Evaluation of Sentinel Lymph Nodes in Complex Atypical Endometrial Hyperplasia

Hala Al Kallas , Pamela Cooper , Shruti Varma , Jenna Peplinski , Yan Hong Kuo , Brianna Miller , Noelle Aikman , Mark Eliot Borowsky , Ashley Haggerty , Karim ElSahwi *

Posted Date: 19 April 2024

doi: 10.20944/preprints202404.1345.v1

Keywords: Complex atypical hyperplasia; robotic surgery; sentinel lymph node; indocyanine green; endometrial cance

 doi:10.20944/preprints202404.1345.v1

Research Article

Evaluation of Sentinel Lymph Nodes in Complex Atypical Endometrial Hyperplasia

Hala Al Kallas [1], Pamela Cooper [2], Shruti Varma [1], Jenna Peplinski [1], Yan Hong Kuo [2], Brianna Miller [1], Noelle Aikman [1], Mark Borowsky [1], Ashley Haggerty [1] and Karim Elsahwi [1]

[1] Department of Obstetrics and Gynecology, Hackensack Meridian Healthcare Jersey Shore University Medical Center; hala.alkallas@gmail.com; svarma1016@gmail.com; jnpeplinski13@gmail.com; brianammillerpa@gmail.com; noelle.aikman@hmhn.org; mark.borowsky@hmhn.org; ashley.haggerty@hmhn.org

[2] Department of Research Administration, Hackensack Meridian Healthcare Jersey Shore University Medical Center; pamela.cooper@hmhn.org; yenhong.kuo@hmhn.org

* Correspondence: karim.elsahwi@hmhn.org; Tel.: 732-776-3790

Abstract: Complex atypical endometrial hyperplasia (CAH) carries a high probability of cancer. Intraoperative evaluation of endometrial cancer in cases of CAH has not been reliable. The safety and sensitivity of sentinel lymph node (SLN) sampling has been validated. **We aim to evaluate the efficacy and safety of SLN sampling in CAH managed by the da Vinci robotic platform.** A total of 113 patients with a preoperative diagnosis of CAH were included in this retrospective cohort study. All underwent a robot assisted total laparoscopic hysterectomy and bilateral salpingo-oophorectomy with 69 patients undergoing SLN sampling. Statistical analysis calculated the probability of cancer, SLN map rate, and surgical complications. Predictors of cancer were evaluated. Forty-seven percent of the entire cohort were diagnosed with endometrial cancer. Median age was 63 years in the SLN cohort (N = 69) and 61 in the No SLN cohort (N = 44) (p= 0.363). Median BMI was 34 Kg/m^2 in the SLN cohort and 40 in the No SLN cohort (p= 0.004). Bilateral SLN map was 92.8% and unilateral SLN map rate was 7.2%. There were no grade 3-4 complications in the SLN cohort, and 4 grade 3-4 complications in the No SLN group (p=0.021). A preoperative diagnosis of CAH bordering on or cannot rule out cancer was the only predictor of cancer. Sentinel lymph node sampling has a high map rate and low complications in CAH. We recommend a prospective study investigating the clinical benefit of the procedure.

Keywords: Complex atypical hyperplasia; robotic surgery; sentinel lymph node; indocyanine green; endometrial cancer

1. Introduction

Complex atypical hyperplasia (CAH) of the endometrium is a precursor lesion for endometrial cancer. Up to 42% of cases of CAH diagnosed on endometrial biopsy are found to harbor endometrial cancer on hysterectomy specimens [1]. Guidelines for the management of complex endometrial hyperplasia lack clear direction [2] and practice patterns vary from no staging, intraoperative endometrial assessment, and conventional lymph node sampling [3–6]. This lack of consistency ultimately results in some endometrial cancer cases being un-staged, undertreated, or overtreated [7].

The American College of Obstetrics and Gynecology Committee currently recommends a total abdominal hysterectomy, with or without bilateral salpingo-oophorectomy, including an option for intraoperative evaluation for possible staging of an endometrial cancer [2].

Most of those cancers are low risk [8] defined as grade 1-2 endometrioid adenocarcinomas that are less than or equal to 2 cm in size that invade less than or equal to 50% of the myometrium. Those cancers have been found to have a low risk of Lymph node metastasis and therefore do not need staging by lymph node dissection [9,10].Nevertheless, evaluating these factors by frozen section analysis has been found to lack validity in most institutions, as evidenced by low accuracy rates

 doi:10.20944/preprints202404.1345.v1

reported in various studies [11–13]. This poses a challenge, as the procedure requires time and resources that are not universally available [14].

Sentinel lymph node sampling is now an established staging procedure for endometrial cancer[15] that obviates the need for comprehensive lymph node dissection with its attendant potential morbidity and cost [16–19]. The validity of this technique has now been well documented in large studies [20,21] and an NCCN guideline algorithm exists that informs its use in endometrial cancer [22].

Laparoscopic staging of endometrial cancer by identifying sentinel lymph nodes under near-infrared light after injecting Indocyanine Green (ICG) dye in the cervix has a high map-rate and negative predictive value and its safety has been well documented [15,16,20,21].

The use of sentinel lymph node sampling in CAH stems from studies that have demonstrated that up to 10% of cases were classified as high-risk for metastatic disease [1–8], with a risk of lymph node metastasis of 3-7% [8]. Sentinel lymph node sampling in CAH had a high map-rate and negative predictive value, and without adding morbidity or surgical time [7,8,23].

