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Role of intraoperative Sentinel lymph node sampling in the management of women with early-stage epithelial ovarian cancer

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Abstract:
Background:

Ovarian cancer represents the 7th most common malignant tumor and, the 8th cause of mortality in women worldwide. Only twenty to thirty percent of patients with ovarian cancer are diagnosed with clinically early-stage (FIGO stage I–II) disease at first presentation. According to FIGO classification, ovarian cancer with LN metastases is classified as FIGO stage IIIA, even in the absence of peritoneal metastases. Those patients are obliged to receive adjuvant chemotherapy, in contrast to patients with FIGO stage I ovarian cancer. Therefore, the recognition of LN metastases is of major importance. Preoperative imaging has low sensitivity in detecting LN metastasis; therefore, complete pelvic and paraaortic lymphadenectomy is recommended as part of surgical staging for early stages. However, this procedure is associated with high morbidity. The concept of the SLN is to determine whether the cancer has spread to the first LN, If the sentinel node is negative for malignancy, then there is a high likelihood that the tumor has not spread to other LNs, so if we can prove its accuracy, we can skip complete lymphadenectomy and its associated co-morbidities. The study aims to assess the feasibility and the accuracy of the SLNP in early epithelial ovarian cancer. **Methods**: This is a prospective single-arm study that included patients with presumed early stages of epithelial ovarian cancer planned for surgical staging. After abdominal exploration and before removal of the ovary, 0.5 ml of methylene blue dye 1% was injected on the dorsal and ventral side of both the ovarian ligament and the infundiblo-pelvic ligament. The retroperitoneum is then accessed and inspected to identify and remove the sentinel nodes, and then staging is completed including systematic pelvic and paraaortic lymphadenectomy. **Results:** 37 patients were included. Sentinel nodes were identified in 20 patients (detection rate, 54%). 3 patients had positive nodes out of 4 patients with lymphatic dissemination, (sensitivity, 75%). the false-negative rate of 5%; the negative predictive value of 93.7%, and 3 (8%) intra- and 1 postoperative complication occurred. **Conclusion**: The detection rate of sentinel nodes in early epithelial ovarian cancer is considered relatively low using blue dye alone. However, the sentinel node procedure is feasible and has good sensitivity and specificity. SLN procedure can provide reliable and useful information on nodal status and may allow the avoidance of systematic lymphadenectomy in the future.

Keywords: early ovarian cancer; blue dye; lymphadenectomy; sentinel lymph nod

introduction

Ovarian cancer represents the seventh most common malignant tumor and the eighth cause of death in women worldwide. In EGYPT, ovarian cancer represents the fourth most common cancer among Egyptian women with an estimated more than three thousand cases in 2020.[3]

Although the overall incidence of ovarian cancer has been stable during the last decades, it remains the commonest cause of death from gynecologic malignancies worldwide. The detection of this cancer has been problematic as there is no screening program for its early detection and as a result, most ovarian cancers are detected in advanced stages. [1] only 20% to 30% of patients with ovarian cancer are diagnosed with clinically early-stage (FIGO stage I–II) disease at first evaluation [2].

According to FIGO classification, ovarian cancer with LN metastases is classified as FIGO stage IIIA, even in the absence of peritoneal metastases. Those patients are supposed to receive adjuvant chemotherapy in contrast to patients with FIGO stage I ovarian cancer. Therefore, the recognition of LN metastases is of great importance [4].

In a systematic review, the incidence of upstaged cases from an apparent clinical stage I-II to III because of LN involvement was about thirteen percent [5].

Preoperative imaging has low sensitivity in detecting LN metastasis; as a result, complete pelvic and paraaortic lymphadenectomy is recommended as part of surgical staging for early stages (I, II) only and should be avoided in advanced stages according to LION trial [6, 7].

However, the importance of full nodal dissection must be balanced against the morbidity related to such a radical surgery as major vessel injuries, excessive bleeding, nerve injury , lymphocysts formation, lymphorrhea, lower extremities edema and increased operative time. All have been described as possible complications of lymphadenectomy. Although some guidelines recommend paraaortic LN dissection up to the level of the renal vessels, the extent of LN dissection differs from center to center, mostly because of the technical difficulty of the procedure and the possible presence of patients' comorbidities [8].

