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A Low-Cost and Reproductible Method to Obtain Mapping of Lymphatic Drainage in Patient with Early Endometrial Cancer

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Rezumat

O metodă accesibilă și reproductibilă pentru efectuarea unui mapping de drenaj limfatic la pacientele cu cancer endometrial precoce

Introducere: Cancerul endometrial este cea mai frecventă formă de cancer ginecologic în țările dezvoltate. Managementul terapeutic recomandat în prezent ia în considerare o serie de factori, cum ar fi: stadiul TNM, justificarea intervenției chirurgicale primare, dorința de a păstra fertilitatea. Pentru cazurile operabile primar, stadializarea chirurgicală a devenit un pilon extrem de important, în care trebuie cunoscut statusul ganglionilor limfatici pelvini (1-3). *Material şi Metodă:* În perioada cuprinsă între lunile August 2015 - Iunie 2021, în cadrul Institutului Oncologic "Prof. Dr. I. Chiricuță" Cluj Napoca, Clinicii de Chirurgie Generală II a Spitalului Județean "Pius Brînzeu" Timişoara, Clinicii de Chirurgie Generală I a Spitalului Județean Arad, Clinicii de Obstetrică şi Ginecologie II "Dominic Stanca" Cluj Napoca şi Spitalului Universitar de Urgență Militar Central "Dr. Carol Davila" Bucureşti România, s-a realizat un studiu prospectiv observațional multicentric, având ca obiectiv principal examinarea ratei de detecție a ganglionului limfatic santinelă utilizând albastru de metilen ca trasor. Intervențiile chirurgicale au fost efectuate de către echipa de chirurgi a clinicilor menționate, iar pacientele au fost informate despre acest studiu şi au semnat un consimțământ informat pentru înscriere.

Rezultate: Un total de 116 cazuri au îndeplinit criteriile de includere pentru acest studiu prospectiv. Vârsta medie a pacienților incluşi a fost de 62,3 ani (minim - 38, maxim - 83). Indicele mediu de masă corporală a fost de 31,8 (minim - 19,9, maxim - 48,2). În ceea ce priveşte tipul histologic al cancerului endometrial, majoritatea cazurilor au fost de cancer endometrioid, reprezentând 72,5% din total (n=84). Un număr considerabil de cazuri au fost de tip mixt, fie cu carcinom cu celule clare (8,6%, n=10), fie cu carcinosarcom mixt (17,2%, n=20). Abordarea preferată pentru intervenția chirurgicală a fost chirurgia laparoscopică mai degrabă decât chirurgia tradițională (72% vs. 28%). Un alt element investigat din punct de vedere histologic este gradingul tumoral, gradul de diferențiere a celulelor cu dezvoltare anarhică, observăm că 50% (n=58) au fost G2. Din cele 116 cazuri de carcinom endometrial incluse în studiu, în 83% din cazuri (n=96) injectarea de trasor albastru de metilen a fost un succes şi a fost identificat ganglionul santinelă. Tehnica SLN continuă să fie de mare interes şi să fie utilizată în centrele chirurgicale din întreaga lume. Metoda de detectare a ganglionilor limfatici santinelă variază în funcție de individ. Conform studiilor din literatură, indocianina (ICG- Indocyanine green) este standardul de aur pentru cartografierea ganglionilor limfatici, cu rate de detecție superioare în comparație cu alte versiuni existente. Un alt factor cheie care trebuie luat în considerare atunci când se selectează o metodă de identificare a ganglionului santinelă este raportul cost-eficiență. Utilizarea albastru de metil ca marker de urmărire este cea mai rentabilă opțiune cu rezultate echivalente în ceea ce priveşte rata de detecție.
Concluzii: Pe baza rezultatelor studiului nostru şi a altor studii din literatura de specialitate, cartografierea limfatică folosind albastru de metilen ca marker în cancerul endometrial este o metodă eficientă din punct de vedere al costurilor, cu o rată de detecție favorabilă. Cu această procedură cu costuri reduse se poate realiza o stadializare corectă a tumorii, evitând supratratamentul. Există mai multe modalități de identificare a ganglionului santinelă folosind diferiți trasori cu o acuratețe mai mare, dar obiectivul studiului nu a fost acela de a face o comparație între diferiți trasori, ci de a prezenta fezabilitatea cartografierii ganglionilor limfatici folosind albastru de metilen ca trasor cu costuri reduse, cu o reproductibilitate bună, o curbă de învățare scurtă şi o rată de detecție optimă.