The aim of this study is to evaluate the efficacy and safety of sentinel lymph node sampling in cases of complex atypical endometrial hyperplasia surgically managed by the da Vinci (Intuitive Surgical, Sunnyvale CA) robotic platform using cervical injection of ICG dye under near-infrared light.

2. Results

One-hundred and thirteen (N=113) patients were included in the study. Sixty-nine patients underwent Sentinel lymph node sampling (SLN), and 44 did not (NO SLN). The average age in the SLN cohort was 63 years, and in the NO SLN cohort was 61.2 years. The median BMI was significantly lower in the SLN cohort (34.3 Kg/m^2) compared to the NO SLN cohort (40.0 Kg/m^2) (p= 0.004). Twenty-six percent of the cohort had diabetes mellitus, 65% had hypertension, and 34% had hyperlipidemia with no statistical difference between the two sub-cohorts. Most patients had an ASA grade of 2-3 with no statistical difference between the two cohorts (Table 1).

Table 1. Patient characteristics.

Variable	SLN N = 69	No SLN N = 44	Total N = 113	P-value
Median Age (Q1-Q3) – years	63[57 – 70]	61 [53 – 67.25]	62 [56 – 69]	0.363
Median BMI (Q1-Q3) - Kg/m^2	34 [30.0 - 38.6]	40.0 [33.7 - 44.0]	36.3 [31.7 - 41.0]	**0.004**
Diabetes Mellitus	16 (23.2%)	14 (31.8%)	30 (26.5%)	0.427
Hypertension	44 (63.8%)	30 (68.2%)	74 (65.5%)	0.781
Hyperlipidemia	21 (30.4%)	18 (40.9%)	39 (34.5%)	0.348
ASA grade				0.789
1	1 (1.4%)	0 (0%)	1 (0.9%)	
2	30 (43.5%)	16 (36.4%)	46 (40.7%)	
3	37 (53.6%)	28 (63.6%)	65 (57.5%)	
4	1 (1.4%)	0 (0%)	1 (0.9%)	

SD: Standard deviation. SLN: Sentinel lymph node. ASA: American Society of Anesthesiologists Classification.

Table 2 summarizes the histopathological variables of our cohort. Sixty-three (55.8%) patients had their diagnosis through hysteroscopy dilation and curettage, and fifty (44%) patients were diagnosed by endometrial biopsy (p=0.44). Thirty-nine (34.5%) patients were diagnosed with complex atypical hyperplasia of the endometrium either bordering on endometrial cancer or cannot rule out endometrial cancer (CAH/EAC) (p= 1.00). Fifty-two (46%) patients were diagnosed with endometrial cancer on final pathology, 32 (46.4%) in the SLN cohort and 20 (45.5%) in the NO SLN cohort (p= 0.215).

 doi:10.20944/preprints202404.1345.v1

Table 2. Histopathological data.

Variable	SLN N=69	NO SLN N=44	Total N=113	P-value
Preop. Diagnosis				1.000
CAH	45 (65.2%)	29 (65.9%)	74 (65.5%)	
CAH/EAC	24 (34.8%)	15 (34.1%)	39 (34.5%)	
Postop. diagnosis				0.215
No hyperplasia	9 (13%)	11 (25%)	20 (17.7%)	
CAH	28 (40.6%)	13 (29.5%)	41 (36.3%)	
EAC	32 (46.4%)	20 (45.5%)	52 (46%)	
Biopsy Method				0.444
EMB	33 (47.8%)	17 (38.6%)	50 (44.2%)	
D&C	36 (52.2%)	27 (61.4%)	63 (55.8%)	

SLN: Sentinel lymph node. CAH: Complex atypical hyperplasia. CAH/EAC: complex atypical hyperplasia bordering on cancer or cannot rule out cancer. Preop.: preoperative. Postop.: post operative.

Table 3 describes the characteristics of patients with endometrial cancer. Fifty-two (46%) patients were diagnosed with **endometrial cancer** on post operative histopathological analysis, 32 were in the SLN cohort and 20 were in the NO SLN cohort (Table 3). All patients had **endometrioid histopathology**, there were no cases of uterine carcinosarcoma, uterine serous cancer or clear cell carcinoma of the endometrium. Fifty (96.2%) patients had **FIGO grade** 1 or 2 disease, and 2 (3.8%) had grade 3 disease. There was no statistical difference between the two cohorts.

Table 3. Characteristics of patients with endometrial cancer (N=52).

Variable Number (%)	SLN N=32	NO SLN N=20	Total N=52	P-value
EAC Grade				
1/2	30 (93.7%)	20 (100.0%)	50 (96.2%)	0.517
3	2 (6.3%)	0 (0.0%)	2 (3.8%)	
Stage				
IA	20 (62.5%)	16 (80.0%)	36 (69.2%)	0.427
IB	11 (34.4%)	4 (20.0%)	15 (28.8%)	
II	1 (3.1%)	0 (0%)	1 (1.9%)	
DOI				
< or equal to 50%	20 (62.5%)	16 (80.0%)	36 (69.2%)	0.307
> 50%	12 (37.5%)	4 (20.0%)	16 (30.8%)	
Size				
(not specified %)	*3 (9.3%)*	*3 (15%)*	*6 (11.5%)*	
< or equal to 2 CM	11 (34.3%)	8 (40%)	19 (36.5%)	0.767
> 2 CM	18 (56.2%)	9 (45%)	27 (51.9%)	
LVI				
ABSENT	29 (90.6%)	20 (100%)	49 (94.2%)	0.276
PRESENT	3 (9.4%)	0 (0%)	3 (5.8%)	
Cytology				1.000**
NEGATIVE	25 (78.1%)	19 (95.0%)	44 (84.6%)	
POSITIVE	0 (0%)	0 (0%)	0 (0%)	
Missing data	7 (21.9%)	1 (5.0%)	8 (15.4%)	0.132***
Preop Diagnosis			23 (44.2%)	0.707