With a SLNP, the 1st node that receives primary lymphatic flow can be identified. When the sentinel node is negative, one can assume that the remaining nodes are also free from tumor cells, so, the patient can spare radical lymphadenectomy, and the possible complications [9].

The SLN technique has been proven effective in different tumors such as breast cancer and malignant melanoma. In gynecological tumors, it is effective in endometrial and vulvar cancer.[10]

Several tracers have been developed to detect SLNs either alone or in combination, however, the optimal method of SLN identification remains a matter of debate [12].

1. Blue dye:

Methylene blue, isosulfane blue, or patent blue are approved for SLN mapping. They gained widespread popularity in low-income countries and in China because of their low cost. Methylene blue also has other advantages over isosulfan blue and patent blue, which include the

absence of life-threatening anaphylaxis and worldwide availability. However, the main drawback is that the use of blue dye alone leads to a lower SLN identification rate [13].

2. Radioisotopes

A gamma-ray detection probe was utilized for intraoperative identification of the sentinel node, which was introduced subsequent to the injection of radiolabeled colloids. Radioisotopes are presently the standard tracers utilized for the detection of SLNs. The confluence of a radioisotope and a blue dye results in a high detection rate, a low false negative rate, and better specification of the location and quantity of sentinel nodes, as stated in the American Society of Clinical Oncology guidelines. The combination of these two lymphatic mapping techniques is currently employed worldwide [14].
Despite their effectiveness and good safety data, the use of radioisotopes presents logistical challenges. These include handling and disposal of isotopes, staff training, legislative requirements, and reluctance of patients and personnel to be exposed to radiation. Additionally, some institutions have limited availability of radioisotopes, leading to variations in the time interval between injection and operation. Furthermore, a special gamma detector device is needed for detection [15].

3. Indocyanine green

Indocyanine green (ICG) is a water-soluble tricarbocyanine that fluoresces in near-infrared (NIR) imaging systems. It can be used in open, laparoscopic, or robotic surgery. ICG contains 5% sodium iodide and undergoes hepatic metabolism. Therefore, it should not be used in individuals with iodine allergy or significant liver dysfunction. Additionally, a high body mass index can reduce detection rates [16].
This technique provided a success rate comparable to that of the radioisotope method in preliminary studies with reported SLN identification rates of 94–100% [17].

4. Superparamagnetic iron oxide nanoparticles injection detected by Sentimag® instrument.

A new magnetic technique for sentinel lymph node biopsy (SLNB) avoids the use of radiation. It involves a brown dye for color change and a handheld probe for node detection [18].

The lymphatic drainage pathways of the ovaries always run through the infundibulopelvic ligament, ovarian ligament, as well as the round ligament of the uterus. Ovarian cancer cells may spread through these routes, so the sentinel node can be found in the para-aortic and paracaval regions, obturator fossa, iliac region, and inguinal regions [10].

According to a feasibility study conducted by Kleppe et al., the use of tracers injected into the ovarian ligaments to perform the SN procedure is both feasible and promising, and it is also considered safe for the personnel involved [19].

Patients and Methods:

This is a prospective interventional study in which 37 patients (according to case availability) were admitted to our university hospital and were enrolled from October 2019 to September 2022. All patients were followed for at least one month postoperative.

Patients are eligible if they have an apparent International Federation of Gynecology and Obstetrics stages I-II epithelial ovarian cancer, age between 18 and 80 years; an Eastern Cooperative Oncology Group performance status 2 and adequate respiratory, hepatic, cardiac, and liver functions.

Patients are excluded in case of evidence of carcinomatosis, advanced or metastatic stages, recurrent tumors, previous vascular surgery of the aorta, inferior vena cava, or iliac vessels; previous lymphadenectomy or LN sampling in the iliac or paraaortic region, hepatic dysfunction, renal dysfunction, allergy to blue dye, previous abdominal radiation therapy, pregnancy or lactation; or refusal to provide written informed consent.

