

The Role of Lymph Node Sampling in Early Stage Endometrial Cancer

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Abstract: Objective: To determine the role of lymph node sampling in detection of occult metastasis in early stage endometrial cancer and its impact on prognosis. **Methods:** This was a prospective randomized study that include 51 patients who clinically diagnosed to have stage I endometrial carcinoma after dilatation and curettage and had low risk for lymph node metastasis (Low risk was defined as grade 1 or 2 endometrioid type with myometrial invasion (MI) $\leq 50\%$ and primary tumour diameter (PTD) ≤ 2 cm). Data were analyzed with SPSS version 21 to compare survival rates. **Results:** Lymph node sampling did not appear to convey a survival benefit in early stage endometrial cancer also it does not increase operative time or intraoperative blood loss as systematic lymphadenectomy. D & C biopsy is a good diagnostic tool but it carries a small percentage of fallacies especially if specimens are inadequate. Tumour stage is the most important prognostic factor in endometrial carcinoma. **Conclusions.** Lymph node sampling did not appear to have an important role in early stage endometrial cancer, so it should be restricted only to enlarged or suspicious lymph nodes when complete lymphadenectomy couldn't be done. In high risk patients for metastasis systemic pelvic lymphadenectomy should be done with or without para-aortic lymphadenectomy. When Lymph node sampling is the only choice (as in patients with comorbidities) sentinel lymph node mapping may help if available. Also frozen section may be a good intraoperative diagnostic tool in cases with suspicious lymph nodes. Accurate determination of grade and extent of tumour is necessary to decide the type of surgery. A surgeon with expertise in performing lymphadenectomy should be available in surgeries of uterine corpus malignancy. Further studies concerning combination of CA 125 level and other investigations such as P53 gene mutation should be done to recognize patients who may benefit from lymphadenectomy.

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1. Introduction

Endometrial cancer is considered as the most common cancer of the female reproductive tract in developed countries and the third most common cause of death from women's cancers, behind ovarian and cervical cancer¹. Based on FIGO staging guidelines, clinically early-stage endometrial cancer patients should undergo comprehensive surgical staging. However, the disadvantages of surgical staging may outweigh the risks in patients with low-grade endometrioid tumours. In this subset of patients, intraoperative frozen pathology may be used as a method of triaging patients to lymphadenectomy². In patients with confirmed extrauterine disease, adjuvant therapy will undoubtedly be recommended. In those with a thorough and negative evaluation of lymph node tissues, adjuvant treatment recommendations can be tailored towards the goal of preventing local recurrence. Over 10% of clinical stage I disease is associated with positive occult lymphatic spread³. The obvious mortality associated with untreated metastatic disease, have led most surgeons to advocate a comprehensive staging pelvic and para-aortic lymphadenectomy in the majority of patients with

endometrial cancer. But identifying which patients benefit from lymphadenectomy represents a unique challenge². There is no clearly adopted consensus on which low-risk patients benefit from lymphadenectomy. Some studies observed survival benefit associated with lymph node sampling due to identification of women with more advanced endometrial cancer⁴. Numerous studies have identified risk factors associated with metastatic spread of disease: tumour histology, myometrial invasion, and the size of the primary tumour⁵.

Our study aimed to assess the role of lymph node sampling as intraoperative procedure to detect missed LN metastasis by preoperative assessment in early stage endometrial carcinoma.

2. Patient and Methods

This prospective randomized study was conducted at the department of gynecology, Al Azhar university hospital (Damietta) and Damietta oncology institute during the period from August 2015 to October 2017. The study included 51 patients who clinically diagnosed to have stage I endometrial carcinoma and had low risk for lymph node metastasis

(Low risk was defined as grade 1 or 2 endometrioid type with myometrial invasion (MI) $\leq 50\%$ and primary tumour diameter (PTD) ≤ 2 cm).