 doi:10.20944/preprints202404.1345.v1

CAH	13 (40.6%)	10 (50%)	29 (55.8%)	
CAH/EAC	19 (59.4%)	10 (50%)		
Biopsy Method				
EMB	16 (50%)	10 (50%)	26 (50%)	1.000
D&C	16 (50%)	10 (50%)	26 (50%)	

SLN: Sentinel lymph node. EAC: Endometrioid adenocarcinoma. USC: Uterine serous cancer. UCS: Uterine carcinosarcoma. CCC: Clear cell carcinoma. DOI: Depth of invasion. LVI: Lymphovascular space invasion. CAH: Complex atypical hyperplasia. CAH/EAC: complex atypical hyperplasia bordering on endometrial cancer or cannot rule out cancer. Notes: *: The p-value is for the distribution of "< OR EQUAL TO 2 CM" vs. ">2 CM". **: The p-value is for the distribution of "NEGATIVE" vs. "POSITIVE". The percentages are based on "NEGATIVE", "POSITIVE" and "Missing data". ***: The p-value is for the distribution of "NEGATIVE" vs. "Missing data". The percentages are based on "NEGATIVE", "POSITIVE" and "Missing data".

Thirty-six (69%) patients were diagnosed with **stage** 1A cancer, and 15 (28.8%) had stage 1B. There was no statistical difference between the two cohorts. Only one patient -in the SLN cohort- had stage II cancer. One patient with stage IB disease had positive isolated tumor cells (ITC) LN metastasis. According to consensus guidelines [15] this did not up-stage the patient to stage III C1, and the patient was treated with adjuvant brachytherapy to the vaginal cuff following NCCN guidelines[22] for treatment of stage IB disease (Table 3).

Thirty-six (69.2%) patients had a **depth of invasion** less than or equal to 50%, and 16 (30.8%) patients had the depth of invasion more than 50%. There was no statistical difference between the two cohorts. The **size** of the tumor was less than or equal to 2 centimeters in 19 (36.5%) patients, and more than 2 centimeters in 27 (51.9%) patients. The size of the tumor was not determined in 6 (11.5%) patients. There was no statistical difference between the two cohorts. **Lymphovascular space invasion** was reported in 3 (5.8%) patients in the SLN cohort. **Peritoneal cytology** was not reported to be positive for malignant cells in any patient (Table 3).

There was no statistical difference between the two cohorts regarding the **preoperative diagnosis** or the **biopsy method** with 29 (55.8%) patients diagnosed with complex atypical hyperplasia bordering on or cannot rule out cancer (CAH/EAC), and 26 (50%) patients diagnosed by curettage (D&C) (Table 3).

Twenty seven out of 52 cancer patients did not meet low-risk **Mayo Clinic criteria** (grade 1-2; less than or equal to 2 cm in greatest diameter; and depth of myometrial invasion less than or equal to 50%). These patients comprised 23.8 % of the entire cohort and would have required lymph node assessment [9,10].

On multivariate analysis, only preoperative histology (complex atypical hyperplasia bordering on or cannot rule out cancer (CAH/EAC) vs. complex atypical hyperplasia (CAH)) was found to be a significant **predictor of cancer** (P<0.001). Age, BMI, Diabetes mellitus, hypertension, hyperlipidemia, and biopsy method did not predict cancer in our model (Appendix A).

Thirty-nine (34.5%) patients were diagnosed with CAH bordering on EAC **(CAH/EAC)** preoperatively. Twenty-nine out of thirty-nine (74.3%) were diagnosed with cancer postoperatively versus 23/74 (31%) in those preoperatively diagnosed with CAH (P<0.001) **(Table 3)**. There was no statistical difference between those two subgroups regarding age, BMI, diabetes mellitus, hypertension, hyperlipidemia, biopsy method, postoperative grade or stage, size of the tumor or depth of invasion (Appendix B). Multiple logistic regression analysis using the same variables demonstrated no significant difference between the two subgroups (Appendix C).

Bilateral mapping to the sentinel **lymph nodes** (Table 4) was achieved in 64 (92.8%) of the 69 patients in the SLN cohort while unilateral mapping was achieved in the remaining 5 (7.2%) patients. A lymph node was recovered from both hemi-pelvises in 63/64 bilaterally mapped patients and from all patients that mapped unilaterally (Table 4). Pelvic lymph node dissection was performed in 4 patients in the SLN cohort and in 4 patients in the NO SLN cohort, while para-aortic lymph node dissection was performed in 1 patient in the NO SLN cohort. A lymph node was reported to be positive for isolated tumor cells (ITC) LN in 1 patient in the SLN cohort (Table 4).

 doi:10.20944/preprints202404.1345.v1

Table 4. Lymph node data (N=113).