The protocol was approved by the Institutional Review Board of the faculty of Medicine Mansoura University, code "MD.18.09.95. R1 "

Full history was taken from all patients, and general and abdominal examination was done. All patients had radiological evaluation by TAS/TVS and MRI or CT abdomen and pelvis. The serum level of CA125 was measured to calculate the risk of malignancy index (RMI). The metastatic work-up was done as usual (CT chest and bone survey). All patients with inclusion criteria were counseled about the procedure and written informed consent was taken. Full preoperative preparation (full CBC, liver function test, serum creatinine, RBS, ECG) and anesthetic consultation were done.

Technique

After abdominal exploration and before removal of the ovary, methylene blue dye was injected on the dorsal and ventral side of the proper ovarian ligament and the infundiblo-pelvic ligament, close to the suspected ovary and just underneath the peritoneum. Each of the 4 injections contains 0.5 mL of 1 % Methylene blue dye.

The adnexal mass was removed and sent for frozen histopathological examination, followed by an examination of the different lymph node regions for the presence of SNs.

SN was identified by its dense blue color in relation to the perivascular sheath in the anatomical sites (para-aortic, pelvic, and obturator fossa). Then systemic lymphadenectomy was done for all cases proved to be malignant by frozen histopathological examination and the steps of staging laparotomy were completed.

Paraffin histopathological examination was done afterward for all tissue removed, SNs and non SNs.

Statistical analysis:

The data was analyzed using SPSS program version 26. Continuous variables were presented as mean when symmetrical or median and range when asymmetrical. Categorical variables were presented as proportions. Sensitivity, specificity, positive and negative predictive values, and accuracy of SN detection were assessed in comparison to histopathological examination of the other dissected non-sentinel nodes.

Primary outcome: Accuracy of SNLB in ovarian cancer in comparison with sampling/ radical lymphadenectomy.

Secondary outcomes: Site and number of sentinel node(s), time to SNL identification, and complications related to the technique.

Results:

A total of 37 patients were considered eligible and provided their consent to the procedure and have been included in the study. Baseline and epidemiological characteristics of the entire population were stratified according to the mapping results and are provided in (Table 1). In 20 out of the total of 37 cases, at least 1 SLN was identified, with an overall detection rate of 54% and 46% of cases have not been detected.

There were no significant differences between the group in which SLN was identified and the group in which SLN was not detected as regards the epidemiological characteristics, site, and size of the tumor preoperative assessment or intra-operative surgical characteristics (Table 1, 2, 3).

33 patients underwent hysterectomy, and 4 patients only underwent adnexectomy for fertility preservation.

In 55% of the 20 cases with successful SLN mapping, only 1 SLN was retrieved average time of SLN detection was 20 minutes (figure 1). The sites of detection are described in (figure 2) with 50% of cases detected in the aortic region. Most SLNs are detected on the same side of the ovarian mass, while only 15% are detected on the contralateral side.

Out of the 37 cases, 24 cases were proved to be malignant or at least borderline and completed the surgical staging and systemic lymph node dissection and 1 case was Krukenberg tumor metastatic from colonic cancer, so, it was excluded from further analysis. High-grade serous carcinoma was the prevalent histo-type in our study, the pathological characteristics are detailed in (Table 4) and staging results in (table 5).

In 11 patients out of the 24 proved primary malignant cases, SLNs were identified, and their histology was compared with that of the non SLNs.

All patients with positive SNs had other infiltrated non-SLNs. While SLNB was true positive in 3 patients out of 4 with lymphatic dissemination (table 6).

Thus, the SLNB had a sensitivity of 75%, a specificity of 100 %, and an accuracy of 90.9%. In addition, the false-negative rate was 5%; the negative predictive value was 93.7%, positive predictive value was 100%.

Three intraoperative complications (superficial bladder injury and 2 intestinal injuries) and 1 postoperative complication (incisional hernia) were registered, however, none of the complications or side effects were related to either the SLNB or the lymphadenectomy procedure.