Cuvinte cheie: tumoră endometrială, metastaze limfatice, biopsie ganglionului santinelă, limfadenectomie, albastru de metilen

Abstract

Introduction: Endometrial cancer is the most common form of gynecological cancer in developed countries. Current recommended therapeutic management takes into account a number of factors such as: TNM stage, justification for primary surgery, desire to preserve fertility. For primary operable cases, surgical staging has become an extremely important pillar, in which the status of the pelvic lymph nodes needs to be known (1-3).
Material and Method: Between August 2015 and June 2021, a multicenter prospective observational study was performed in the "Prof. Dr. I. Chiricuta" Oncological Institute Cluj Napoca, 2nd Department of Surgery of "Pius Brînzeu" County Hospital Timisoara, 1st Department of General Surgery of Arad County Hospital, 2nd Department of Obstetrics and Gynecology "Dominic Stanca" Cluj Napoca and "Dr. Carol Davila" Central Military Emergency University Hospital Bucharest, Romania with the main aim of examining the sentinel lymph node detection rate using methylene blue as a tracer. Surgeries were performed by the team of surgeons of the mentioned clinics, and patients were informed about this study and signed an informed consent form for enrollment.
Results: A total of 116 cases met the inclusion criteria for this prospective study. The mean age of the included patients was 62.3 years (minimum - 38, maximum - 83). The mean body mass index was 31.8 (minimum - 19.9, maximum - 48.2). In terms of histological type of the endometrial cancer, the majority of cases were endometrioid cancer, amounting to 72.5% of the total (n=84). A

considerable number of cases were of mixed type, either with clear cell carcinoma (8.6%, n=10) or mixed carcinosarcoma (17.2%, n=20). The preferred approach for surgery was laparoscopic surgery rather than traditional surgery (72% vs 28%). Another element investigated from a histological point of view is the tumour grading, the degree of differentiation of cells with anarchic development, we note that 50% (n=58) were G2. Of the 116 cases of endometrial carcinoma included in the study, in 83% of cases (n=96) methylene blue tracer injection was successful and sentinel node was identified. The SLN technique continues to be of great interest and use in surgical centers around the world. The method of detecting sentinel lymph nodes varies depending on the individual. According to literature studies, indocyanine (ICG- Indocyanine green) is the gold standard for lymph node mapping, with superior detection rates when compared to other existing versions. Another key factor to consider when selecting a sentinel node identification method is cost-effectiveness. The use of methyl blue as a marker tracer is the most cost-effective option with equivalent detection rate outcomes.

Conclusions: Based on the results of our study and other studies in the literature, lymphatic mapping using methylene blue as a tracer in endometrial cancer is a cost-effective method with a favourable detection rate. With this low-cost procedure we can achieve a correct tumor staging, avoiding overtreatment. There are multiple ways to identify the sentinel node using different tracers with higher accuracy, but the objective of the study was not to make a comparison between different tracers, but to present the feasibility of lymph node mapping using methylene blue as a low cost tracer with good reproducibility, short learning curve and optimal detection rate.

Key words: endometrial tumor, lymphatic metastasis, sentinel lymph node biopsy, lymphadenectomy, methylene blue

Introduction

Endometrial cancer is the most common form of gynecological cancer in developed countries. The current recommended therapeutic management takes into account a number of factors such as: TNM stage, justification for primary surgery, desire to preserve fertility. For primary operable cases, surgical staging has become an extremely important pillar in which the status of the pelvic lymph nodes needs to be known. Extended pelvic lymphadenectomy or lymph node sampling by sentinel node technique are the currently accepted options for surgical staging. The benefits of performing sentinel lymph node surgery over extended pelvic lymphadenectomy are many, including the avoidance of lymphedema, lymphoceles, and vasculonervous injury (1-3).

Regarding the sentinel lymph node technique, a variety of techniques and tracers have been investigated and used over the years. Methylene blue, indocyanine green, and Technetium are the most frequently used techniques. Sentinel node detection rate, false negative rate, bilaterality of detection are some of the parameters analyzed when comparing different techniques for surgical staging by sentinel node technique. It is also particularly important to analyze the accessibility and cost-effectiveness of each technique (4-6).