Variable	Value	SLN N=69	NO SLN N=44	Total N=113	P-value
Mapping	No	0 (0%)	44 (100%)	44 (38.9%)	<0.001
	Unilateral	5 (7.2%)	0 (0%)	5 (4.4%)	
	Bilateral	64 (92.8%)	0 (0%)	64 (56.6%)	
SLNB	No	1 (1.4%)	44 (100%)	45 (39.8%)	<0.001
	Unilateral	6 (8.7%)	0 (0%)	6 (5.3%)	
	Bilateral	62 (89.9%)	0 (0%)	2 (54.9%)	
PLND	No	65 (94.2%)	40 (90.9%)	105 (92.9%)	0.844
	Unilateral	3 (4.3%)	3 (6.8%)	6 (5.3%)	
	Bilateral	1 (1.4%)	1 (2.3%)	2 (1.8%)	
PALND	No	69 (100%)	43 (97.7%)	112 (99.1%)	0.389
	Yes	0 (0%)	1 (2.3%)	1 (0.9%)	
Cytology	Negative	56 (81.2%)	43 (97.7%)	99 (87.6%)	1.000*
	Positive	0 (0%)	0 (0%)	0 (0%)	
	N/A	13 (18.8%)	1 (2.3%)	14 (12.4%)	0.008*

Notes: *: The p-value is for the distribution of "0" vs. "1". The percentages are based on "0", "1" and "n/a". **: The p-value is for the distribution of "0" vs. "n/a". The percentages are based on "0", "1" and "n/a".

Operative findings are summarized in Table 5. The mean operative time was 148.8 minutes in the SLN cohort and 144.3 minutes in the NO SLN cohort (p = 0.918). The mean estimated blood loss was 92 milliliters in the SLN cohort and 109 milliliters in the NO SLN cohort (p = 0.009). There was no conversion to laparotomy. Grade 3 or 4 Clavien-Dindo [26,27] complications were reported in no patients in the SLN cohort and 4 (9%) patients in the NO SLN cohort (P = 0.021), with 3 patients with grade-3 and 1 patient with grade-4 complications (Table 5). A detailed narrative of those complications is provided in Appendix D.

Table 5. Operative data.

Variable	SLN N=69	NO SLN N=44	Total N=113	P-value
Mean LOS (SD) -min	148.8 (58.2)	144.3 (38.4)	147 (51.2)	0.918
Mean EBL (SD) - ml	91.9 (87.9)	109.1 (55.0)	98.6 (77.0)	0.009
Complications Grade 3/4[$]	0 (0%)	4 (9.1%)	4 (3.5%)	
Bowel perforation/fistula	0	2	2	**0.021**
Vaginal cuff dehiscence	0	1	1	
Wound infection	0	1	1	

SD: Standard deviation. SLN: Sentinel lymph node. LOS: Length of surgery. EBL: estimated blood loss. [$]Clavien-Dindo classification system of complications [26,27]. ml: milliliters.

3. Discussion

In this single institution retrospective cohort study, the prevalence of endometrial cancer in patients with a preoperative diagnosis of CAH was 46%. Most patients with cancer had a low-grade disease. All of them had early-stage disease, but 23.8% met Mayo criteria for lymph node dissection. When sentinel lymph node sampling was attempted, bilateral mapping was achieved in 92.8% of patients and unilateral mapping was achieved in 7.2%. Sentinel lymph node sampling was not associated with additional complications.

SLN evaluation has become a widely adopted technique for endometrial cancer staging due to its safety and high sensitivity in detecting lymph node metastasis when combined with ultra-staging using immunohistochemistry [20,21,28,29], and an NCCN algorithm is a sanctioned standard of care

 doi:10.20944/preprints202404.1345.v1

in its management [22,24]. SLN Mapping using cervical injection of ICG dye under near infrared light has shown an improved sensitivity and negative predictive value [16; 20-21], and although the technology is available in different platforms, it is safe to assume that most gynecological oncologists in the United States are currently well trained to perform the procedure expeditiously and safely using the da Vinci (Intuitive Surgical, Sunnyvale CA) robotic platform [7,20,30,31].

Given that the risk of endometrial cancer is up to 42% [1] in patients with a preoperative diagnosis of CAH investigators have begun to study sentinel lymph node sampling in the management of such patients [5,7,8]. The necessity for this research has stemmed from the fact that the sensitivity of a preoperative biopsy in the diagnosis of cancer is low with a high rate of inter and intra-observer variability on the largest prospective GOG trial [1,32]. Intraoperative diagnosis of cancer by frozen section analysis has been reported in studies as an effective method [9,33], however the technique has not been shown to be reliable outside of a few centers with dedicated personnel, time and resources [11–14] additionally, sentinel lymph node sampling after a hysterectomy has severed the uterine lymphatics is technically challenging.

It is true, however, that the prevalence of high-intermediate risk cancer or high-risk cancer in this population is about 10% [1,8] and the incidence of lymph node metastasis is about 3-7% [8]. Although identifying those patients would inform adjuvant treatment and prevent either reoperation or overtreatment with radiation therapy [34,35], a surgical technique that benefits such a relatively small number of patients must have an equally low risk of complications.

Retrospective studies on the use of SLNS in CAH have consistently reported a low complication rate [7,36]. We used a validated surgical complication score [26,27] and found no grade 3 or 4 morbidity associated with SLNS. Indeed, all 4 of our grades 3-4 complications were in the NO SLN cohort likely reflecting the statistically unbalanced nature of our retrospective cohort where patients with a higher BMI and more comorbidities did not undergo SLNS.