Discussion:

The sentinel node technique is effective in various gynecological and non-gynecological cancers, such as breast cancer, malignant melanoma, endometrial cancer, and vulvar cancer [10].

LN mapping in patients with early-stage ovarian cancer is still an experimental procedure in which diffrent tracers, injection methods, and technical procedures have been described in many studies.

In 1991 Vanneuville et al. were the first to study SLNP in ovary. During abdominal surgeries for individuals with normal ovaries or benign ovarian cysts, radiotracers are injected in the mesovarium, and lymphoscintigraphy is used to detect the sentinel lymph node approximately 4 to 6 hours after injection. These nodes are primarily found in the para-aortic or pelvic and para-aortic regions. Additionally, a study by the same authors noted that isolated para-aortic drainage is more common in post-menopausal women compared to pre-menopausal women [20, 21].

Studies have shown that over 80% of ovarian drainage occurs in the para-aortic region, with the remaining 20% draining in the pelvic region alone or both pelvic and para-aortic regions.[20]. Metastases in the paraaortic region might be caused by cancer cells spreading through the lymph vessels alongside the ovarian vessels, while metastases in the pelvic nodes could be due to the movement of cancer cells along the ovarian ligament to the para-uterine vessels, the broad ligaments, and then to the iliac vessels and the surrounding nodes.[22].

In our study, 50% of SLNs were detected in the aortic region and the other half was detected in the pelvic area.

Various tracers have been extensively researched, including blue dyes such as Methylene blue, isosulfane blue, patent blue, radioisotopes, and indocyanine green. These tracers are characterized by their ability to quickly spread from the injection site into the lymphatic system due to their small size.. dual mapping method using two tracers blue dye and radioactive tracer or ICG seems to decrease the failure rate or false negative SLN detection. The combination of tracers especially ICG and 99mTc resulted in better results than blue dye alone in most studies using the SLN technique.[19]

As for ovarian lymphatic mapping, only one study used blue dye alone, showing a 100% detection rate. However, this study included only 11 patients.[23] , while in combination with Technetium 99 in 21 patients the detection rate was 80.9% [19]. ICG alone was utilized in three studies, involving 43 patients, indicating a detection rate of 90.5%.[24-26]. Tc99 was used alone in 9 patients with a detection rate of 88.9% [27, 28] and in combination with ICG in 30 patients shows a 100% detection rate [25, 29].

Blue dyes are popular in developing countries due to their low cost and lack of radioactive hazards. Methylene blue also has advantages over isosulfan blue and patent blue, such as not causing life-threatening anaphylaxis and being widely available internationally. However, using blue dye alone can result in a lower SLN (sentinel lymph node) identification rate.[13]. The overall detection rate in our study using methylene blue dye alone was 54%.

As for the injection site, like our study, the infundibulopelvic and the ovarian ligament are the most common sites of injection used in most studies. The first study which evaluated the injection of the ovarian ligaments was conducted by Kleppe et al.[19] Other injection sites as the ovarian cortex, the broad ligament, the hilum of the ovary, and the ovarian parenchyma, however, these sites might be more risky because of possible tumor spillage. the overall SLN detection rate when the injection site was in the ovarian ligaments was 92.9% higher than other injection sites with a pooled detection rate of 88.5% [28].

Neither the age, BMI, histotype, or associated co-morbidities affected the detection of SLN in our study. In comparison, Sniadecki et al., who claimed BMI was an obstacle to SLN identification, and Aliakbarian et al., concluded BMI and age were the main factors for the failure of lymph node identification.[30, 31]

In a recent systematic review and meta-analysis, it was found that SLN mapping demonstrated a high detection rate of 93.3% and a negative predictive value of 100% in patients with early-stage ovarian cancer. This is in contrast to our study, which reported a detection rate of 54% and a negative predictive value of 93.7%. The detection rate varied widely among the included studies, ranging from 27% to 100%. Despite this variance, the detection rate is comparable to that observed in other gynecological cancers. Additionally, the SLN technique accurately identified 91.7% of patients with lymph node metastases, in contrast to the 75% identified in our study.[32]

Like our study, no complications were reported for the tracer injection. All complications reported in the literature are related to the lymphadenectomy as lymphorrhea and vessel injury and not the SLN dissection [32]

The possible limitations of our study include the relatively small number of patients included and the absence of other tracers in our hospital either due to their cost as ICG or the logistics needed in the case of radioactive materials.

