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Original Research Article

Sentinel lymph node biopsy in early-stage endometrium cancer using methylene blue dye

Mannar Mannan Govindan*, Ayyappan Srinivasan, Ajit Pai

Department of Surgical Oncology, Apollo Hospitals, Chennai, Tamil Nadu, India

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***Correspondence:**
Dr. Mannar Mannan Govindan,
E-mail: mannarg@gmail.com

ABSTRACT

Background: The nodal evaluation of early-stage carcinoma endometrium has evolved rapidly, with various methods and dyes explored for sentinel lymph node biopsy (SLNB). Our study specifically aims to investigate the utilization of 1% methylene blue in SLNB for carcinoma endometrium at our center.
Methods: In our prospective study of 105 patients with early-stage CA endometrium in our center between June 2021 and August 2022, we used 1% methyl blue dye for SLNB identification. We followed each patient for a minimum of 6 months. We documented demographic characteristics, SLNB features, and postoperative outcomes.
Results: Out of 105 patients,94 patients (93%) of the study population belong to clinical FIGO stage IA disease, 82 patients (81%) had biopsy specimens that showed endometrioid variant grade 1, followed by grade 2 in 13 patients (12.9%). 82 patients (81.2%) had unilateral SLNB visualisation 48 patients (47.5%) had bilateral visualization of nodes, 19 patients (18.8%) of the study population had negative visualization of nodes on both sides. The average number of sentinel nodes retrieved was 2 nodes in 48 patients (45.5%), with a false negative rate of 4%.
Conclusions: In our study, using a 1% methylene blue dye for an SLNB in Ca endometrium showed less than 50% success in visualizing both sides. Therefore, we do not recommend using it as a standard method. However, in resource-limited settings where indocyanine green (ICG) and radiocolloid are not available, considering methylene blue as an alternative is a viable option provided the SLNB algorithm is followed.

Keywords: Lymphadenectomy, Early-stage endometrium cancer, Endometrial cancer, Methylene blue, SLNB

INTRODUCTION

Endometrial cancer is the sixth-most common malignant disease worldwide. It is the most common gynecologic malignancy in resource-rich countries and the second most common gynecologic cancer in developing countries, with 418,000 new cases and 98,000 deaths worldwide in 2020. India reported around 26,800 new cases in 2020. The most common type is the endometroid variant. Lymph node status is a major criterion for determining adjuvant therapy in endometrial cancer. Despite having uterus-confined disease, most of the patients will undergo complete lymph node dissection, resulting in detrimental side effects.[1] Pelvic lymphadenectomy has side effects like increased operative time, blood loss, injury to a blood vessel, nerve damage, and lymphocele formation.[2,3] The literature reports a long-term lymphedema rate of around 23%. Randomized studies on lymphadenectomy indicate no therapeutic benefit for complete lymphadenopathy in early-stage endometrial cancer.[4,5] Over the years, investigators have actively explored SLNB as a less morbid alternative for assessing nodal status in endometrial carcinoma. Sentinel lymph node mapping may provide an appropriate middle ground between the two schools of thought of complete lymphadenectomy versus no nodal evaluation in early endometrial cancer. The NCCN guidelines 2021 for uterine cancer recommend the routine use of SLNB whenever available in early-stage endometrial cancer.[6] Burke et al first introduced the concept of SLN mapping in endometrial cancer, but it has only gained popularity over the last two decades.[7]

The great challenge in planning the adequate surgical management of endometrium cancer (EC) lies in the inconsistent staging process. Especially in lymph node dissection, which varies from lymph node sampling alone in those who have a low risk of lymph node metastasis to complete lymph node dissection in all cases of EC. Regarding lymphadenectomy for the treatment of endometrial cancer (CA), Frost et al found no evidence that, in women with assumed stage I disease, lymphadenectomy lowers the risk of death or disease recurrence when compared with no lymphadenectomy.[8] The FIRES study using ICG had a sensitivity of 96.9% and a negative predictive value of 99.56 percent.[9] By using methylene blue dye, Barlin, Abu-Rustum et al. demonstrated application of a surgical SLNB algorithm that goes beyond the removal of colored blue nodes.[10] Rajanbabu et al and Nayyar et al found similar results.[11,12]