Patients were admitted and joined our study after a written consent and scientific committee agreement and for each patient the following were done: careful history taking, general, abdominal and local examination, laboratory investigations; including complete blood count, fasting and post prandial blood sugar, liver functions, renal functions and carcinogenic antigen 125 (CA125), abdominal ultrasound, transvaginal ultrasound to detect; uterine size, endometrial thickness, endometrial mass and its size, myometrial invasion and any combined lesion, CT or MRI to detect the extent of lesion and possible metastasis.

After that patients were subjected to surgical treatment and were classified into two groups:

Group (A): In which total abdominal hysterectomy and bilateral salpingo-oophorectomy with pelvic lymph node sampling were done.

Group (B): In which total abdominal hysterectomy and bilateral salpingo-oophorectomy was done as group A but without lymph node sampling.

The two groups were randomly chosen from the study group. Patients were followed up every 3 months for 1 year, then every 6 months by: history and physical examinations, ultrasound, MRI every 6

months in the first year then yearly. Then the two groups were compared as regard to survival and recurrence rate.

3. Results

The 51 patients with stage I endometrial carcinoma and a low risk for lymph node metastasis were followed up postoperatively for a mean duration of 19 months, range (6 – 27 months).

The mean age at diagnosis was 57.82 ± 7.54 for the study group. Grade, histologic cell type, and depth of myometrial invasion were diagnosed by the local pathologist.

In our study about 74.5% of patients were overweight or obese with a significant difference in survival with increased BMI; obesity was associated with increased mortality in our study ($P < 0.008$) (table 1).

History of breast cancer and tamoxifen therapy was present in two cases 3.9% of the study group. Diabetes was present in 41.1% of patients. Also 49% of cases were hypertensive. There was no significant difference in survival with diabetes or hypertension ($P = 0.165$), ($P = 0.235$) (table 2).

Group (A) included 28 patients whom were treated with total abdominal hysterectomy and bilateral salpingo-oophorectomy with pelvic lymph node sampling.

Table (1): The relation between body mass index and survival in the studied group.

	Died (n=2)		Survived (n=49)		p-value
	No	%	No	%	
Non obese	0	0.0	13	26.5	0.399
Obese	2	100.0	36	73.5	
BMI Mean \pm SD	38.00 \pm 1.41		30.77 \pm 6.88		0.008*

Table (2): The relation between hypertension, diabetes and survival in the studied group.

	Died (n=2)		Survived (n=49)		p-value
	No	%	No	%	
DM	2	100.0	19	38.8	0.165
HTN	2	100.0	23	46.9	0.235

The median number of lymph nodes obtained by sampling from each patient in group A was 8 nodes with a range of (1-24). There was no statistically significant improvement in survival with increased number of surgically removed lymph nodes ($P = 0.283$). The post-operative histopathology revealed no detected nodal metastasis in all patients who had undergone lymph node sampling.

The post-operative histopathology revealed that 1 case was papillary serous endometrial carcinoma in group A (3.6%) and 2 cases were adenosquamous

carcinoma (7.1%). In group B there was 1 case of adenosquamous carcinoma (4.3%) all other cases were endometrioid (95.7%) (table 3).

The post-operative grading revealed that in group A there were 8 cases G1 (28.6%), 16 cases G2 (57.1%) and 4 cases G3 (14.3%), in group B it was 9 (39.1%), 12 (52.2%) and 2 (8.7%) cases respectively. G3 was undergraded in (14.3%) of cases in group A and (8.7%) of cases in group B.

There was a higher survival rate in endometrioid type than non endometrioid type of endometrial

carcinoma that was statistically significant ($P < 0.026$) (table 4). There was no significant difference in survival regarding the tumour grade ($P = 0.193$).

Recurrence occurred in 1 case in group A (3.6%) that was diagnosed to have a papillary serous endometrial carcinoma post-operatively. But there was no significant difference in recurrence between both groups ($P = 1$). 2 patients in group A (7.1%) died at the end of follow up period and 92.9% survived, all patients in group B were survived with no significant difference between both groups ($P = 1$).

