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Perioperative Algorithm as a Novel Method for Lymph Node Assessment in Stage I Endometrial Cancer

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Background: The uterus has a complex lymphatic drainage consisting of many groups that are in danger of endometrial cancer (EC) spread. Lymph node metastasis is a genuine pointer of poor prognosis requiring adjuvant therapy. Lymphatic mapping surgically can be done by blue dye labeling and perioperative algorithm.
Aim: To assess the role of perioperative sentinel lymph nodes (SLN) mapping algorithm in reducing the necessity of pelvic lymphadenectomy.
Methods: Fifty patients with early stage I EC underwent surgical staging. Transcervical injection of methylene blue was used, laparotomy was done and retroperitoneal spaces were opened. All lymph nodes were histopathologically examined and the negative SLN were ultrastaged.
Results: Methylene blue dye injection resulted in blue lymph nodes in 20 (40%) cases, suspicious in 2 (4%) and negative in 28 (56%). Histopathological examination of sampled lymph node showed metastases in 18/20 (90%) of blue nodes, 1/2 (50%) of suspicious nodes and 0/28 (0%) of negative nodes. There were no false negative cases in this study and the detection rate was 89%.
Conclusion: Perioperative algorithm accuracy and simplicity make it a reliable approach for lymph node assessment in early stage EC.

Keywords: Sentinel lymph nodes, Perioperative algorithm, Stage I, Endometrial cancer
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INTRODUCTION

Endometrial cancer (EC) is a frequent tumor of the female reproductive system [1]. It is ranked 4th among common cancers in females in the United States and 6th worldwide. The burden of EC is increasing; for example, in the United States from 2017 to 2018, the number of new cases increased from 61.380 to 63.230 and number of deaths caused by it increased from 10.920 to 11.350 [2, 3]. In a number of countries, the rates of EC have risen between 1980 and 2010. This rising incidence may be due to population aging and increasing obesity [4].

Endometrial cancer is diagnosed at an early stage in most patients and carries a favorable prognosis with an overall survival rate ranging from 85 to 91% for stage I disease [5, 6]. Spread to regional lymph nodes occurs in around 10% of patients with clinical stage I and this percentage increases in higher clinical stages [5].

In addition to lymph node status which an important prognostic factor in EC, other factors like histological type and grade, tumor DNA ploidy and estrogen and progesterone receptors status are implicated in prognosis [7, 8]. Of these prognostic factors, lymph node metastasis is the most important in earlier stage EC [8].

Six nodal groups constitute the pelvic lymphatics, iliacs (external, internal and common), obturator, pre-sacral and parametrial lymph nodes. Lymph node metastasis from EC is usually to pelvic lymph nodes and less frequently to para-aortic lymph nodes [9]. Because of the poor prognosis associated with para-aortic lymph node metastases from EC, the FIGO modified its staging of EC and classified stage IIIC into 2 subgroups according to the paraaortic lymph nodes status [10-12].

European guidelines restricted the removal of lymph nodes to the pelvic group in most stage I EC patients, whereas the FIGO guidelines recommend routine sampling of pelvic as well as para-aortic nodes [13].

The majority (90%) of stage I EC patients will not have lymph node metastases and when subjected to lymphadenectomy may have side effects like surgical complications, lymphedema and post-operative lymphocyst formation [14].

Sentinel lymph node (SLN) biopsy is to detect and remove selectively the first node(s) to receive lymph flow from the primary tumor. Pathological status of SLNs may predict the node status of the patient accurately. When the SLN is negative, it is hypothesized that all the other non-SLN will be also free of metastasis [15]. Consequently, complete lymphadenectomy may be avoided when SLNs are negative, resulting in reduced morbidity [16].

Although blue dye labeling of SLNs is an easy and simple, it is frequently unreliable method alone because

of its low sensitivity and specificity. However, the integration of SLN dye labeling into peri-operative algorithm (POA) may improve its predictive value and help in avoiding pelvic lymphadenectomy in a significant proportion of patients with early stage EC [17].

The aim of this work was to assess the status of lymph nodes in stage I EC patients using POA.

METHODS

This prospective study was approved by the institutional Ethics Committee and all patients signed a written informed consent.

Patients

Fifty EC patients recruited from the oncology outpatient clinic at El-Shatby University Hospital – Alexandria in the period from March 2016 to March 2017

Inclusion criteria included: EC (endometrioid, grade I or II) as proved by histopathological examination of dilation and curettage biopsies and stage I (tumor limited to the corpus with no pelvic or abdominal extension) as proved by clinical and radiological examinations [18].

Exclusion criteria: > stage I (tumor extending outside the corpus with pelvic or abdominal extension), type I, grade III and other EC types.