However, this may be the first study to address the feasibility of dye SLN mapping in ovarian cancer in our region.

Conclusion:

Sentinel lymph node mapping in patients with early-stage epithelial ovarian cancer appears to be feasible and safe with no related complications and a promising method to lower the rate of unnecessary lymph node dissection without missing involved lymph nodes, however, using blue dye alone showed a low detection rate but high positive and negative predictive values and overall high accuracy.

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Conflict of interest:

Authors have no conflict of interest to declare.

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TABLE 1: Epidemiological characteristics according to sentinel lymph node mapping

Characteristics	Group I SLN identified (n=20)	Group II SLN not identified (n=17)	P value
Age Mean±SD; years	51.7+/- 13.34	50 +/-13.67	0.697
The BMI Median (Range); kg/m^2	30 (23-42)	33 (25-48)	0.158
Menopausal state; n (%) a. Postmenopausal b. Childbearing period	 12 (60) 8 (40)	 9 (52.9) 8 (40)	 0.720
The parity Median (Range)	3 (0-6)	3 (0-7)	0.179
Methods of delivery; n (%) Vaginal delivery Cesarean section Nullipara	 14 (70) 5 (25) 1 (5)	 11 (64.7) 2 (11.7) 4 (11.7)	 0.199
Associated co-morbidities; n (%) Yes No	 10 (50) 10 (50)	 10 (58.8) 7 (41.1)	 0.591

Table 2: pre-operative assessment according to sentinel lymph node mapping

	Total (n=37)	Detected (n=20)	Not detected (n=17)	P value

Site of tumor **a. right** **b. left** **c. bilateral**	 16 (43.2%) 8 (21.6%) 13 (35.1%)	 9 (45%) 6 (30%) 5 (25%)	 7 (41.2%) 2 (11.7%) 8 (47 %)	0.257
Maximum diameter of the tumor median (range)	11 (5-30)	10.5 (5-22)	12 (7-30)	0.684
Lymph nodes by MRI **a. no** **b. yes**	 31 (83.8%) 6 (16.2%)	 15 (75%) 5 (25%)	 16 (94.1%) 1 (5.9 %)	0.189
Free fluid **a. no** **b. yes (mild)**	 12 (32.4%) 25 (67.6%)	 6 (30%) 14 (70%)	 6 (35.3 %) 11 (64.7 %)	1.00
CA125 (u/ml) median (range)	125 (5-1950)	94.5 (12.7-1255)	180 (5-1950)	0.419

Table 3: surgical characteristics according to sentinel lymph node mapping

	Detected (n=20)	**Not detected (n=17)**	**P value**
Estimated blood loss (ml) median (range)	650 (200-3000)	500 (300-1500)	0.27
Operative time (hours) median (range)	2.25 (1.5-6)	2 (1.5-4)	0.65
Intra-operative complications	2 (10%)	1 (5.9%)	
Postoperative complications	1 (5%)	0	

