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Robot Assisted Comprehensive Surgical Staging for Endometrial Cancer: A Validation Study

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ABSTRACT

Objective

The study sought to evaluate the historical surgical-pathological trends in Gynecologic Oncology Group (GOG) 33 in a cohort of patients who underwent robot-assisted staging of uterine carcinomas.

Materials and Methods

This is a retrospective study from June 2016 through December 2018 at Catholic Health Services Hospitals in Long Island (CHS-LI), NY, USA. All patients underwent robotic surgical staging with hysterectomy, bilateral salpingo-oophorectomy, and pelvic and para-aortic lymphadenectomy. Fifty patients were included, and patients were separated into cohorts with endometrioid or non-endometrioid histology for analysis. Patients were staged using the International Federation of Gynecology and Obstetrics (FIGO) 2009 classification.

Results

For all patients undergoing surgical staging, the rate of pelvic and para-aortic nodal metastases occurred at 10% and 8%, respectively. Sixty percent of the grade 1 endometrioid tumors had less than 50% myometrial invasion. No patients had positive para-aortic lymph nodes in the absence of pelvic node involvement. High-risk histologies were associated with nodal disease thirteen percent of the time. A correlation between increasing depth of invasion and positive lymph nodes was demonstrated. Increasing grade of tumors was correlated with the frequency of nodal metastasis. Intraperitoneal spread was highly correlated to metastatic lymph nodes. Deep invasion was positively correlated with nodal disease.

Conclusion

The results of this study validate the trends previously known from GOG 33 in a population undergoing robot-assisted surgical staging for uterine carcinomas.

Keywords

Gynecologic Oncology Group (GOG) 33; Robotic; Surgery; Uterine cancer; Lymph nodes; Trends.

INTRODUCTION

Endometrial cancer is the most common gynecologic malignancy in the United States, afflicting approximately 61,380 annually.[1] It is well-known today that most clinical stage I endometrial carcinomas are limited to the uterus, but 20% have occult metastatic disease on final pathology after surgical staging.[2] Prior to 1988, endometrial adenocarcinomas were clinically staged diseases, primarily relying upon physical examination and radiological evidence. A landmark trial by the Gynecologic Oncology Group (GOG), known as GOG 33, was conducted in 1987 and paved the way for the adoption of surgical staging for all endometrial carcinoma. The study prospectively examined patients with clinical stage 1 carcinoma of the endometrium and evaluated the surgical-pathologic behaviors of these tumors. The results were remarkable that 22% of patients assumed to have stage 1 uterine confined disease were found to have extrauterine spread at the time of surgery with microscopic pelvic and/or para-aortic metastases in 11% of women.[3] After the results of this study were published, the International Federation of Gynecology and Obstetrics (FIGO) soon

thereafter reclassified endometrial carcinomas as a surgically staged disease.

The patients in GOG 33 underwent abdominal surgical staging, including hysterectomy with pelvic and para-aortic lymphadenectomy. Since the publication of the study, minimally invasive techniques have become the standard of care for the comprehensive surgical staging of endometrial carcinomas.[4,5] In gynecologic surgery, the 1990s were notable for the advancement of laparoscopic techniques, as well as for the development of more advanced surgical equipment. Multi-institutional clinical trials followed to compare laparotomy and laparoscopy. For example, in 2009, the GOG LAP 2 study was the most prominent prospective trial to compare these techniques during surgical staging procedures. Laparoscopy was found to be feasible, safe, and equivalent in nodal counts, and resulted in fewer complications and shorter hospital stays.[5]

Since abdominal staging has become largely replaced with laparoscopy, robotic surgery is increasingly utilized within gynecologic oncology. For example, the FIRES trial published in 2017 investigated the diagnostic accuracy of sentinel lymph nodes in uterine cancer using robotic surgery. The results of the trial showed a high sensitivity (97.2%), and a low false negative rate (3%) with the use of robotic surgery.[6] Advantages of robotic surgery include improved visualization with three dimensional (3D) optics, greater dexterity with wristed instruments, and more comfortable ergonomics. The authors of this study sought to evaluate the historical surgical-pathological trends in GOG 33 in a cohort of patients with uterine carcinomas who underwent robot-assisted staging of uterine carcinomas. Subset analyses were performed based upon histology and high-risk factors.