In order to answer the question "Is methylene blue an outdated technique to perform sentinel node in endometrial cancer?" we have proposed in the current study, on the one hand, a brief review of the literature regarding the detection rate of sentinel node using methylene blue and, on the other hand, to report the experience of our center regarding this technique in a prospective study.

Review from Literature

The literature review process was performed using the PubMed electronic database, using the following keywords in the search engine: blue dye, sentinel lymph node, endometrial cancer. Also, other criteria were the study to be meta-analysis or trial, published in the last 5 years (2016-2021).

Inclusion criteria being

- endometrial cancer as a condition;
- use of methylene blue for sentinel node identification;
- transparency of statistical results.

The review of the linkage was performed independently by 2 authors, and any controversy was resolved by the opinion of a third author.

A total of 7 meta-analyses were identified using the above criteria. Of these, 4 were excluded as they did not meet the predetermined inclusion criteria. The 3 remaining meta-analyses included in our study totaled 7540 cases. The average detection rate was 82.36% (min. 81%, max. 96%), of which 52.9% of cases had bilateral sentinel nodes (min. 50%, max. 73%). The detection sensitivity was 94.5% (min. 91%, max. 96.3%).

Regarding the trials, 26 articles were identified corresponding to the selected period using the electronic search engine in the PubMed database. Of these, only 3 met the predefined criteria, totaling 499 cases. The average detection rate of sentinel lymph node using methylene blue was 74.54% (min. 64.4%, max. 90.2%), in 52% of cases detection was bilateral. Sensitivity in selected articles was 96%.

Material and Method

Between August 2015 and June 2021, a multicenter prospective observational study was performed in the "Prof. Dr. I. Chiricuta" Oncological Institute Cluj Napoca, 2nd Department of Surgery of "Pius Brînzeu" County Hospital Timisoara, 1st Department of General Surgery of Arad County Hospital, 2nd Department of Obstetrics and Gynecology "Dominic Stanca" Cluj Napoca and "Dr. Carol Davila" Central Militar Bucharest, Romania with the main aim of examining the sentinel lymph node detection rate using methylene blue as a tracer. Surgeries were performed by the team of surgeons of the mentioned clinics, and patients were informed about this study and signed an informed consent form for enrollment.

The study cohort included one of 116 patients diagnosed with FIGO I and II endometrial cancer.

Inclusion criteria

- patients with histopathologically documented diagnosis of endometrial cancer (all histopathological subtypes) who underwent surgical treatment per primam.

Exclusion criteria

- patients with histopathologically documented diagnosis of benign endometrial pathology;
- patients who did not give informed consent for enrolment in the study;
- patients with locally-regionally advanced malignant endometrial pathology ineligible for per primam surgical treatment.

Injection of the tracer (methylene blue) was performed in all patients at the level of the uterine cervix, at 4 points (horizontal - time 11,2,5,8; or vertical - time 12,3,6,9), both superficial and deep. The amount of tracer used was between 4 and 6 ml, supplementing in cases where excessive tracer accumulation was evident at vaginal level either by retrograde deviation or through the cervical canal, in which cases more injection sites were added. The time interval between tracer injection and dissection of lymph node clusters to identify tracts and lymph nodes was between 15 and 20 minutes.

All cases underwent lymph node sampling by sentinel node technique during surgery (total hysterectomy with bilateral adnexectomy followed or not by ilio-obturator lymphadenec-

tomy). Lymph node sampling by the sentinel node technique was performed by excising all the capturing lymph nodes.

For schematic purposes, the targeted lymph node groups were divided into 4 distinct areas:

- External iliac group - above and lateral to the external iliac vessels;
- Internal iliac group - posterior to the external iliac vein, superior to the obturator nerve,
- Common iliac group - located along the common iliac artery, up to its bifurcation;
- Parametrial group - at the level of the parametrium.

Para-aortic lymphadenectomy was performed only in cases where an extra pelvic tract was identified. Histopathological examination was performed using hematoxylin-eosin staining in multiple sections, followed by completion with immunohistochemistry in cases selected as necessary.