Table 4: Pathological characteristics according to sentinel lymph node mapping

	Total (n=37)	**Detected**	**Not detected**	**P value**

		(n=20)	(n=17)	
Tumor type				0.258
Malignant	**20 (54%)**	12 (60%)	8 (47%)	
Borderline	**5 (13.5%)**	1 (5%)	4 (23.5%)	
Benign	**12 (32.4%)**	7 (35%)	5 (29.4%)	
Tumor pathology				0.187
Serous carcinoma	**15 (40.5%)**	9 (45%)	6 (35%)	
Mucinous carcinoma	**1 (2.7%)**	1 (5%)	0	
Endometrioid carcinoma	**1 (2.7%)**	1 (5%)	0	
Carcinosarcoma	**2 (5.4%)**	0	2 (11.8%)	
Krukenberg	**1 (2.7%)**	1 (5%)	0	
Borderline serous	**4 (10.8%)**	1(5%)	3 (17.6%)	
Borderline sero-mucinous	**1 (2.7%)**	0	1 (5.9%)	
Benign fibroma	**2 (5.4%)**	1 (5%)	1 (5.9%)	
Cystadenofibroma	**2 (5.4%)**	1 (5%)	1 (5.9%)	
Mucinous cystadenoma	**3 (8.1%)**	0	3 (17.6%)	
Fibrothecoma	**2 (5.4%)**	2 (10%)	0	
Adult granulosa tumor	**1 (2.7%)**	1 (5%)	0	
Struma ovarii	**1 (2.7%)**	1 (5%)	0	
Sclerosing stromal tumor	**1 (2.7%)**	1 (5%)	0	
Grading				0.569
Low	**3 (8.1%)**	1 (5%)	2 (11.8%)	
High	**12 (32.4%)**	7 (35%)	5 (29.4%)	
Unapplicable	**22 (59.5%)**	12 (60%)	10 (58.8%)	

Table 5: Staging results in malignant and borderline patients

	Total (n=24)
FIGO staging	
IA	**5 (20.8%)**
IC	**6 (25%)**
IIA	**4 (16.7%)**
IIIA	**4 (16.7%)**
IIIB	**1 (4.2%)**
IIIC	**4 (16.7%)**
Lymph nodes removed (Median per patient)	**3 (1-22)**
≥ 10	**6 (25%)**
< 10	**18 (75%)**

Table 6: Sentinel lymph node vs. sentinel lymph node pathology

	SLN	Non-SLN=actual lymphatic dissemination
Negative	**8/11 (72.7%)**	**7/11 (63.6%)**
Positive	**3/11(27.3%)**	**4/11 (36.3%)**
True positive	**3**	
True negative	**7**	
False positive	**0**	
False negative	**1**	