Pre-operative assessment

Pre-operatively, patients were subjected to: full history taking, complete general examination, pelvic examination (to assess the size of the uterus, cervix, vagina, and parametrial affection), transvaginal ultrasound using a 3D probe of General Electric (GE) Voluson P8 ultrasound machine (to assess endometrial thickness, echogenicity and myometrial invasion), multi-detector computerized tomography scan of the abdomen and pelvis (to assess myometrial invasion, pelvic extension, nodal involvement and distant metastases).

Operative details

The operative intervention is summarized in the following steps:

a. Injection of methylene blue dye: patients were injected with 1% methylene blue into the cervix at 2 injection sites, 3 and 9 O'clock. Four mL of methylene blue were entirely injected into the 2 sites of the cervix (2 mL into each site).
b. Laparotomy: midline incision was done.
c. Perioperative Algorithm steps:
    1. Peritoneal and serosal evaluation and washing.
    2. Retroperitoneal evaluation (access through paravesical and pararectal spaces) including excision of all mapped SLNs and suspicious nodes regardless of mapping.
    3. If there is no mapping on a hemipelvis, a side-specific pelvic, common iliac and inter-iliac lymph node dissection was performed. Para-aortic lymphadenectomy was left to the attendant's discretion.
d. Total abdominal hysterectomy with bilateral salpingo-oophrectomy and pelvic lymphadenectomy were done.

Histopathology

For each case, 5 micron-thick sections were cut from the formalin-fixed, paraffin-embedded blocks. Sections were stained using the conventional hematoxylin and eosin (H & E stain) and examined under light microscopy as follows [19]:

a. Sections of the endometrial tumor were examined for histopathologic diagnosis.
b. Sections of all sampled lymph nodes were examined for assessment of tumor metastasis.
c. For the negative lymph nodes, 2 adjacent 5-micron thick sections were cut from each paraffin block at each of 2 levels, 50 micron apart for the assessment of any micro-metastasis that was not detected on initial histologic examination [20].

Statistical analysis

The data was collected and entered into a personal computer. Statistical analysis was done using the IBM Statistical Package for Social Sciences version 22 software for Windows (IBM Corp; Armonk, NY). Data was described as arithmetic mean ±standard deviation or as numbers and percentages. For categorized parameters, chai square test was used. Sensitivity, specificity and accuracy of the test were determined. The level of significant was <0.05.

RESULTS

Table 1 shows the characteristics of patients. The majority was diabetic and more than half had hypertension.

Table 1: Patients' characteristics

Characteristic	n (%)
Age (years)	
<55	17 (34%)
>55	33 (66%)
Range	49-60
Mean ± SD	55.4 ± 3.38
BMI (kg/m^2)	
Range	30-37
Mean ± SD	33.51 ± 2.13
Menstrual status	
Menopause	35 (70%)
Perimenopause	15 (30%)
Comorbidities	
Diabetes mellitus	40 (80%)
Hypertension	30 (60%)

SD: Standard deviation

The pre-operative tumor assessment by ultrasound and dilatation and curettage biopsy is shown in table 2. The majority had grade I tumor with <50% myometrial invasion.

Table 2: Pre-operative tumor assessment

Assessment parameter	n (%)
Endometrial thickness (mm) by ultrasound examination	
Range	15.8 – 34.7
Mean ± SD	24.57 ± 5.43
Myometrium invasion by ultrasound examination	
<50%	40 (80%)
≥50%	10 (20%)
Tumor grading of the D&C biopsy	
I	42 (84%)
II	8 (16%)

SD: Standard deviation

The intra-operative lymph nodes status in the studied group according to methylene blue dye uptake was as follows: blue nodes in 20 (40%) patients, suspicious in 2 (4%) and negative in 28 (56%).

The histopathological findings of lymph node sampling according to dye uptake are illustrated in table 3. Histopathological examination of negative nodes (ultrastaging) were negative so there were no false negative cases in this study.

Table 3: Histopathological findings of the lymph node sampling according to dye uptake

Dye uptake by lymph nodes	**Histopathological finding of sampled lymph nodes**	
	-ve	**+ve**
Blue (n=20)	2 (10%)	18 (90%)
Suspicious (n=2)	1 (50%)	1 (50%)
Negative (n=28)	28 (100%)	0

The sensitivity, specificity and accuracy of intra-operative methylene blue dye uptake in detecting positive lymph nodes by histopathological examination are presented in table 4. The most appropriate cut-off value resulted in 85% sensitivity, 100% specificity and 90% accuracy.

Table 4: Sensitivity, specificity and accuracy of intra-operative methylene blue dye uptake in detecting lymph node metastases

Parameter	**Value**
Sensitivity	85%
Specificity	100%
Accuracy	90%
Detection rate	86%

Factors associated with lymph node status as determined by histopathological examination are illustrated in table 5. Lymphovascular invasion, ≥50% myometrial invasion and grade II were significantly associated with lymph node positivity for metastases.