As mentioned above our study is limited by its retrospective nature and hence the selection bias inherent in our analysis. The small sample size allowed for a limited multiple logistic regression analysis model which, consistent with findings by Touhami et al. [5] identified a preoperative diagnosis of complex atypical hyperplasia, cannot rule out or bordering on cancer (CAH/EAC) as a significant predictive factor of a postoperative diagnosis of cancer.

However, we did not evaluate the contribution of other predictive factors such as preoperative endometrial thickness, which was found to predict cancer where an endometrial thickness of ≥ 15 mm was associated with a 1.5 times risk of cancer and a 2.5 times risk of meeting Mayo clinic criteria for lymph node dissection [37,38]. Furthermore, Laskov et al. [39] reported on 79 patients with CAH where CAH in a polyp was associated with significantly less incidence of not only cancer but also higher grade and stage disease [39]. Including as many relevant factors as possible in a preoperative algorithm to instruct the most efficient management policy is certainly warranted.

Another possible selection bias that appeared in our study is the significantly higher BMI in patients in the NO SLN cohort. This most likely reflects the surgeon's reluctance to perform a procedure whose risk may outweigh its benefit. Kogan et al. [40] reported on 223 obese (median BMI 40.6 Kg/m^2) patients with endometrial cancer where SLN sampling was not associated with a difference in overall survival or progression free survival while being associated with a significant increase in operative time and blood loss although the clinical significance of the small change reported is unclear. Whether obesity is a risk factor for unsuccessful SLN mapping is controversial in the literature [41,42].

Nevertheless, this study elucidated the low sensitivity of preoperative sampling whether by endometrial biopsy or curettage to diagnose cancer in contradistinction to the high reliability and safety of performing sentinel lymph node sampling in this population where 10%-28% meet criteria for lymph node dissection [8,37].

In conclusion, given the low risk of SLNS, we support a prospective study into its clinical benefit in patients with a preoperative diagnosis of CAH. As conceptualized by others, such a study should include a preoperative radiological [38] histopathological [5,39] and molecular [7] classification algorithm of specimens to further the diagnosis and inform the management of this entity.

 doi:10.20944/preprints202404.1345.v1

4. Materials and Methods

This was a retrospective cohort study conducted between December of 2016 and March of 2023 after obtaining Institutional Review Board l (IRB) approval [number 201504071 J]. The study included all patients ranging in age between 18 and 90 years with complex atypical endometrial hyperplasia diagnosed on preoperative biopsy or on a dilation and curettage sample and managed surgically using the da Vinci (Intuitive Surgical, Sunnyvale CA) robotic platform. The authors excluded all patients with hyperplasia of the endometrium without atypia.

This cohort was treated by two surgeons at our institution. All patients underwent a robot (da Vinci platform, Sunnyvale, CA) assisted total laparoscopic hysterectomy and bilateral salpingo-oophorectomy. Sentinel lymph node sampling was conducted when feasible or when deemed necessary by the surgeon based on their interpretation of the preoperative histopathological findings. Complex atypical hyperplasia of the endometrium bordering on endometrial cancer or cannot rule out endometrial cancer (CAH/EAC) was an indication for sentinel lymph node sampling unless contraindicated by other variables such as morbid obesity, serious comorbidities such as coagulopathy or heart disease, or, in some cases, lack of mapping under near-infrared light after injection of indocyanine green (ICG) dye in the cervix. The da Vinci platform-mounted near-infrared light camera was used for the identification of sentinel lymph nodes and ICG dye (0.5mg/ml) was injected in the cervix in the standard manner reported previously at 3 o'clock and 9 o'clock, 2 millimeters deep and 1 centimeter deep [24]. The National Comprehensive Cancer Network (NCCN) [22] algorithm for sentinel lymph node sampling in endometrial cancer was followed in most cases undergoing SLN dissection. If mapping for SLN was negative in one hemi-pelvis then a systematic lymph node dissection of this hemi-pelvis was performed [22] unless the risk was deemed to outweigh the benefit. Additionally, excision of suspicious lymph nodes and para-aortic lymph node dissection were performed at the surgeon's discretion. An intraoperative frozen section analysis was inconsistently used, and the findings shall not be reported in this analysis.

The numerical variables were summarized using median and interquartile range (first quartile – third quartile). The categorical variables were summarized using frequencies and percentage. To compare the cohorts, the Student's t-test or Wilcoxon Rank Sum test was used for numerical variables as appropriate. The chi-square test or Fisher exact test was used for the categorical variables, based on the sample size. Multiple logistic regression analysis was used to assess the chance of having cancer with the variables of interest. The 2-sided p value was reported for each test. A p value less than 0.05 was considered an indication of statistical significance. Statistical analysis was performed using the R language [25].

Author Contributions: Conceptualization, K.E.; methodology, K.E, H.A., S. V., J. P.; formal analysis, Y. H. K.; investigation, K. E.; resources, K.E, M. B.; data curation, H. A., P. C.; writing—original draft preparation, K.E., H. A; writing—review and editing, N.A., M.B., and A. H.; supervision, K.E; project administration, P. C. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Hackensack Meridian Health (approval number 201504071 J on April 4th, 2022).

Informed Consent Statement: Patient consent was waived due to the retrospective nature of the study and as it presents no risk to the subjects.