Figure 1

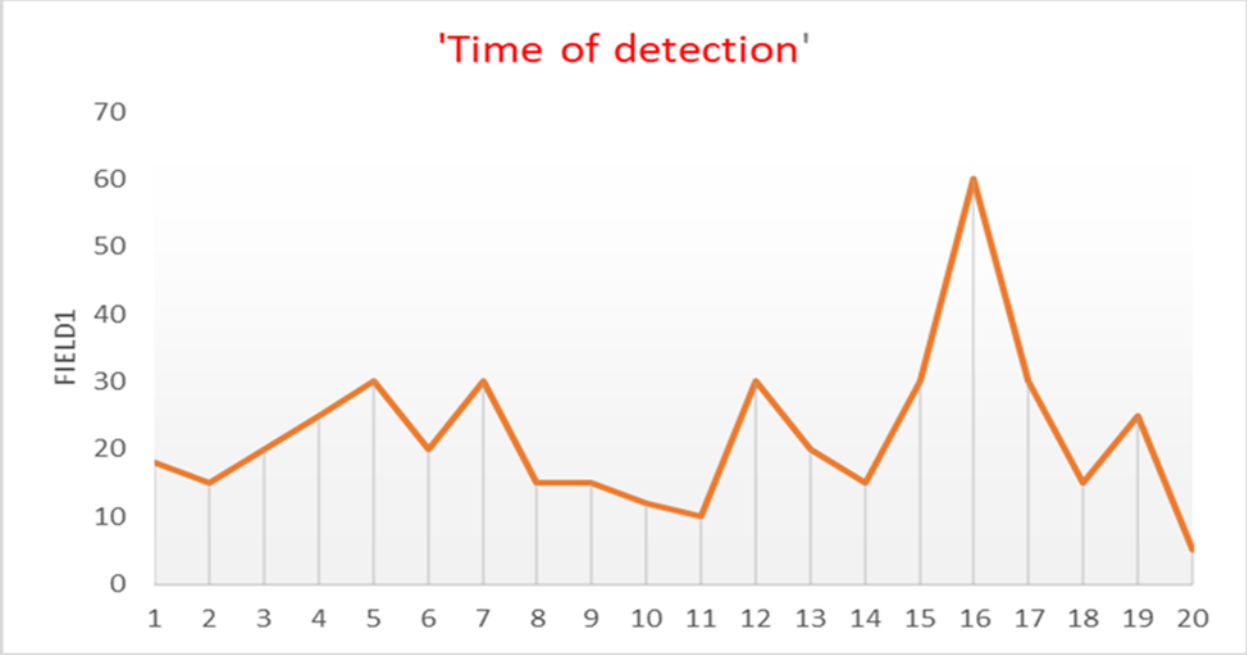
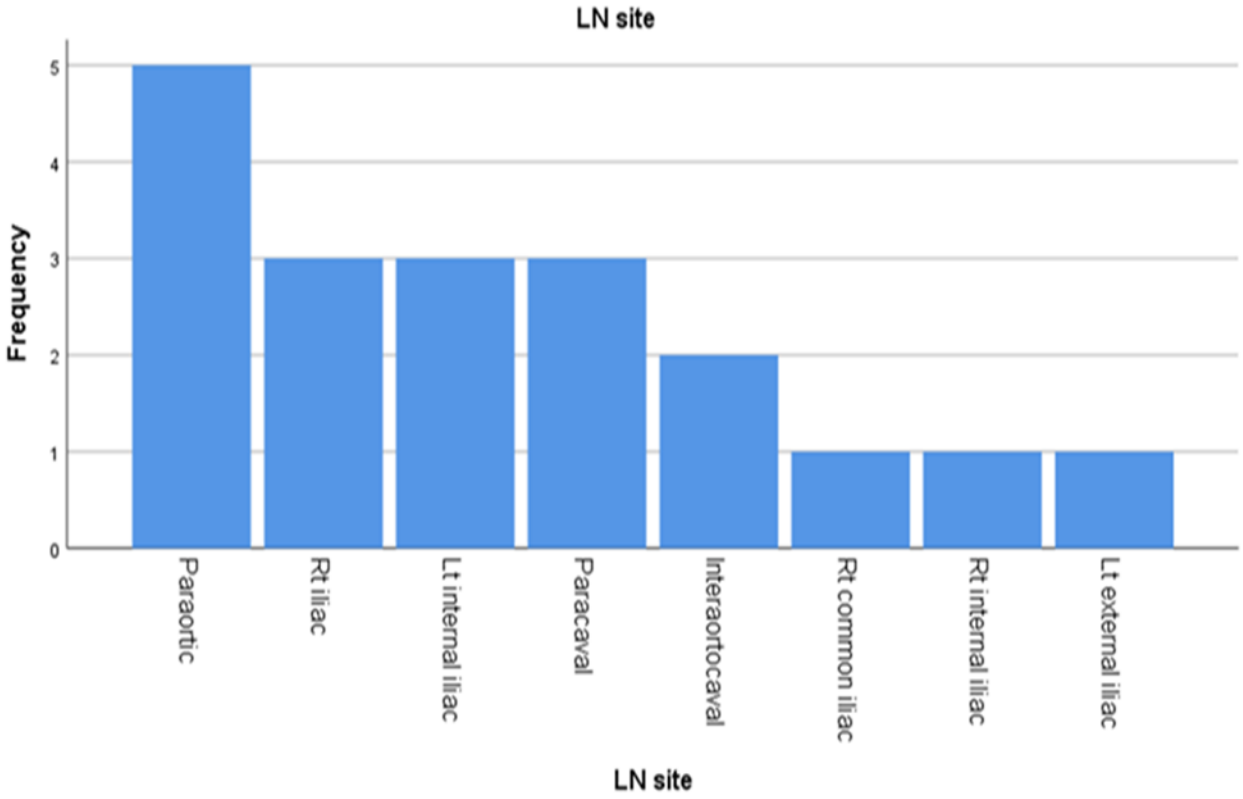


Figure 2


LN site
Frequency
0
1
2
3
4
5
Paraortic
Rt iliac
Lt internal iliac
Paracaval
Interaortocaval
Rt common iliac
Rt internal iliac
Lt external iliac
LN site