The rate of lymphovascular invasion (LVI) was 35.5% (11/42) in grade I tumors and 87.5% (7/8) in grade II ($\chi^2 = 10.96$, $p = 0.0009$).

Post-operative cytological examination of peritoneal wash was positive for malignant cells in 5(10%) patients.

Table 5: Factors determining lymph node status by pathological examination

Factor	**Lymph nodes status**		χ^2	p value
	-ve	+ve		
	n (%)	n (%)		
Lymphovascular space invasion				
No	30 (93.8)	2 (6.3)	9.35	0.002
Yes	1 (5.6)	17 (94.4)		
Myometrial invasion				
<50	29 (72.5)	11 (27.5)	9.35	0.002
≥50	2 (20)	8 (80)		
Tumor grade				
I	30 (71.4)	12 (28.6)	9.904	0.0016
II	1 (12.5)	7 (87.5)		

DISCUSSION

While the prognosis of early stage EC is good, the prognosis of patients with unfavorable pathological characteristics and advanced disease is poor [5-21]. Metastasis to lymph nodes is among the proven prognostic factors in EC which occurs in around 10% of patients with stage I disease and around 20% of patients with stages II and IIIA-B [5, 22]. This is the rationale behind recommending pelvic and para-aortic lymphadenectomy during surgical staging in addition to total abdominal hysterectomy plus bilateral salpingo-oophorectomy [5, 22, 23]. Because of the significant morbidity that may complicate lymphadenctomies, we conducted this study to assess the capability of a perioperative SLN algorithm for reduction of pelvic lymphadenectomy.

In the current study, methylene blue dye injection resulted in blue lymph nodes in 20 (40%) cases, suspicious in 2 (4%) and negative in 28 (56%). Histopathological examination of sampled lymph node showed metastases in 18/20 (90%) of blue nodes, and 1/2 (50%) of suspicious nodes. None (0%) of the negative nodes was positive on histopathological examination. These results are generally comparable to the results of other studies that examined SLN mapping algorithms in EC [17, 23-25].

Barlin et al investigated the value of SLN mapping algorithm similar to the one applied in the current study

in 498 patients with EC and reported results in agreement with ours [23]. Lymph node metastases were correctly diagnosed with SLN in 40 out of 47 patients with false negative rate of 15%. The false negative rate was reduced to only 2% after applying the investigated algorithm. While the results were promising, Barlin et al recommended further research to validate the false-negative rate resulting from SLN mapping algorithm used by them. The reduction in the false-negative rate in their study highlights the need to integrate SLN mapping into an algorithm with the removal of suspicious lymph nodes plus ipsilateral lymphadenectomy when SLN mapping fails.

The reduction of false-negative rate after inclusion of SLN mapping into algorithm was confirmed in the retrospective multi-center study that included smaller number of patients (n=66) with stage I EC that was conducted by Vidal et al [17]. In their study, when SLN was used alone, the false-negative rate was 40%. When an algorithm integrating SLN was applied, the false-negative rate was reduced to 14% which is still higher than what is reported by Barlin et al [23]. Vidal et al suggested that 53% of lymphadenectomies may be avoided using their SLN Algorithm [17].

Sentinel lymph node mapping plus a histopathologic ultrastaging protocol for low-grade EC patients with superficial myometrial invasion was evaluated in a study from the Memorial Sloan-Kettering Cancer Center and included 425 patients [24]. In addition to 13 cases with lymph node metastases detected by routine hematoxylin and eosin examination, another 12 cases were detected by the ultrastaging protocol. Patients without myometrial invasion were less likely to have positive SLNs using both the routine hematoxylin and eosin examination and the ultrastaging protocol. Based on that, the authors suggested that applying the ultrastaging protocol may be unnecessary in patients without invasion to the myometrium [24].

The potential benefit of SLN mapping algorithm is not limited to early stage EC and may be applicable in patients with more advanced stages of EC [25]. This was tested by Ducie et al in a study that included 412 patients with intermediate/high risk EC from two institutions. Two-hundred and ten patients from one institution underwent complete pelvic and paraaortic lymphadenectoy, while the remaining 202 patients underwent SLN mapping algorithm in the other institution. Stage IIIC detection rate was similar among both groups, suggesting that SLN mapping algorithm may be an alternative to routine lymphadenectomy in intermediate/high risk EC [25].

Conclusions

Sentinel lymph node mapping is applicable and accurately predicts lymph nodes status in women with early stage EC when incorporated into a perioperative algorithm.

Sentinel lymph node procedure is a minimally invasive technique that can be used as an alternative to decrease the surgical morbidity after lymphadenectomy.

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