While SLNB is becoming a routine practice in many centers worldwide for early-stage carcinoma endometrium, its adoption in India is limited. Only a few centers in country have incorporated the SLNB technique for carcinoma endometrium. Several factors contribute to the limited practice of SLNB in countries like India. These include a shortage of adequate training and facilities, a scarcity of experienced pathologists, and the complexity associated with technique itself. Blue dye is cost-effective, safe, and readily accessible. It can serve as a tracer in many healthcare centers in India without incurring additional expenses. Moreover, use of blue dye technique does not necessitate specialized devices for visualizing lymph nodes. This study aims to investigate effectiveness of SLNB using only blue dye in early-stage endometrial cancer within specific population group.

METHODS

The primary objective of our study is to assess the sensitivity, specificity, and negative predictive value of SLNB using methylene blue dye in cases of documented carcinoma endometrium of endometrioid histology, specifically, those clinically identified as FIGO Stage 1 disease without any clinical or radiological evidence of extrauterine disease. As secondary objectives, the study aims to investigate sentinel lymphatic mapping characteristics and evaluate early complication rates associated with the SLNB procedure. The study included patients aged 18 to 70 who meet the ECOG status 0-1 criteria and are physically fit for surgical staging procedures. The study, conducted at our institute from June 2021 to August 2022, includes patients meeting the inclusion criteria while excluding those with clear cell and non-endometrioid histologies, individuals with a history of previous endometrial cancer treatment (such as radiotherapy or chemotherapy), those who underwent prior retroperitoneal surgery or lymphadenectomy, and patients with a history of pelvic radiation for other pelvic cancers. Additionally, individuals with a history of surgical procedures on cervix or multiple myomectomies, allergies to blue dyes, and pregnant patients excluded. To achieve the primary goal of assessing sensitivity, we established a target sensitivity of 89%, derived from a reference study. Using the formula $n=(z^2pq)/d^2$, we determined the required sample size to be 105 patients.

Procedure

The open method involves injecting the dye after completing the draping and before making a skin incision. In contrast, in the laparoscopy method, the injection occurs before the insertion of the first port or the creation of pneumoperitoneum. Procedure includes placing patient in high lithotomy position under anaesthesia. Initially, conduct a vaginal examination to identify the cervix. Subsequently, inject 1% methylene blue dye into the cervix at the 3 and 9 o'clock positions. Injection comprises 1 ml of dye superficially at 2-3 mm and 1 ml deeply at 2-3 cm, resulting in total injection of 2-4 ml. After injecting the dye, wait for 15-20 min. Then, examine the pelvic nodes for the presence of blue-coloured nodes and lymphatics by directly visualizing peritoneum, involving the opening of peritoneum. This comprehensive approach facilitates the identification and assessment of sentinel lymph nodes through visualization of blue-coloured dye.

Successful mapping involves visualizing a blue-coloured node or lymphatic channel originating from the cervix or uterus, leading to at least one node on at least one side of the pelvis. If there is no visualization of lymphatic channels or dyed nodes on both sides of the pelvis, we consider the mapping procedure unsuccessful. We then remove the dyed nodes, label them for location, and send them for frozen sections and also for permanent routine histopathological examination (HPE). Colored lymphatic channels ending in nodes undyed are also included under sentinel nodes. We also remove any suspicious and grossly enlarged nodes regardless of mapping status. We document the location of the sentinel lymph node in a graphical representation. We completed bilateral pelvic lymphadenectomy on both sides. We determine the decision to perform para-aortic lymph node dissection on a case-by-case basis, considering factors such as tumor characteristics and imaging features following the SLNB algorithm by MSKCC as shown in Figure 1.

