Predictors of uncommon location of sentinel nodes in endometrial and cervical cancers

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ABSTRACT

Objective: Sentinel node mapping is widely used in the treatment of gynecologic cancers. The current study aimed to identify predictors of uncommon sentinel lymph node (SLN) locations.
Methods: The current study included women who were operated for endometrial or cervical cancer with attempted sentinel lymph node mapping during surgical staging. Data were collected from electronic charts. The pelvis and the external ilia and obturator basins were common node locations. Para-aortic, pre-sacral, common iliac, internal iliac, and parametrial nodes were considered uncommon locations. We conducted analyses stratified according to common, uncommon, and very uncommon (*para*-aortic, pre-sacral, parametrial) node location sites.
Results: A total of 304 women were enrolled in the current study; 15.8% had SLN in uncommon locations and 4.3% had very uncommon node locations. Body mass index (BMI) was a negative predictor for uncommon SLN locations (OR 0.88, p = 0.03). The use of either indocyanine green (ICG) or Tc[99] & blue dye was an independent predictor for uncommon SLN locations (OR 8.24, p = 0.006). More recent surgeries and the presence of positive nodes were independent predictors for very uncommon node locations (OR 2.13, p = 0.011, and OR 9.3, p = 0.002, respectively).
Conclusions: BMI, tracer type, surgical year, and positive nodes were independent predictors for uncommon SLN locations. These findings suggest that surgical effort, technique and experience may result in better identification of uncommon SLN locations.

1. Introduction

Sentinel lymph node (SLN) mapping during surgical staging in early stage endometrial and cervical cancer has become a common practice and is incorporated into the surgical guidelines for these diseases. (Nicole McMillian et al., 2019) In cervical cancer, sentinel node biopsy (SNB) has a pooled sensitivity of 90%. Using indocyanine green (ICG) and near infra-red (NIR) techniques, sensitivity is reported as 96%, reaching 100% in tumors ≤ 2 cm in diameter. (Kadkhodayan et al., 2015; Diab, 2017) SNB in cervical cancer has been shown to be more sensitive for lymph node metastases than formal lymph node dissection. (Gortzak-uzan et al., 2010)

The pooled sensitivity of SNB in endometrial cancer is 96%. (Anna, 2017) In the FIRES trial, the largest prospective study of sentinel lymph node mapping in endometrial cancer patients to date, the detection rate was 86% and the sensitivity was 97.2%. (Rossi et al., 2017) Similar to cervical cancer, ultra-staging of sentinel nodes allows for identification of micro-metastases. Therefore, the rate of positive nodes is higher using this technique. (Anna, 2017)

Approximately 80% of the sentinel nodes in cervical cancer cases and 70% of the nodes in endometrial cancer cases are located at the external iliac and obturator basins. Less common locations include the common iliac, *para*-aortic, presacral, internal iliac, parametrial, and inguinal nodes. (Rossi et al., 2017; Marnitz et al., 2006) In a study by How et al., 14.6% of the positive sentinel nodes were located in these uncommon areas. (How et al., 2017)

However, the factors that affect the distribution of sentinel nodes remain unclear. Although node locations may represent variations in lymphatic drainage of the cervix and uterus, other factors, such as a woman's habitus, tumor characteristics, surgical technique, and surgeon experience, could contribute to influencing the specific locations of identified nodes. (Balaya et al., 2019)

Hence, the objective of this study was to identify predictors for the detection of SLN in uncommon locations among patients with endometrial and cervical cancer.

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2. Methods

This retrospective case series study was conducted at two medical centers. The institutional review boards at both institutions (the Meir Medical Center Helsinki committee and the Kaplan Medical Center Helsinki committee) approved the study, waiving the standard requirement for patient consent due to the retrospective nature of this investigation. This study enrolled patients ages 18 and older who were operated for endometrial or cervical cancer between January 1, 2013 and July 31, 2019 with attempted SNB. We reviewed electronic medical records for demographic, surgical, and pathologic data. Node locations were extracted from surgical records. External iliac, obturator, and pelvic nodes were defined as common locations. Presacral, parametrial, *para*-aortic, common iliac, and internal iliac nodes were defined as uncommon locations. We conducted comparative analyses among patients with nodes detected in uncommon locations as compared to those with nodes in common locations.