Data collected were entered and schematized using Microsoft Office Excel. Data processing was performed using SPSS Statistics version 21 and RapidMiner version 9.6.

Results

A total of 116 cases met the inclusion criteria for this prospective study. The mean age of the included patients was 62.3 years (minimum - 38, maximum - 83). The mean body mass index was 31.8 (minimum - 19.9, maximum - 48.2). All characteristics of the study group are presented in *Table 1*.

In terms of histological type, the majority of cases were endometrioid cancers, accounting for 72.5% of the total (n=84). A considerable number of cases were of mixed type, either with clear cell component (8.6%, n=10) or mixed carcinosarcoma (17.2%, n=20). The preferred approach for surgery was laparoscopic surgery rather than traditional surgery (72% vs 28%). Another important element is the degree of differentiation of anarchically developing cells (tumor grading), in our study, 50% (n=58) of cases were classified as G2.

For the purpose of surgery aiming at radicality it is important to extend the tumor, and thus to stage it. The most frequent situation was a tumor invading more than 50% of the myometrial thickness, but not exceeding the uterine serosa - T1b, totaling 34% of cases (n=40), followed by T1a - a tumor invading less than 50% of the endometrial thickness (31%, n=36). In a much smaller percentage, there were situations of carcinoma in situ - 2% (n=2), T2 ≥ 13% (n=15) and T3 ≥ 3% (n=4).

Table 1. Patients' characteristics (n=116)

Characteristics	Results (p=116)
Age (average age)	62.2
BMI (average)	31.8
Histology (final results)	
endometrioid	82 (72.5%)
serous	2 (1.7%)
mixed with clear cells	10 (8.6%)
mixed carcinosarcoma	20 (17.2%)
Type of operation	
classical	33 (28%)
laparoscopic	83 (72%)
Histology grade	
G1	32 (27.6%)
G2	58 (50%)
G3	16 (13.8%)
pT (final)	
Tis	2 (2%)
T1a	36 (31%)
T1b	40 (34%)
T2	15 (13%)
T3	4 (3%)

Of the 116 cases of endometrial carcinoma included in the study, in 83% of cases (n=96) methylene blue tracer injection was successful, with sentinel node identification. Of the 96 cases with sentinel lymph node, identification was unilateral in 40.6% of cases (n=39) and bilateral in 59.4% of cases (n=57) (*Table 2*).

The locations of the identified sentinel nodes were internal iliac in 59.4% of cases (n=57), external iliac - 49% (n=47), common iliac - 12.5% (n=12) and parametrial - 2.1% (n=2). A total of 17 cases with positive sentinel lymph node (with neoplastic invasion) were identified. The location of tumor-invaded nodes was as follows: internal iliac - 59% (n=10), external iliac - 29% (n=5), and common iliac - 12% (n=2). The size of the primary endometrial tumor in sentinel node positive cases was T1a - 12 % (n=2), T1b - 47 % (n=8),

Table 2. Patient characteristics with identified SLN (n=96)

Characteristics	Results (p=116)
SLN detection	
overall	96 (83%)
unilateral	39 (40.6%)
bilateral	57 (59.4%)
SLN localization	
external iliac	47 (49%)
internal iliac	57 (59.4%)
common iliac	12 (12.5%)
parameters	2 (2.1%)
positive SLN localization	
external iliac	5 (29%)
internal iliac	10 (59%)
common iliac	2 (12%)
pT for positive SLN	
T1a	2 (12%)
T1b	8 (47%)
T2	4 (23%)
T3	3 (18%)
Macrometastasis	6 (35.3%)
Micrometastasis	11 (64.7%)

Table 3. Application of FIGO classification on the group of patients included in the study

	G1	G2	G3	
FIGO IA:	15	16	3	29.3%
FIGO IB:	7	23	7	31.9%
FIGO II:	1	11	3	12.9%
FIGO III	0	2	0	1.7%

Table 4. Calculation of the specificity and sensitivity of the study

		"+"	"-"	
GS	"+"	6	8	PPV= 43%
	"-"	2	59	NPV= 97%
	75% Sensitivity	88% Specificity		False negative rate (FNR)= 2.08%

T2 - 23 % (n=4), and T3 - 18 % (n=3).