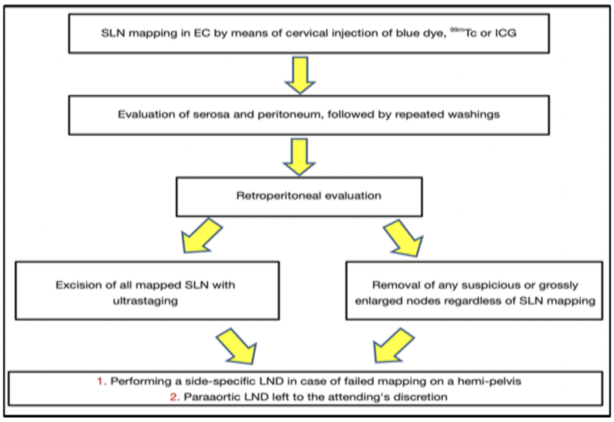

Figure 1: SLNB algorithm.

For the pathological evaluation, we cut SLNs at 3 mm intervals using the bread-loaf technique or halved them if less than 1.5 cm horizontally or longitudinally. We created two paraffin-embedded slides for each section, with one unstained slide at 50 micrometers apart-for HPE-and the other for immunohistochemistry (IHC) anti-cytokeratin AE1:AE3. IHC is conducted only if a routine histopathology examination is negative. We audit pathology reports for every 25 patients to ensure compliance. Adverse events are monitored and recorded for 12-24 hours after the procedure.

All continuous variables will be tested for normality using the Shapiro-Wills test. Normal distributed continuous variable by mean ± standard deviation Non-normally distributed continuous variables will be represented by the median interquartile range. The categorical variable will be represented by the percentage. Sensitivity, specificity, negative predictive value, and positive predictive value will be computed. Data analysis and validation will be done by IBM SPSSsStatistics for the Windows version 25.0.

RESULTS

Between June 2021 and August 2022, we conducted a study on 105 patients who met the inclusion criteria according to the study protocol. We excluded four patients from statistical analysis as they had clear cell histology in the final HPE. We actively followed each patient for a minimum of 6 months and a maximum of 1 year. The clinicopathologic and demographic characteristics of the patients are shown in Table 1.

The study enrolled patients with a mean age of 58 years, ranging from 45 to 67 (SD 5.2). Of the 105 patients, 56 (55.4%) had no comorbidities, while the remaining 45 (44.6%) presented with comorbidities such as diabetes mellitus (DM), systemic hypertension (SHT), coronary artery disease (CAD), and chronic obstructive pulmonary disease (COPD). Diabetes and hypertension affected 49% of the study population, categorized as overweight according to the WHO BMI classification. Additionally, 37 patients (36.7%) in the study population had class 1 obesity. Regarding the clinical FIGO stage, 94 patients (93.1%) were in stage IA, while 7 patients (6.7%) were in stage IB. Biopsy specimens in 82 patients (81.2%) showed endometrioid variant grade 1, followed by 13 patients (12.9%) with grade 2, and 6 patients (5.9%) with grade 3. Laparoscopy was the chosen surgical approach for 76 patients (75.2%), while the open method for the remaining 25 patients (24.8%).In terms of sentinel node mapping, 82 patients (81.2%) had successful mapping, defined by the presence of one dye node on at least one side. Of these, 48 patients (47.5%) had bilateral visualization of nodes, while 18.8% had negative visualization of nodes as shown in Table 2.

In 46 patients (45.5%), the surgical team retrieved an average of 2 sentinel nodes, while 34 patients (33.7%) had one node retrieved. On the right side, the team observed the most sentinel lymph nodes (SLNs) at the right internal iliac node in 41 patients (40.6%), followed by obturator nodes in 22 patients (21.8%) and external iliac nodes in 10 patients (9.9%). On the left side, 21 patients (20.8%) presented nodes in the obturator area, 25 patients (24%) exhibited nodes in the internal iliac area, and 11 patients (10.9%) showed external iliac nodes.Out of 101 cases, the frozen section analysis identified positive nodes in 25 cases, and permanent section examination revealed positive nodes in 29 patients, resulting in a false negative rate of 4%. We performed para-aortic node dissection in only 25 patients (23.8%) with frozen section-positive nodes in the pelvis; in the remaining cases, para-aortic node dissection was not performed. Of the 25 cases with para-aortic node dissection, all nodes were negative on HPE. No adverse reactions to the blue dye were observed in the patients studied. In the short-term follow-up of 6 months to 1 year, the surgical team noted mild grade 1 lymphedema in 2 patients (1.9%) among the study participants as shown in Table 3 and Table 4.