Due to the concern that external iliac nodes may occasionally be misidentified as common iliac nodes and that obturator nodes may be misidentified as internal iliac nodes, patients with *para*-aortic, presacral and parametrial SLN (i.e., very uncommon locations) and the rest of the cohort (i.e., patients with nodes in the pelvic region and the external iliac, obturator, common iliac, and internal iliac basins) were compared in the current study.

At Meir Medical Center, sentinel node mapping was initiated in the second half of 2014. Blue dye was initially used. ICG was the primary dye used beginning in January 2016. Blue dye and Tc^{99} were used in laparotomies and blue dye was used for patients allergic to iodine.

At Kaplan Medical Center, blue dye and Tc^{99} were used for all patients throughout the study period.

Both centers performed cervical injections at the 3:00 and 9:00 points. One mL was injected into the cervical submucosa and 1 mL was injected into the cervical stroma at each point.

All patients with cervical cancer who had tumors > 2 cm and all patients with grade 3 or non-endometrioid type endometrial cancer underwent complete pelvic lymphadenectomy in addition to SNB. Para-aortic dissection was performed at the surgeon's discretion, excluding patients with significant comorbidities.

Both medical centers used the SLN algorithm described in the National Comprehensive Cancer Network guidelines. (Nicole McMillian et al., 2019) When nodes were not detected in cervical cancer patients, ipsilateral lymphadenectomy was performed. Ipsilateral lymphadenectomy was performed in patients with grade one and grade two endometrial cancer when an intra-operative examination revealed > 50% myometrial invasion. Any suspicious nodes seen on pre-operative imaging or intra-operative impression were removed.

In both centers, the same surgeons performed surgeries throughout the entire study period, with the exception of one surgeon who joined the Meir Medical Center team in 2017; however, this surgeon was experienced in SLN mapping in cervical and endometrial cancers.

The pathologic processing of the sentinel nodes was as follows: each node was sectioned into layers and at least three paraffin-embedded slides were prepared. Half of the slides were stained with hematoxylin and eosin and half of the slides were examined through pan keratin immunohistochemistry. The sections were not uniformly wide. Non-sentinel nodes were divided into two sections; each half was stained with hematoxylin and eosin.

Disease stage was determined by the 2009 International Federation of Gynecology and Obstetrics (FIGO) staging system for endometrial cancer and the 2018 FIGO staging system for cervical cancer. Grade one and grade two endometrial carcinoma were defined as low-risk endometrial cancer and grade three and non-endometrioid type endometrial carcinoma were defined as high-risk endometrial cancer (Tables 2 and 3).

Table 1
Patient characteristics (n = 304).