Conflicts of Interest: The authors declare no conflicts of interest.

 doi:10.20944/preprints202404.1345.v1

Appendix A: Endometrial cancer patients stratified by preoperative diagnosis (N=52)

Variable	CAH (N=23)	CAH/EAC (N=29)	P Value
Median Age (Q1-Q3) - years	64.7 (10.0)	61.6 (11.6)	0.312
Median BMI (Q1-Q3) – Kg/m²	36.3 (6.5)	38.1 (7.4)	0.357
DM			0.786
No	16 (69.6%)	18 (62.1%)	
Yes	7 (30.4%)	11 (37.9%)	
HTN			0.188
No	4 (17.4%)	11 (37.9%)	
Yes	19 (82.6%)	18 (62.1%)	
HPL			0.843
No	15 (65.2%)	17 (58.6%)	
Yes	8 (34.8%)	12 (41.4%)	
ASA			
I	NA	NA	
II	8 (34.8%)	10 (34.5%)	0.648
III	14 (60.9%)	19 (65.5%)	
IV	1 (4.3%)	0 (0%)	
Biopsy method			1.000
EMB	11 (47.8%)	15 (51.7%)	
D&C	12 (52.2%)	14 (48.3%)	
Any LND (SLNB *OR* PLD *OR* PPALND)			0.752
No	9 (39.1%)	9 (31.0%)	
Yes	14 (60.9%)	20 (69.0%)	
Grade			
I	17 (73.9%)	21 (72.4%)	1.000
II	5 (21.7%)	7 (24.1%)	
III	1 (4.3%)	1 (3.4%)	
Stage			
IA	16 (69.6%)	20 (69.0%)	0.740
IB	6 (26.1%)	9 (31.0%)	
II	1 (4.3%)	0 (0.0%)	
DOI			1.000
< 50%	16 (69.6%)	20 (69.0%)	
> OR EQUAL TO 50%	7 (30.4%)	9 (31.0%)	
Size			
(not specified %)	5(21.7%)	1 (3.4%)	0.513
< 2 CM	9 (39.1%)	10 (34.5%)	
> OR EQUAL TO 2 CM	9 (39.1%)	18 (62.1%)	
LVI			1.000
No	22 (95.7%)	27 (93.1%)	
Yes	1 (4.3%)	2 (6.9%)	

ASA: American Society of Anesthesiologists Classification. BMI: Body mass index. DM: Diabetes Mellitus. HTN: Hypertension. HPL: Hyperlipidemia. DOI: Depth of invasion. SLN: Sentinel lymph node. EAC: Endometrioid adenocarcinoma. LVI: Lymphovascular space invasion. CAH: Complex atypical hyperplasia. CAH/EAC: complex atypical hyperplasia bordering on endometrial cancer or cannot rule out cancer.

 doi:10.20944/preprints202404.1345.v1

Appendix B: Multiple logistical regression. Predictors of Endometrial cancer

Risk factor		Standard Error	P Value
Age	0.023	0.023	0.3
BMI	0.013	0.03	0.66
Diabetes	0.344	0.524	0.51
Hypertension	0.636	0.511	0.21
Hyperlipidemia	-0.121	0.478	0.8
Preop. Diagnosis	1.99	0.484	0.001
Biopsy Method	-0.436	0.44	0.32

Appendix C: Simple logistical regression. Preoperative diagnosis CAH vs. CAH/EAC

Variable	P-value
AGE	0.532
BMI	0.338
DM	0.076
HTN	0.243
HLD	0.416
Biopsy Method	0.257
Post op Grade	0.813
Post op Size	0.422
DOI	0.813
LVI	0.984
Stage	0.813

BMI: Body mass index. DM: Diabetes Mellitus. HTN: Hypertension. HPL: Hyperlipidemia. DOI: Depth of invasion. EAC: Endometrioid adenocarcinoma. LVI: Lymphovascular space invasion. CAH: Complex atypical hyperplasia. CAH/EAC: complex atypical hyperplasia bordering on endometrial cancer or cannot rule out cancer.

Appendix D: Narrative description of postoperative complications (N=4)

One 90-year-old patient in the NO SLN cohort with a history of extensive diverticular disease underwent reoperation, sigmoid colectomy and colostomy 10 days after a full robotic hysterectomy and bilateral salpingo-oophorectomy for a ruptured diverticular abscess. Another 62-year-old patient with a BMI of 40 and severe diverticular disease encountered during the operation underwent primary bladder repair and sigmoid serosal repair by colorectal surgery service during the robotic hysterectomy however developed a colo-vesical fistula 3 months later requiring a low anterior resection and anastomosis.

A 46-year-old patient with a BMI of 36.6 diabetes mellitus renal failure and chronic anticoagulation developed vaginal cuff bleeding and dehiscence requiring repair in the operating room two weeks after her robotic Surgery.

And finally, a 59-year-old patient with a BMI of 33 developed an incisional site infection necessitating incision and drainage in the operating room about 10 days after her robotic surgery.