According to *Tables 2* and *3*, a correlation was made between FIGO stage of the disease and the degree of tumour differentiation. A series of study specificity and sensitivity indices were also calculated (*Table 4*).

Discussions

The SLN technique remains a topic of great interest and continuous expansion among surgical centers worldwide. The mode of sentinel lymph node detection shows inter-individual technical variety. Based on literature studies in terms of the marker tracer used, indocyanine (ICG- Indocyanine green) is considered the gold standard for lymph node mapping with superior detection rates compared to other existing variants. Cost-effectiveness is another important consideration in the choice of sentinel node identification method. The use of methylene blue as a marker tracer is the most cost-effective method with comparable results in terms of detection rate (6-13).

According to specialized literature articles there is a higher detection rate using the Tc99 tracer, ICG or combinations thereof. Regardless of the type of tracer used, there is a directly proportional relationship between the sentinel node detection rate and the learning curve (13-17).

A study published by Khoury-Collado et al., demonstrates that a number of 30 cases is required to increase the detection rate above 77%. From a technical point of view, the cervical injection mode remains an important operator time in achieving lymph node mapping.

Regarding the detection rate, studies in the literature report a rate between 45-92% and bilateral detection between 50-60% (18-24). In our study, the bilateral detection rate was 59.4%, which is comparable to studies in the literature.

A study published by Bezu et al. reports a percentage between 0- 47.4% for the presence of micrometastases in endometrial cancer with a median of 28.3%. Analyzing the data obtained in our study, in 96 of the cases sentinel lymph node was identified, and reporting to microscopic analysis 17 cases showed lymph node tumor invasion (17.7%) with a presence of 11.45% of micrometastases respectively 6.25% of macrometastases. Literature data show uncertainty related to the significance of lymph node micrometastases in endometrial cancer and their prognostic value remains to be demonstrated by studies in progress (25-26).

A study published by Singh et al. in 2022

about using methylene blue dye for sentinel lymph node mapping in early-stage gynecology cancers showing that methylene blue dye is an efficient, feasible and safe dye for SLN mapping in early-stage gynecology cancer with a detection rate of 76% and a negative predictive value of 100%.

In a meta-analysis of 16995 patients conducted by Kim and Suh, the following aspects were highlighted. In all studies, systematic lymphadenectomy improved overall survival compared to unsystematic lymphadenectomy, whereas its efficacy was not shown in two randomized controlled trials. Removal of 10-11 lymph nodes improved overall survival, despite no difference in overall survival between systematic dissection of lymphatic tissues and no lymphadenectomy other than suspicious lymph nodes. Additionally, systematic lymphadenectomy increased overall survival in patients with intermediate- or high-risk endometrial cancer, despite no efficacy in those with low-risk endometrial cancer (27).

The usefulness of SLND in endometrial cancer is evident, resolving many controversies related to the indications for pelvic lymphadenectomy or lymph node sampling. The use of 1% methylene blue in SLND in patients with endometrial cancer represents a feasible modality with optimal detection rates offering the possibility of accurate staging and standardized therapeutic management (28-35).

Conclusions

Based on the results of our study and other studies in the literature, lymphatic mapping using methylene blue as a tracer for endometrial cancer is a cost-effective method with a favorable detection rate.

With this low-cost procedure, we can achieve correct tumor staging in endometrial cancer, avoiding overtreatment. As we know, there are multiple ways to identify the sentinel node using different tracers with higher accuracy, but the objective of our study was not to perform a comparison between different tracers, but to present the feasibility of lymph node mapping using methylene blue as a low-cost tracer with good reproducibility, short learning curve, and optimal detection rate.

Conflicts of Interests

The authors declare no conflicts of interests.

Authors' Contributions

Flaviu Ionut Faur - content and analysis; Ioana Adelina Clim - content and analysis; Paul Pasca, - content and analysis; Catalin Prodan - text and figures technoediting, participation in the statistical part; Ionel Nati - content and analysis; Amadeus Dobrescu - supervision and verification of content; Sabrina Florea - text and figures technoediting; Mihai Rosu - text and figures technoediting; Bogdan Totolici - supervision and verification of content; Ciprian Duta - supervision and verification of content; Gabriel Lazar - supervision and verification of content.

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