MATERIALS AND METHODS

This study is a retrospective, institutional review board (IRB)-exempt analysis from June 2016 through December 2018. Subjects included were women who underwent surgical staging of endometrial cancer at Good Samaritan Hospital in West Islip (GSHWI), NY, USA which is part of the Catholic Health Services Hospitals in Long Island (CHSLI), NY, USA. Sixty-five patients were identified during this time period. Fifteen patients were excluded for a variety of reasons, such as the inability to perform a complete surgical staging or the necessity to convert to a laparotomy.

Fifty patients with carcinoma of the endometrium were evaluated who had undergone a robot-assisted total laparoscopic hysterectomy, bilateral salpingo-oophorectomy, bilateral pelvic lymphadenectomy, and para-aortic lymphadenectomy. No patient was excluded if lymphadenectomy was performed, irrespective of the number of lymph nodes removed.

As performed in GOG 33, the surgical pathologic findings of these patients were evaluated. Additionally, two cohorts were developed, dependent upon the uterine histology, and subgroup analyses were separately performed. Thirty-five patients with endometrioid endometrial adenocarcinoma were grouped together, as were fifteen patients with high-risk histologies. For the purposes of this study, the high-risk histologies included uterine serous, clear cell, carcinosarcoma, and undifferentiated adenocarcinomas. The FIGO stage was classified according to the 2009 guidelines.

Surgical Procedures

A robot-assisted total laparoscopic hysterectomy and bilateral salpingo-oophorectomy was performed. In the pelvis, the bilateral retroperitoneal spaces were opened and the lymph bearing tissues were removed. The anatomic boundaries included the deep circumflex iliac vein distally; the midpoint of the common iliac artery proximally; the genitofemoral nerve laterally and the superior vesical artery medially. The obturator nerve served as the posterior boundary. If a suspicious node was identified in any area, it was removed. The peritoneum over the aorta and vena cava was opened. The fat pad above the inferior mesenteric artery extending to the proximity of the renal vessels was removed *in toto*. Peritoneal cytology was obtained at the conclusion of the lymphadenectomy.

Descriptive analyses were performed to determine the significance of each factor to the frequency of positive pelvic and paraaortic nodes. The findings of this study were compared to the results in GOG 33.

RESULTS

Overall, with all uterine histologies combined, our results were significant for a pelvic and para-aortic nodal metastases rate of 10% and 8%, respectively. Four percent (4%) had spread to the adnexa, and 2% had other extrauterine metastases at the time of surgery.

Table 1.1. *Descriptive Statistics for Scale Variables of Interest*

	Age (Years)	Height (in)	Weight (kg)	BMI	Stay (hrs)	OR Time (min)	Tumor Size (cm)	Uterine Weight (gm)
n	50	50	50	50	48	48	45	50
Missing	0	0	0	0	2	2	5	0
Mean	63.50	76.00	81.82	31.84	28.21	172.9	2.909	96.62
Median	61.50	64.00	80.75	31.86	25.00	173.0	2.600	82.50
SD	11.17	32.97	19.91	7.638	14.85	60.38	1.916	99.55
Range	43.00	110.0	97.80	33.80	72.00	347.0	9.500	475.0
Minimum	46.00	60.00	45.50	18.80	0.000	50.00	0.000	0.000
Maximum	89.00	170.0	143.3	52.60	72.00	397.0	9.500	475.0

Table 1.2. *Descriptive Statistics*

		n	Percent
Smoking History	Yes	22	44.0
	No	28	56.0
Diabetes Mellitus	Yes	10	20.0
	No	40	80.0
Hypertension	Yes	29	58.0
	No	21	42.0
Hyperlipidemia	Yes	14	28.0
	No	36	72.0

When analyzed as distinct cohorts, the results in the endometrioid and high-risk subgroups were different. Patients with endometrioid uterine histologies had a rate of metastasis of 9% to the pelvic lymph nodes, 6% to the para-aortic nodes, 3% to the adnexa, and 3% had other extrauterine metastases at the time of surgery. In the high-risk cohort, our results found that 13% of patients had pelvic nodal metastases, 13% had para-aortic lymphadenopathy, 7% had spread to the adnexa, and 0% had other extrauterine metastases at the time of surgery.