References

1. Trimble CL, Kauderer J, Zaino R, et al. Concurrent endometrial carcinoma in women with a biopsy diagnosis of atypical endometrial hyperplasia: A gynecologic oncology group study. *Cancer*. 2006;106(4). doi:10.1002/cncr.21650
2. Management of Endometrial Intraepithelial Neoplasia or Atypical Endometrial Hyperplasia: ACOG Clinical Consensus No. 5. *Obstetrics and Gynecology*. 2023;142(3). doi:10.1097/AOG.0000000000005297

3. Costales AB, Schmeler KM, Broaddus R, et al. Clinically significant endometrial cancer risk following a diagnosis of complex atypical hyperplasia. In: *Gynecologic Oncology*. Vol 135. ; 2014. doi:10.1016/j.ygyno.2014.10.008
4. Morotti M, Menada MV, Moioli M, et al. Frozen section pathology at time of hysterectomy accurately predicts endometrial cancer in patients with preoperative diagnosis of atypical endometrial hyperplasia. In: *Gynecologic Oncology*. Vol 125; 2012. doi:10.1016/j.ygyno.2012.02.011
5. Touhami O, Grégoire J, Renaud MC, Sebastianelli A, Grondin K, Plante M. The utility of sentinel lymph node mapping in the management of endometrial atypical hyperplasia. *Gynecol Oncol*. 2018;148(3):485-490. doi:10.1016/j.ygyno.2017.12.026
6. Lim SL, Moss HA, Secord AA, Lee PS, Havrilesky LJ, Davidson BA. Hysterectomy with sentinel lymph node biopsy in the setting of pre-operative diagnosis of endometrial intraepithelial neoplasia: A cost-effectiveness analysis. *Gynecol Oncol*. 2018;151(3). doi:10.1016/j.ygyno.2018.09.020
7. Mueller JJ, Rios-Doria E, Park KJ, et al. Sentinel lymph node mapping in patients with endometrial hyperplasia: A practice to preserve or abandon? *Gynecol Oncol*. 2023;168. doi:10.1016/j.ygyno.2022.10.017
8. Matanes E, Amajoud Z, Kogan L, et al. Is sentinel lymph node assessment useful in patients with a preoperative diagnosis of endometrial intraepithelial neoplasia? *Gynecol Oncol*. 2023;168. doi:10.1016/j.ygyno.2022.10.023
9. Kumar S, Medeiros F, Dowdy SC, et al. A prospective assessment of the reliability of frozen section to direct intraoperative decision making in endometrial cancer. *Gynecol Oncol*. 2012;127(3):525-531. doi:10.1016/j.ygyno.2012.08.
10. Mariani A, Dowdy SC, Cliby WA, et al. Prospective assessment of lymphatic dissemination in endometrial cancer: A paradigm shift in surgical staging. *Gynecol Oncol*. 2008;109(1). doi:10.1016/j.ygyno.2008.01.023
11. Frumovitz M, Slomovitz BM, Singh DK, et al. *Frozen Section Analyses as Predictors of Lymphatic Spread in Patients with Early-Stage Uterine Cancer*.; 2004.
12. Case AS, Rocconi RP, Straughn JM, et al. *A Prospective Blinded Evaluation of the Accuracy of Frozen Section for the Surgical Management of Endometrial Cancer LEVEL OF EVIDENCE: II-2*.; 2006.
13. Visser NCM, Reijnen C, Massuger LFAG, Nagtegaal ID, Bulten J, Pijnenborg JMA. Accuracy of endometrial sampling in endometrial carcinoma: A systematic review and meta-analysis. *Obstetrics and Gynecology*. 2017;130(4). doi:10.1097/AOG.0000000000002261
14. Giglio A, Miller B, Curcio E, et al. Challenges to intraoperative evaluation of endometrial cancer. *Journal of the Society of Laparoendoscopic Surgeons*. 2020;24(2). doi:10.4293/JSLS.2020.00011
15. Holloway RW, Abu-Rustum NR, Backes FJ, et al. Sentinel lymph node mapping and staging in endometrial cancer: A Society of Gynecologic Oncology literature review with consensus recommendations. *Gynecol Oncol*. 2017;146(2). doi:10.1016/j.ygyno.2017.05.027
16. Bodurtha Smith AJ, Fader AN, Tanner EJ. Sentinel lymph node assessment in endometrial cancer: a systematic review and meta-analysis. *Am J Obstet Gynecol*. 2017;216(5). doi:10.1016/j.ajog.2016.11.1033
17. Leitao MM, Zhou QC, Gomez-Hidalgo NR, et al. Patient-reported outcomes after surgery for endometrial carcinoma: Prevalence of lower-extremity lymphedema after sentinel lymph node mapping versus lymphadenectomy. In: *Gynecologic Oncology*. Vol 156. ; 2020. doi:10.1016/j.ygyno.2019.11.003
18. Polan RM, Rossi EC, Barber EL. Extent of lymphadenectomy and postoperative major complications among women with endometrial cancer treated with minimally invasive surgery. *Am J Obstet Gynecol*. 2019;220(3). doi:10.1016/j.ajog.2018.11.1102
19. Bogani G, Murgia F, Ditto A, Raspagliesi F. Sentinel node mapping vs. lymphadenectomy in endometrial cancer: A systematic review and meta-analysis. *Gynecol Oncol*. 2019;153(3). doi:10.1016/j.ygyno.2019.03.254
20. Rossi EC, Kowalski LD, Scalici J, et al. A comparison of sentinel lymph node biopsy to lymphadenectomy for endometrial cancer staging (FIRES trial): a multicentre, prospective, cohort study. *Lancet Oncol*. 2017;18(3). doi:10.1016/S1470-2045(17)30068-2
21. Frumovitz M, Plante M, Lee PS, et al. The FILM Trial: A randomized phase III multicenter study assessing near infrared fluorescence in the identification of sentinel lymph nodes (SLN). *Gynecol Oncol*. 2018;149. doi:10.1016/j.ygyno.2018.04.023
22. NCCN Guidelines: uterine neoplasms. Version 2.2024; Available from: https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf. NCCN Guidelines Uterine Cancer.
23. Dioun S, Chen L, Gockley A, et al. Uptake and outcomes of sentinel lymph node mapping in women with atypical endometrial hyperplasia. *Gynecol Oncol*. 2021;162. doi:10.1016/s0090-8258(21)00665-x
24. Barlin JN, Khoury-Collado F, Kim CH, et al. The importance of applying a sentinel lymph node mapping algorithm in endometrial cancer staging: Beyond removal of blue nodes. In: *Gynecologic Oncology*. Vol 125. ; 2012:531-535. doi:10.1016/j.ygyno.2012.02.021
25. RC. R Core Team 2023 R: A language and environment for statistical computing. R foundation for statistical computing. https://www.R-project.org/. *R Foundation for Statistical Computing*. Published online 2023.
26. Dindo D, Demartines N, Clavien PA. Classification of Surgical Complications. *Ann Surg*. Published online 2004. doi:10.1097/01.sla.0000133083.54934.ae