There was no significant difference in the operative time between the two groups, the mean operative time for group A was 155 min while for group B was 136.9 min ($P = 0.061$). In group A 21.4% of cases had intraoperative blood transfusion and 13% in group B with no significant difference between both groups.

There was no statistically significant difference in the overall complications between both groups; it was 10.7% in group A and 13% in group B ($P = 1$).

Table (3): Post-operative histopathological type of endometrial carcinoma in the studied groups.

	Group A (n=28)		Group B (n=23)		χ^2	p-value
	No	%	No	%		
Endometrioid	25	89.3	22	95.7	1.045	0.593
Papillary serous	1	3.6	0	0.0		
Adenosquamous	2	7.1	1	4.3		

Table (4): The relation between postoperative histopathology and survival in the studied group.

	Died (n=2)		Survived (n=49)		p-value
	No	%	No	%	
Endometrioid	1	50.0	46	93.9	0.026*
Papillary serous	0	0.0	1	2.0	
Adenosquamous	1	50.0	2	4.1	

4. Discussion

The role of surgical lymphadenectomy has been continuously debated since the FIGO staging criteria were adopted. Assessment of the lymph node-bearing tissue has been interpreted by some to include lymph node inspection and/or palpation with selective biopsies of suspicious areas.

Data suggest that this technique is of limited value as microscopic metastases can be frequently missed by inspection/palpation. These micrometastases also tend to be below the detectable limits of conventional imaging modalities⁵. In our study we assessed the role of lymph node sampling as a procedure to detect missed LN metastasis by preoperative assessment and its impact on prognosis.

We summarized the clinical and pathological criteria of the studied group as follows; the mean age of patients at time of diagnosis was 57.82 and 58.52 year for group A and B respectively with no significant difference between both groups nearly similar results was reported by Linkov et al.⁶.

In our study there were only 2 cases that died during the follow up period with a mean survival time 18 months for them and the age of both was above 60 years. Also the study of Linkov et al.⁶ and Kellert et al.⁷ revealed that age is an important prognostic factor in endometrial carcinoma.

As regard to parity of the studied group. there were 6 cases nullipara and 14 cases of low parity i.e; about 39% of cases. Although nulliparity and low parity were risk factors of occurrence of endometrial carcinoma in our study group, it was not associated with poor prognosis. These results were in agreement with that obtained by cetin et al.⁸. On the other hand Linkov et al.⁶ reported that nulliparity and low parity were major risk factors for occurrence of endometrial carcinoma and also associated with poor prognosis.

Regarding the body mass index and endometrial carcinoma in our studied group about 74.5% were overweight or obese; obesity is a risk factor for occurrence of endometrial carcinoma. Similar results were obtained by Orekoya et al.⁸. Our study also showed that obesity was associated with poor prognosis. Similar findings were also reported by Orekoya et al.⁸

History of breast cancer and tamoxifen therapy was present in two cases 3.9%, it is nearly similar to the results of DeMichele⁹.

Diabetes is an important risk factor for endometrial carcinoma, in our study diabetes was present in 42.9% of patients in group A and 39.1% of patients in group B. These results are higher than that obtained by Salazar et al.¹⁰ who reported association in about 20% of their cases.

The explanation about higher incidence of diabetes in our study group may be the association of high incidence of obese and overweight about 74.5% which acts as a risk factor for diabetes and endometrial carcinoma.

Diabetes in our study was not associated with poor prognosis. This finding was in agreement with that reported by Linkov et al.⁶. On the other hand these results are not in agreement with that reported by Chia et al.¹¹ and Álvaro et al.¹² who reported that diabetes mellitus was associated with poor prognosis in endometrial cancer patients. The association between hypertension and endometrial carcinoma in our study group was studied, 50% of cases were hypertensive in group A and 47.8% in group B.

Weiderpass et al.¹³ stated that hypertension increased the risk of endometrial cancer in obese women only. Hypertension in our studied group was not associated with poor prognosis. These findings were in agreement with Linkov et al.⁶

In our study the preoperative histopathology of D & C specimen was of endometrioid type for all patients with degree of differentiation either G1 or G2 in both groups.

