvic and lower paraaortic lymph nodes metastasis than cases with superficial myometrial invasion. In agreement with the present study, Turan *et al.*, study proved that deep myometrial invasion showed significant increase in pelvic and para-aortic lymph nodes group metastasis than in superficial myometrial invasion in endometrial adenocarcinoma patients (19). From the previous finding we can conclude that deep myometrial invasion is an important causative factor of regional lymph nodes metastases, has an upper role than pathological grading in relation to this aspect in type 1 endometrial cancer and is associated with more pelvic and lower para-aortic lymph nodes metastasis. The present study showed the importance of regional pelvic and lower para-aortic lymphadenectomy in cases with deep myometrial invasion stage 1 type 1 endometrial cancer but not in cases with superficial myometrial invasion but its limitation was not to study the effect of lymphovascular space invasion on regional lymph nodes metastases so we recommend it to be studied in further research.

## Conclusion

Deep myometrial invasion in type 1 endometrial cancer is associated with a significant increase in regional lymph nodes metastases whether pelvic or paraaortic than with superficial myometrial invasion, has an upper role than pathological grading in this aspect and this finding denoting that there is no need for regional lymphadenectomy in endometrial adenocarcinoma type 1 stage 1A. Further study is needed to analyze the effect of lymphovascular space invasion on regional lymph nodes metastases in stage 1A endometrial cancer, as this point is the main limitation of the present study.

## Ethical approval

The study was approved by the Institutional Ethics Committee of Alexandria university medical school.

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## Conflict of Interest

The author declares no conflict of interest.

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