Parameter	Value
Age, mean (range ± SD)	64.05 (27 – 92 ± 11.86)
BMI, mean (range ± SD)	30.54 (18.4 – 58 ± 6.51)
Nulliparous, N (%)	34 (11.2)
Uterine cancer, N (%)	272 (89.5)
Cervical cancer, N (%)	32 (10.5)
Surgical approach, N (%)	
Laparotomy	50 (16.4)
Laparoscopy	233 (76.6)
Robotic	21 (6.9)
Tracer, N (%)	
Blue dye	66 (21.7)
ICG	100 (32.9)
T^{99} & blue dye	138 (45.4)
Detection rate, N (%)	
One side	88 (29)
Bilateral	143 (47)
Not detected	73 (24)
Node locations, N (%)	
External iliac	170 (39.3)
Obturator	173 (40)
Pelvic	38 (8.8)
Common iliac	26 (6)
Internal iliac	10 (2.3)
Para-aortic	8 (1.8)
Pre-sacral	6 (1.4)
Parametrial	2 (0.5)
Mean number of sentinel nodes	3.4 (1–14 ± 2.4)
Mean number of non-sentinel nodes	10.79 (1–52 ± 9.03)
Positive nodes, N (%)	36 (11.84)
Sentinel only	22 (7.2)
Non-sentinel only	7 (2.3)
Sentinel and non-sentinel	7 (2.3)
Histologic type[a], N (%)	
Endometrial endometrioid grade 1	93 (30.59)
Endometrial endometrioid grade 2	95 (31.25)
Endometrial endometrioid grade 3	22 (7.23)
Non-endometrioid endometrial carcinoma	58 (19.07)
Endometrial stromal sarcoma	4 (1.31)
Cervical squamous cell carcinoma	22 (7.23)
Cervical adenocarcinoma	8 (2.63)
Other cervical carcinoma	2 (0.66)
Disease stage – uterine cancer, N (%)	
Stage 1	215 (79)
Stage 2	10 (3.6)
Stage 3	33 (12.1)
Stage 4	2 (0.7)
No residual malignancy	12 (4.4)
Disease stage – cervical cancer, N (%)	
Stage 1	26 (81.2)
Stage 2	3 (9.4)
Stage 3	3 (9.4)
Stage 4	0
Lymph-vascular space involvement, N (%)	78 (27.5)

[a] Post-operative histology, for the 12 patients where tumor was completely resected during the diagnostic procedure, the pre-operative histology was used.

2.1. Statistical analysis

Continuous parameters are presented as means, standard deviations, and ranges. Categorical data are presented as numbers and percentages. Continuous variables were tested for adherence to a normal distribution via the Shapiro-Wilk test; non-parametric tests were performed when an abnormal distribution was detected. The Mann-Whitney test was implemented for intergroup comparisons. Pearson chi-square tests were used for examining associations between categorical variables. Logistic regression was used to model the probability of uncommon and very uncommon SLN; variables with P values < 0.3 in univariate analyses were included in the multivariate analyses. Two-sided P values < 0.05 were considered statistically significant. Data were analyzed using Statistical Package for the Social Sciences software (version 25; SPSS, Inc., Chicago, IL, USA).

Table 2
Comparison between patients with common or uncommon nodes.

Factor	Patients with common or undetected nodes N = 256	Patients with uncommon nodes N = 48	P-value
Age, mean (range ± SD)	63.89 (29–93 ± 11.4)	64.88 (27 – 86 ± 14.7)	0.277
BMI, mean (range ± SD)	31.04 (18.4 – 58 ± 6.67)	27.7 (19 – 44.4 ± 4.45)	0.002
Operated on 2019, n (%)	20 (7.8)	8 (16.7)	0.244
Nulliparous, n (%)	30 (11.7)	4 (8.3)	0.495
Surgical approach, n (%)			
Laparotomy	40 (15.6)	10 (20.8)	0.668
Laparoscopy	198 (77.3)	35 (72.9)	
Robotic	18 (7)	3 (6.3)	
Tracer, n (%)			
Blue dye	63 (24.6)	3 (6.3)	0.005
ICG/ T^{99} & blue dye	193 (75.4)	45 (93.8)	
Post-operative histology, n (%)	153 (62.7)	26 (55.3)	
Low-risk endometrial	62 (25.4)	16 (34)	0.129
High-risk endometrial	2 (0.8)	2 (4.3)	
Endometrial stromal sarcoma	27 (11.1)	3 (6.4)	
Cervical cancer			
Tumor size in mm, mean (range ± SD)	30.5 (2.5 – 100 ± 19.54)	28.38 (2.5–80 ± 17.39)	0.626
Lymph-vascular space invasion, n (%)	63 (26.1)	15 (34.9)	0.237
Number of sentinel nodes, mean (range ± SD)	3.3 (1 – 14 ± 2.4)	3.8 (1–14 ± 2.7)	0.179
Positive nodes, n (%)	30 (11.7)	6 (12.5)	0.878
Disease stage, n (%)			
Stage 1	204 (83.3)	37 (78.7)	0.685
Stage 2	11 (4.5)	2 (4.3)	
Stage 3	28 (11.4)	8 (17)	
Stage 4	2 (0.8)	0	
Medical center, n (%)			
Kaplan	118 (46.1)	29 (60.4)	0.068
Meir	138 (53.9)	19 (39.6)	

Table 3
Comparison between patients with common nodes or very uncommon nodes.