Table 1: Clinicopathological summary.

Characteristics	Number of patients (%)
Age (median) (In years)	58 (45-67)
BMI (kg/m^2)	Median 27
Stage IA	94 (93)
Stage IB	7 (7)
Endometrioid grade 1	82 (81.2)
Endometrioid grade 2	13 (12.9)
Endometrioid grade 3	6 (5.9)
Average SLN nodes retrieved	2 nodes in 50 (45.5)
	1 node in 34 (33.7)
Bilateral visualization	48 (47.5)
Unilateral visualization	34 (33.7)
Both sides negative visualization	19 (18.1)
Frozen section positive	25 (23.8)
Final HPE positive	29 (27.6)
Lymphedema (6 month to 1 year)	2 (1.9)
Adverse reactions to dye	Nil

Table 2: Dye visualization.

Dye visualization	N	Percentages (%)
Right side visualization	25	24.8
Left side visualization	9	8.9
Both side visualization	48	47.5
Both sides negative-not visualized	19	18.8
Total	101	100.0

Table 3: Cross tabulation.

Test	Disease				Total
	Present	N	Absent	N	
+ve	True positive	25	False positive	0	25
-ve	False negative	4	True negative	76	80
Total		29		76	

Table 4: Analysis results.

Statistic	Value (%)	95% CI
Sensitivity	86.21	68.34 to 96.11
Specificity	100	95.26 to 100
Negative predictive value	95.15	88.75 to 97.99
Accuracy	96.28	90.65 to 99

DISCUSSION

Our cohort of 101 patients exhibits clinicopathological characteristics consistent with various studies conducted on SLN mapping in early-stage endometrial cancer. Hagen et al. reported the median BMI as 28.5 in their study, while our study places the median BMI within the range of 25-30. In Hagen et al. study, endometrioid was the most common histologic type, accounting for 83% of cases, whereas in our current study, this histologic type comprises 99% (101 patients).[13] In their study, Hagen et al. assigned most patients to stage IA, constituting 48% of cases, while our study shows a higher proportion, specifically 94 patients (93.1%) of patients in stage IA. We may attribute these variations in results to the prevalence of low-grade disease among our patient population. Our current study predominantly includes patients in FIGO stage IA.

The ASTEC study compared lymphadenectomy versus no lymphadenectomy and reported no significant differences in overall survival or recurrence-free survival.[14] However, concerns have arisen regarding patient selection bias and the fact that researchers did not adequately adjust for the impact of radiotherapy on the results. The investigators concluded that lymphadenectomy is important for prognostic assessment and tailoring adjuvant therapy. The PORTEC trial and the GOG 99 trial also observed a decrease in pelvic recurrences without providing a survival benefit from adjuvant radiation. However, these trials associated radiation treatment with an increase in toxic effects and the potential for overtreatment in patients with early-stage endometrial cancer.[15,16] Similarly, Frumovitz and co-workers have observed variations of up to 27% between preoperative, intraoperative, and postoperative histological grading and staging.[17] These findings indicate that forgoing lymphadenectomy poses the risk of inadequate staging, potentially necessitating secondary lymphadenectomy or the administration of systemic chemotherapy or adjuvant radiotherapy. SLNB presents a viable alternative for a subgroup of patients who may not benefit from a complete lymphadenectomy.

According to the recommendation by Khoury-Collado et al two crucial factors for the practical application of lymphatic mapping are high sensitivity and a low false negative rate, ideally less than 7%.[18] Our study results are in line with previous research in this regard. The overall detection rate in our study 81.9% is comparable to studies that have already investigated the use of blue dye, such as the study conducted by Barlin et al. However, in our study, we implemented a SLNB algorithm that requires performing side-specific lymphadenectomy if no detection is found on a single side. As a result, the false negative rate using the SLNB algorithm in our study was 4%, with a sensitivity of 86.2% and a negative predictive value (NPV) of 95.15%. These results show that the proposed SLNB algorithm performed favourably when compared to SLNB alone. Our findings compare favourably to the study by Barlin et al which used blue dye, technetium, or a combination of both, and reported a sensitivity of 85.1%, an NPV of 98.1%, and a false negative rate of 14.9%.