The post-operative histopathology revealed that 1 case was papillary serous endometrial carcinoma in group A (3.6%) and 2 cases were adenosquamous carcinoma (7.1%) in the same group. In group B there was 1 case of adenosquamous carcinoma (4.3%) all other cases were of endometrioid type.

The overall fallacies in D & C histopathology were about 10% and it may be explained by inadequate specimen. These results were in agreement with the study of Vorgias et al.¹⁴ about the diagnostic accuracy of D & C in endometrial carcinoma.

Regarding the degree of differentiation, the post-operative histopathology revealed that in group A there were 8 cases G1 (28.6%), 16 cases G2 (57.1%) and 4 cases G3 (14.3%), in group B it was 9 (39.1%), 12 (52.2%) and 2 (8.7%) cases respectively. G3 was undergraded in (14.3%) of cases in group A and (8.7%) of cases in group B, this figure was lower than that reported by Vorgias et al.¹⁴, they reported that 37.3% of cases were undergraded preoperatively. This difference may be due to exclusion of advanced cases of endometrial cancer.

In our study there were a higher survival rate in endometrioid type than non endometrioid type of endometrial carcinoma that was statistically significant. These results were in agreement with Sakuragi et al.¹⁵ who found that the prognosis of endometrial carcinoma depends mainly on the histopathologic type and grade of the disease. On the other hand Linkov et al.⁶ found no significant difference in survival of patients with endometrial carcinoma according to the histopathologic type. The

difference in results may be due to different follow up duration and sample size.

In our studied group there was no significant difference in survival regarding the tumour grade. These results were in agreement with Linkov et al.⁶. On the other hand Sakuragi et al.¹⁵ found that grade of the disease was important risk factor for poor prognosis in patients with endometrial cancer.

In this work the recurrence occurred in 1 case in group A (3.6%) that was diagnosed to have a papillary serous endometrial carcinoma post-operatively after a follow period about 21.5 months. These results were much less than that obtained by ASTEC study group¹⁶ as about 17.8% of their patients had recurrence after a mean follow up time 37 months. Also it was less than that obtained by Benedetti et al.¹⁷ as 15.5% of their patients had recurrence after a mean follow up time of 47 months. This may be due to our exclusion of patients with more advanced disease and histopathologic types other than endometrioid carcinoma.

In this work 2 patients in group A (7.1%) died at the end of follow up time and 92.9% survived, all patients in group B also survived. These results were less than that obtained by Benedetti et al.¹⁷, as 10.3% of their patients died after a follow up period 49 months. Also these results were lower than that of ASTEC trial¹⁶ where 13.5% of their patients died after the end of 58 months follow up period. The higher incidence of death in the previous studies may be due to the longer follow up time and inclusion of patients with more advanced disease.

In our study we tried to answer a question; whether to do lymph node sampling or not in low risk patients and is it really safe procedure.

We analyzed all prognostic factors between the two groups according to: age, parity, BMI, diabetes, hypertension, degree of tumour differentiation and adjuvant radiotherapy. There were no significant differences between the two groups regarding these factors.

The use of adjuvant radiotherapy in stage I disease was controversial therefore decision of adjuvant radiotherapy was taken by radiotherapy department on selected cases post-operatively.

Two randomized clinical trials were published by Creutzberg et al.¹⁸ and Keys et al.¹⁹, they showed that adjuvant radiotherapy although decreasing the incidence of local recurrence but it was not associated with any change in the overall survival, thus limiting the relative importance of this bias on the outcome of our trial.

Also we compared the operative time, need for blood transfusion and surgical complications occurred during and after the operations.

In our study there was no significant difference in the operative time between the two groups, the mean operative time for group A was 155 min while for group B was 136.9 min, this indicates that lymph node sampling does not consume much operative time like complete lymphadenectomy. In the study of Benedetti et al.¹⁷ they reported longer operative time than our study in lymphadenectomy group (180 min) and nearly similar operative time in hysterectomy only group (120 min), the longer operative time in the lymphadenectomy group was because patients had systemic pelvic lymphadenectomy that takes more time.