The distribution of the study parameters are detailed in Table 1. There were more patients with endometrioid adenocar-

Table 2: *Surgical-Pathologic Findings*

Surgical-Pathologic Findings of Endometrioid Adenocarcinomas		
	Patients	**Percentage**
Stage		
IA	22	63%
IB	8	23%
II	1	3%
IIIA	1	3%
IIIB	0	0%
IIIC1	1	3%
IIIC2	1	3%
IVA	0	0%
IVB	1	3%
Histology		
Endometrioid Adenocarcinoma	35	100%
Grade		
1 Well	20	57%
2 Moderate	10	29%
3 Poor	5	14%
Myometrial Invasion		
Endometrium only	11	31%
Inner 1/3	8	23%
Middle ½	8	23%
Deep 1/3	8	23%
Peritoneal Cytology		
Positive	6	17%
Negative	22	63%
Not Collected	5	14%
Indeterminate	2	6%
Adnexa Involvement		
Positive	1	3%
Negative	34	97%
Pelvic Node Metastasis		
Positive	3	9%
Negative	32	91%
Aortic Node Metastasis		
Positive	2	6%
Negative	33	94%
Other Extrauterine Metastasis		
Positive	1	3%
Negative	34	97%
Capillary-Like Space Involvement		
Positive	6	17%
Negative	29	83%

Surgical-Pathologic Findings of Non-Endometrioid Adenocarcinomas		
	Patients	**Percentage**
Stage		
IA	8	53%
IB	3	20%
II	1	7%
IIIA	1	7%
IIIB	0	0%
IIIC1	0	0%
IIIC2	2	13%
IVA	0	0%
IVB	0	0%
Histology		
MMMT/Carcinosarcoma	2	13%
Clear Cell	5	33%
Serous	6	40%
Undifferentiated	2	13%
Grade		
1 Well	0	0%
2 Moderate	0	0%
3 Poor	15	100%
Myometrial Invasion		
Endometrium only	5	33%
Inner 1/3	5	33%
Middle ½	3	20%
Deep 1/3	2	13%
Peritoneal Cytology		
Positive	7	47%
Negative	7	47%
Not Collected	1	7%
Indeterminate	0	0%
Adnexa Involvement		
Positive	1	7%
Negative	14	93%
Pelvic Node Metastasis		
Positive	2	13%
Negative	13	87%
Aortic Node Metastasis		
Positive	2	13%
Negative	13	87%
Other Extrauterine Metastasis		
Positive	0	0%
Negative	15	100%
Capillary-Like Space Involvement		
Positive	2	13%
Negative	13	87%

cinoma. Thirty five patients (70%) had endometrioid histology, and fifteen (30%) had a high-risk histology. Well-differentiated and poorly-differentiated tumors were evenly present as 20 patients (40%) had well differentiated tumors, and 20 patients (40%) had poorly differentiated tumors. Forty-two percent (42%) of patients had tumors with middle and deep myometrial invasion (greater than 50% myometrial invasion). Twenty-six percent (26%) of patients had positive cytology. Sixteen percent (16%) of patients had tumors with lymphovascular space invasion (Table 2).

Most endometrioid tumors were grade 1 and confined to the endometrium. Sixty percent (60%) of the grade 1 endometrioid tumors were present within the endometrium or superficial myometrium. Sixty-six percent (66%) of the high-risk histology tumors were present within the endometrium or superficial myometrium (Table 3).