Factor	Patients with common or undetected nodes N = 291	Patients with very uncommon nodes N = 13	P-value
Age, mean (range ± SD)	64.29 (27 – 93 ± 11.69)	58.69 (33 – 76 ± 14.76)	0.271
BMI, mean (range ± SD)	30.69 (18.4 – 58 ± 6.57)	27.53 (20.48 – 32.7 ± 4.31)	0.174
Operated on 2019, n (%)	23 (7.9)	5 (38)	0.013
Nulliparous, n (%)	33 (11.3)	1 (7.7)	0.683
Surgical approach, n (%)			
Laparotomy	45 (15.5)	5 (38.5)	0.085
Laparoscopy	226 (77.7)	7 (53.8)	
Robotic	20 (6.9)	1 (7.7)	
Minimally invasive surgery	246 (84.5)	8 (61.5)	0.029
Tracer, n (%)			
Blue dye	66 (22.7)	0	0.052
ICG/ T^{99} & blue dye	225 (77.3)	13 (100)	
Post-operative histology, n (%)	173 (62.2)	6 (46.2)	0.180
Low risk endometrial	74 (26.6)	4 (30.8)	
High risk endometrial	3 (1.1)	1 (7.7)	
Endometrial stromal sarcoma	28 (10.1)	2 (15.4)	
Cervical cancer			
Tumor size in mm, mean (range ± SD)	30.11 (2.5 – 100 ± 19.08)	31.8 (2.5–80 ± 23.19)	0.91
Lymph-vascular space invasion, n (%)	72 (26.5)	6 (50)	0.07
Number of sentinel nodes, mean (range ± SD)	3.3 (1 – 14 ± 2.3)	4.8 (1 – 14 ± 3.9)	0.246
Positive nodes, n (%)	31 (10.7)	5 (38.5)	0.002
Disease stage, n (%)			
Stage 1	233 (83.5)	8 (61.5)	0.03
Stage 2	13 (4.7)	0	
Stage 3	31 (11.1)	5 (38.5)	
Stage 4	2 (0.7)	0	
Medical center, n (%)			
Kaplan	141 (48.5)	6 (46.2)	0.871
Meir	150 (51.5)	7 (53.8)	

3. Results

This study enrolled a total of 304 patients. Table 1 shows patient demographic and medical characteristics. Among them, 272 (89.5%) had endometrial carcinoma. Only 16.3% underwent an open surgical procedure. The SLN detection rate was 76% and 80% were detected in the obturator and external iliac regions. SLN were detected in more than one location in 55 patients. Forty-eight patients (15.8%) had sentinel nodes in uncommon locations and 13 (4.3%) had sentinel nodes in very uncommon locations. Thirty-six patients (11.8%) had nodal involvement. In seven patients with positive nodes, sentinel nodes were not detected. In all other positive node patients, at least one of the sentinel nodes was involved.

Comparisons among patients with common, uncommon and very uncommon sentinel node locations are shown in Tables 2 and 3. Patients in the uncommon group had a lower body mass index (BMI; 27.7 vs. 31.04 kg/m^2, p = 0.002). Fewer patients in the uncommon group had nodes detected by blue dye only (6.3% vs. 24.6%, p = 0.05).

More patients with very uncommon nodes were operated in 2019 as compared with other study years (38% vs. 7.9%, p = 0.013) and patients operated in 2019 more had positive nodes (38.5% vs. 10.7%, p = 0.002; Table 3). This higher rate of positive nodes resulted in a higher rate of detected stage three disease (38.5% vs. 11.1%, p = 0.03) and a lower rate of stage one disease (61.5% vs. 83.5% p = 0.03). Blue dye was not used in any of the patients with very uncommon node locations (0% vs. 22.7%, p = 0.052). Fewer patients in this group had minimally invasive surgery (61.5% vs. 84.5%, p = 0.029).