In our study we also registered and compared blood transfusion taken by both groups of patients which gave us a rough idea about the blood loss during the operation, in group A 21.4% of cases had intraoperative blood transfusion and 13% in group B with no significant difference between both groups. These results were in agreement with Cragun et al.²⁰ and Benedetti et al.¹⁷.

In our study the complications which occurred during and after the operations in the two groups were reported and compared, there were no statistically significant difference in the overall complications between both groups, it was 10.7% in group A and 13% in group B. These results were in agreement with that reported by Cragun et al.²⁰ who reported no significant difference in complications between hysterectomy only patients and patients undergone hysterectomy with pelvic lymphadenectomy.

We also analyzed the outcome between the two groups (recurrence and mortality) and the duration of disease free interval. Our results showed;

The survival rate in group A was 92.9% and 100% in group B, the recurrence occurred in 1 case in group A (3.6%) that was diagnosed to have a papillary serous endometrial carcinoma post-operatively after a follow period about 21.5 months and no cases of recurrence in group B. These results were much less than that obtained by ASTEC study group¹⁶ as about 17.8% of their patients had recurrence after a mean follow up time 37 months. Also it was less than that obtained by Benedetti et al.¹⁷ as 15.5% of their patients had recurrence after a mean follow up time of 47 months. This may be due to our exclusion of patients with more advanced disease and histopathologic types other than endometrioid carcinoma. But also our study was in agreement with the previous two studies that there is no significant difference between hysterectomy group and lymphadenectomy group as regard mortality and recurrence rate in early stage endometrial cancer.

In our study the median number of lymph nodes obtained by sampling from each patient was 8 nodes (range: 1-24). This was nearly similar to the study of Trimble et al.⁴, the median number of lymph nodes in

their study was 7 with range (1-40). But also it was less than that in the study of Benedetti et al.¹⁷, the median number of nodes in their study was 30 with range (22-42) this was because patients in their study had undergone systemic pelvic lymphadenectomy that harvested more number of lymph nodes.

Our study revealed no statistically significant improvement in survival with increased number of surgically removed lymph nodes, these results were in agreement with the study of Benedetti et al.¹⁷. On the other hand Cragun et al.²⁰ found that a more extensive lymphadenectomy (>11 pelvic lymph nodes evaluated), compared with a less extensive lymphadenectomy, was associated with improved survival in women with grade 3 endometrial cancer.

In our study there was no improvement in survival with lymph node sampling, this was in agreement with the study of Trimble et al.⁴ and Benedetti et al.¹⁷ as they reported no overall survival benefit with lymph node sampling in early stage endometrial carcinoma.

The post-operative histopathology revealed no detected lymph node metastasis in all patients who had undergone lymph node sampling. In the study of Benedetti et al.¹⁷ they reported detected lymph node metastasis in 13.3% of patients in the lymphadenectomy group, this result may be due to their inclusion of stage I and II endometrial carcinoma in their study and removal of a larger number of lymph nodes.

Recommendations

- Lymph node sampling did not appear to have an important role in early stage endometrial cancer, so it should be restricted only to enlarged or suspicious lymph nodes when complete lymphadenectomy couldn't be done. In high risk patients for metastasis systemic pelvic lymphadenectomy should be done with or without para-aortic lymphadenectomy.

- When Lymph node sampling is the only choice (as in patients with comorbidities) sentinel lymph node mapping may help if available.

- Also frozen section may be a good intraoperative diagnostic tool in cases with suspicious lymph nodes.

- Accurate determination of grade and extent of tumor is necessary to decide the type of surgery.

- Good cooperation between surgical pathology and gynecology services may be required to ensure adequate examination of the hysterectomy specimen. Also a surgeon with expertise in performing lymphadenectomy should be available in surgeries of uterine corpus malignancy.

- Further studies concerning combination of CA 125 level and other investigations such as P53

gene mutations should be done to recognize patients who may benefit from lymphadenectomy.

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