27. Clavien PA, Barkun J, De Oliveira ML, et al. The clavien-dindo classification of surgical complications: Five-year experience. *Ann Surg*. 2009;250(2). doi:10.1097/SLA.0b013e3181b13ca2
28. Daraï E, Dubernard G, Bats AS, et al. Sentinel node biopsy for the management of early stage endometrial cancer: Long-term results of the SENTI-ENDO study. *Gynecol Oncol*. 2015;136(1):54-59. doi:10.1016/j.ygyno.2014.09.011
29. Curcio EE, Giglio A, Dewan A, ElSahwi K. Robotic-Assisted Sentinel Lymph Node Sampling in Endometrial Cancer. *J Minim Invasive Gynecol*. 2018;25(7). doi:10.1016/j.jmig.2018.09.164
30. Casarin J, Song C, Multinu F, et al. Implementing robotic surgery for uterine cancer in the United States: Better outcomes without increased costs. *Gynecol Oncol*. 2020;156(2). doi:10.1016/j.ygyno.2019.11.016
31. Dioun S, Chen L, Melamed A, et al. Uptake and Outcomes of Sentinel Lymph Node Mapping in Women With Atypical Endometrial Hyperplasia. In: *Obstetrics and Gynecology*. Vol 137. Lippincott Williams and Wilkins; 2021:924-934. doi:10.1097/AOG.0000000000004352
32. Zaino RJ, Kauderer J, Trimble CL, et al. Reproducibility of the diagnosis of atypical endometrial hyperplasia: A gynecologic oncology group study. *Cancer*. 2006;106(4). doi:10.1002/cncr.21649
33. Indermaur MD, Shoup B, Tebes S, Lancaster JM. The accuracy of frozen pathology at time of hysterectomy in patients with complex atypical hyperplasia on preoperative biopsy. *Am J Obstet Gynecol*. 2007;196(5). doi:10.1016/j.ajog.2006.10.886
34. MM, Barakat RR. Clinical Approach to Diagnosis and Management of Endometrial Hyperplasia and Carcinoma. *Surg Pathol Clin*. 2011;4(1). doi:10.1016/j.path.2010.03.002
35. Mueller J, Rios-Doria E, Park K, et al. Sentinel lymph node mapping in patients with endometrial hyperplasia: A practice to preserve or abandon? (117). *Gynecol Oncol*. 2022;166. doi:10.1016/s0090-8258(22)01343-9
36. Dioun S, Chen L, Gockley A, et al. Uptake and outcomes of sentinel lymph node mapping in women with endometrial cancer. *Gynecol Oncol*. 2021;162. doi:10.1016/s0090-8258(21)01263-4
37. Vetter MH, Smith B, Benedict J, et al. Preoperative predictors of endometrial cancer at time of hysterectomy for endometrial intraepithelial neoplasia or complex atypical hyperplasia. In: *American Journal of Obstetrics and Gynecology*. Vol 222. ; 2020. doi:10.1016/j.ajog.2019.08.002
38. Abt D, Macharia A, Hacker MR, Baig R, Esselen KMK, Ducie J. Endometrial stripe thickness: a preoperative marker to identify patients with endometrial intraepithelial neoplasia who may benefit from sentinel lymph node mapping and biopsy. *International Journal of Gynecological Cancer*. 2022;32(9). doi:10.1136/ijgc-2022-003521
39. Laskov I, Tzur Y, Zindel O, et al. The incidence of endometrial carcinoma in patients with atypical endometrial hyperplasia versus atypical endometrial polyp (438). *Gynecol Oncol*. 2022;166. doi:10.1016/s0090-8258(22)01660-2
40. Kogan L, Matanes E, Wissing M, et al. Omitting Lymphadenectomy in Obese Endometrial Cancer Patients Undergoing Sentinel Lymph Node Mapping: More Is Less. *J Minim Invasive Gynecol*. 2020;27(7). doi:10.1016/j.jmig.2020.08.075
41. Tanner EJ, Sinno AK, Stone RL, Levinson KL, Long KC, Fader AN. Factors associated with successful bilateral sentinel lymph node mapping in endometrial cancer. *Gynecol Oncol*. 2015;138(3). doi:10.1016/j.ygyno.2015.06.024
42. Werner S, Gadomski T, Pereira E, Villella J. Lymphatic mapping and obesity with sentinel lymph node biopsy in endometrial cancer. *Gynecol Oncol*. 2021;162. doi:10.1016/s0090-8258(21)01034-9