Multi-variate regression analyses presented in Table 4 showed that lower BMI, the use of ICG or a combination of Tc^{99} and blue dye, the

Table 4
Regression analysis of predictors for uncommon and very uncommon nodes.

Factor	Relative risk	95% CI	p
BMI[a,c]	0.888	0.821–0.96	0.003
Use of ICG or Tc^{99} & blue dye[a]	8.24	1.82–37.26	0.006
Positive nodes[b]	9.3	2.289–37.826	0.002
Year of surgery[b,c]	2.13	1.187–3.842	0.011

[a] Detection of uncommon nodes
[b] detection of very uncommon nodes
[c] calculated as a continuous variable

presence of positive nodes, and a more recent year of surgery were independent predictors for detecting SLN in uncommon or very uncommon locations. A separate analyses of endometrial cancer patients yielded similar results: BMI had relative risk of 0.867 (95% CI 0.971–0.951, p = 0.002) and the use of ICG or a combination of Tc^{99} and blue dye, had relative risk of 5.07 (95% CI 1.076–23.089, p = 0.04) for detection of uncommon nodes.

4. Discussion

This retrospective study evaluated factors affecting the detection of sentinel nodes in uncommon locations within cervical and endometrial cancers. Tumor characteristics were not related to SLN location in the current study. We found that patients with very uncommon SLN locations had a higher rate of positive nodes and were operated more

recently on average. The use of blue dye was less abundant in the uncommon group and the average BMI was lower in this group.

The associations of BMI, surgical year, and tracer type with the detection of SLN in unexpected locations suggests that surgical conditions and surgeon experience (as opposed to tumor characteristics) are the main predictors for node detection. Of note, laparotomy and the use of ICG/Tc^{99} and blue dye were also associated with very uncommon SLN, though not in the multivariate regression analysis.

This assumption is supported by the findings of Balaya et al. who found that lower weight was related to unexpected sentinel node locations in early-stage cervical cancer. However, in their study, larger tumor size was associated with uncommon SLN locations. They theorized that this finding may be due to larger tumor volumes obstructing lymphatic vessels. (Balaya et al., 2019) In the current study, tumor size did not affect the distribution of SLN. Most patients in this study had endometrial cancer and the tumors did not extend to the cervix – the tracer injection site – in most cases. This may be why the lymphatic channels were not obstructed in the current investigation.

Another finding in Balaya's paper was that nulliparity was a predictor for uncommon SLN locations, which was explained by the modification of lymphatics in pregnancy and delivery. (Balaya et al., 2019) This finding was not replicated in our results.

Interestingly, patients in the very uncommon group had more positive nodes. Among the five patients with positive nodes, sentinel nodes were involved in all five patients and two of the patients had both sentinel and non-sentinel node involvement. There were no other statistically significant differences related to tumor characteristics among the groups. There was a trend toward a higher rate of lymph-vascular space involvement (LVSI) in the very uncommon node location group (50% vs. 26.5%, p = 0.07), and four of the five patients who had positive nodes had LVSI. It is possible that there is additional lymphatic drainage in more advanced disease, or that, as proposed by Balaya et al., the usual lymphatic channels are obstructed by cancer cells and the main drainage is deviated to less common channels. (Balaya et al., 2019) Another potential explanation for these findings is that, when the sentinel node exploration is more thorough, the detection rate is more accurate and positive nodes are not missed. This theory highlights the importance of careful evaluation of all nodal basins in order to identify all sentinel nodes and to detect all positive nodes.

Other studies have evaluated predictors for sentinel node detection and unexpected nodes in cervical cancer. However, to our knowledge, this is the first study to evaluate predictors for uncommon sentinel node locations in a heterogenous gynecologic population (mainly endometrial cancer patients). The study represents real-life medical practice and training, as cases were collected since the initiation of sentinel node mapping in each center.