It is important to note that most studies utilizing indocyanine green (ICG) dye report detection rates of over 90% (Fires et al). However, it is important to clarify that our study focused solely on evaluating the performance of blue dye in the context of endometrial cancer. Methylene blue dye alone can achieve acceptable levels of sensitivity of 81% (unilateral), as per Barlin et al. Our aim was not to compare the superiority of one dye over the other. Therefore, we cannot directly compare our results to the FIRES trial, which specifically employed ICG for SLN mapping. The FIRES trial reported a sensitivity of 97.34%, a negative predictive value of 99.56%, and a false-negative rate of less than 3%.

Li et al.'s study on the evaluation of para-aortic lymph node metastasis identified isolated para-aortic sentinel node locations without pelvic nodal metastasis, as observed in a small percentage in previous studies, ranging from 0.6% to 2.1%.[19] Since we did not conduct para-aortic lymph node dissection in all cases in our study, we cannot comment on the exact incidence of isolated para-aortic metastases. Our study found that the most common locations for sentinel lymph nodes were the internal iliac lymph nodes in 41 patients (40.6%) and obturator lymph nodes in 22 patients (21.8%) on the right side, and the internal iliac lymph nodes in 25 patients (24%) and obturator lymph nodes in 21 patients (20.8%) on the left side. Dye visualization was observed on at least one side in 82 patients (81.9%), with bilateral visualization in 48 patients (47.5%), comparable to earlier studies using only blue dye for SLNB. However, recent FIRES trials and other retrospective studies have reported superior visualization rates with the use of indocyanine green (ICG).[20,21]

Considering each side of the pelvis as a separate diagnostic unit and performing a side-specific lymphadenectomy on the negative mapping side have demonstrated the highest accuracy in the SLNB algorithm. This approach is crucial because missing disease in the nodes is possible even with negative mapping. Although 27% of the FIRES study participants had high-risk endometrial cancer histologies, which carry an increased risk of nodal and isolated para-aortic metastases, our study did not evaluate the role of SLNB in these high-risk patients. The 4.5% false-negative rate observed in our study occurred in a patient from the low and intermediate-risk groups.

In our study, we did not observe any complications related to methylene blue dye injection. However, it is important to note that there is a very low risk of anaphylaxis associated with blue dye, estimated at 0.1%.[22] It is crucial to inform the patient about this risk and obtain their informed consent before the procedure. In our study, we observed a lymphedema rate of 1.9% (2 patients) in the study population during the 6-month to 1-year follow-up period. However, it is crucial to note that we did not specifically design this study to investigate lymphedema rates. To accurately determine the incidence of lymphedema, long-term follow-up beyond 3 years would be necessary. The limitations of the study include being a single-institution observational study with a relatively small sample size and shorter follow-up, which may limit the generalizability of the findings. One of the major difficulties encountered in this study was the incorrect injection of dye outside of the cervix or the extravasation of dye in the pouch of Douglas or behind the bladder. The dissection was made challenging in the initial cases due to the bluish discolouration of tissues, emphasizing the importance of this observation.

CONCLUSION

In our study, the SLNB using methylene blue dye exhibited a sensitivity of 86.21% with a negative predictive value of 95%. 48 patients (47.5%) demonstrated bilateral visualization, while 82 patients (81.9%) exhibited unilateral visualization. The use of blue dye resulted in a bilateral detection rate of less than 50%, indicating a lower rate compared to the use of indocyanine green (ICG) in earlier studies. Also, in comparison with ICG and radiocolloid, the sensitivity and specificity are lower. The methylene blue dye technique, when used as a single dye in carcinoma endometrium, results in a lower bilateral detection rate. Therefore, one should not consider it for the standard evaluation of SLNB in carcinoma endometrium. In resource-limited settings where ICG and radio colloid are unavailable, methylene blue is an option, as long as one strictly implements the SLNB algorithm. This approach is essential to achieving an acceptable detection rate while minimizing potential morbidity associated with extensive lymphadenectomy in a considerable number of patients.

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