The limitations of the current study are mainly inherent to its retrospective design. Some data were missing. Of note, BMI was reported in 241 of the 304 patients included. Blue dye was used in 60 patients, though this has been shown to be less effective in node detection. Although more positive nodes were detected in the uncommon node location group, there are no data to show that this improved disease-related outcomes.

In conclusion, we found that uncommon sentinel node detection in cervical and endometrial cancer was mainly related to the surgeon's experience and surgical factors in the current investigation. This finding, if confirmed, will encourage gynecologic oncologists to thoroughly explore the parametrial, pre-sacral, common iliac, and *para*-aortic regions in order to identify all positive nodes, regardless of tumor characteristics.

CRediT authorship contribution statement

Yfat Kadan: Conceptualization, Methodology, Formal analysis, Data curation, Writing – original draft, Project administration. **Alexandra Baron:** Data curation. **Yoav Brezinov:** Data curation. **Alon Ben Arie:** Resources, Supervision. **Ami Fishman:** Resources, Supervision. **Mario Beiner:** Resources, Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Nicole McMillian N, Frederick P, Gaffney DK, George S, Giuntoli RI, Han E, et al. Continue NCCN Guidelines Panel Disclosures Ω Gynecologic oncology † Medical oncology § Radiotherapy/Radiation oncology ≠ Pathology ¥ Patient advocacy Þ Internal medicine *Discussion Section Writing Committee Emily Wyse ¥ Patient Advocate NCCN Guidelines Version 4.2019 Uterine Neoplasms. 2019.

Kadkhodayan S, Hasanzadeh M, Treglia G, Azad A. Sentinel node biopsy for lymph nodal staging of uterine cervix cancer : A systematic review and meta-analysis of the pertinent literature. Eur J Surg Oncol [Internet]. 2015;41(1):1–20. Available from: 10.1016/j.ejso.2014.09.010.

Diab, Y., 2017. Sentinel Lymph Nodes Mapping in Cervical Cancer a Comprehensive Review. Sentinel Lymph Nodes Mapping in Cervical Cancer a Comprehensive Review. 27 (1), 154–158.

Gortzak-uzan L, Jimenez W, Nofech-mozes S, Ismiil N, Khalifa MA, Dubé V, et al. Gynecologic Oncology Sentinel lymph node biopsy vs . pelvic lymphadenectomy in early stage cervical cancer : Is it time to change the gold standard ? Gynecol Oncol [Internet]. 2010;116(1):28–32. Available from: 10.1016/j.ygyno.2009.10.049.

Anna QQ. Sentinel lymph node assessment in endometrial cancer: a systematic review and meta-analysis. Am J Obstet Gynecol [Internet]. 2017; Available from: 10.1016/j.ajog.2016.11.1033.

Rossi, E.C., Kowalski, L.D., Scalici, J., Cantrell, L., Schuler, K., Hanna, R.K., Method, M., Ade, M., Ivanova, A., Boggess, J.F., 2017. A comparison of sentinel lymph node biopsy to lymphadenectomy for endometrial cancer staging (FIRES trial): a multicentre, prospective, cohort study. The Lancet Oncology 18 (3), 384–392.

Marnitz, S., Köhler, C., Bongardt, S., Braig, U., Hertel, H., Schneider, A., 2006. Topographic distribution of sentinel lymph nodes in patients with cervical cancer. Topographic distribution of sentinel lymph nodes in patients with cervical cancer. 103 (1), 35–44.

How, J., Boldeanu, I., Lau, S., Salvador, S., How, E., Gotlieb, R., Abitbol, J., Halder, A., Amajoud, Z., Probst, S., Brin, S., Gotlieb, W., 2017. Unexpected locations of sentinel lymph nodes in endometrial cancer. Gynecologic Oncology 147 (1), 18–23.

Balaya, V., Mathevet, P., Magaud, L., Bonsang-Kitzis, H., Delomenie, M., Montero Macias, R., Ngô, C., Bats, A.S., Lécuru, F., 2019. Predictive factors of unexpected lymphatic drainage pathways in early-stage cervical cancer. Gynecologic Oncology 154 (1), 102–109.