Table 3: *Histologic Grade and Depth of Invasion*

Histologic Grade and Depth of Invasion in Endometrioid Adenocarcinomas

Depth	G1	G2	G3	Total
Endometrium Only	8 (40%)	2 (22%)	1 (17%)	11 (31%)
Superficial	4 (20%)	1 (11%)	3 (50%)	8 (23%)
Middle	5 (25%)	2 (22%)	1 (17%)	8 (23%)
Deep	3 (15%)	4 (44%)	1 (17%)	8 (23%)
Total	20 (100%)	9 (100%)	6 (100%)	35 (100%)

Histologic Grade and Depth of Invasion in Non-Endometrioid Adenocarcinomas

Depth	G1	G2	G3	Total
Endometrium Only	0	0	5 (33%)	5 (33%)
Superficial	0	0	5 (33%)	5 (33%)
Middle	0	0	3 (20%)	3 (20%)
Deep	0	0	2 (13%)	2 (13%)
Total	0	0	15 (100%)	15 (100%)

Five patients (10%) had metastasis to the pelvic and/or to the para-aortic lymph nodes. Four patients (8%) had nodal metastasis to both pelvic and para-aortic lymph nodes. Zero patients had positive para-aortic lymph nodes in the absence of pelvic node involvement. Eighty percent of patients who had positive pelvic lymph nodes also had positive para-aortic lymph nodes (Table 4).

Table 4: *Relationship of Positive Pelvic Nodes to Aortic Nodes*

Relationship of Positive Pelvic Nodes to Aortic Nodes in Endometrioid Adenocarcinomas

	Aortic		
Pelvic	**Negative**	**Positive**	**Total**
Negative	32 (91%)	0 (0%)	32 (91%)
Positive	1 (3%)	2 (6%)	3 (9%)
Total	33 (94%)	2 (6%)	35 (100%)

Relationship of Positive Pelvic Nodes to Aortic Nodes in Non-Endometrioid Adenocarcinomas

	Aortic		
Pelvic	**Negative**	**Positive**	**Total**
Negative	13 (87%)	0 (0%)	13 (87%)
Positive	0 (0%)	2 (13%)	2 (13%)
Total	13 (87%)	2 (13%)	15 (100%)

Differing histologic cell types were related to pelvic lymph nodes metastasis. Clear cell and undifferentiated histologies were associated with positive pelvic and para-aortic lymph nodes 29% of the time. Any non-endometrioid histology was associated with nodal disease 13% of the time (n=2). Endometrioid adenocarcinoma affected pelvic and para-aortic lymph nodes 9% of the time (n=3).

Grade of the tumors was correlated with the frequency of nodal metastasis. No grade 1 tumors had any positive lymph

Table 5. *Frequency of Nodal Metastasis Among Risk Factors*

		Pelvic		Aortic	
Risk Factor	**N**	**Number**	**Percentage**	**Number**	**Percentage**
Histology					
MMMT/ Carcinosarcoma	2	0	0%		
Clear Cell	5	1	20%	1	20%
Serous	6	0	0%	0	0%
Undifferentiated	2	1	50%	1	50%
Endometrioid Adenocarcinoma	35	3	9%	2	6%
Grade					
1 Well	20	0	0%	0	0%
2 Moderate	10	1	10%	1	10%
3 Poor	20	4	20%	3	15%
Myometrial Invasion					
Endometrium only	16	0	0%	0	0%
Inner 1/3	13	0	0%	0	0%
Middle 1/3	11	2	18%	1	9%
Deep 1/3	10	3	30%	3	30%
Peritoneal Cytology					
Positive	13	2	15%	2	15%
Negative	29	1	3%	0	0%
Not Collected	6	1	17%	1	17%
Indeterminate	2	1	50%	1	50%
Adnexa Involvement					
Positive	2	0	0%	0	0%
Negative	48	5	10%	4	8%
Other Extrauterine Metastasis					
Positive	1	1	100%	1	100%
Negative	49	4	8%	3	6%
Capillary-Like Space Involvement					
Positive	8	3	38%	3	38%
Negative	42	2	5%	1	2%

nodes. Four patients with grade 3 tumors had positive lymph nodes (20%). The same trend was present for para-aortic lymph nodes (Tables 5 and 6).

Table 6: *Grade, Depth of Invasion, and Pelvic Node Metastasis*

Grade, Depth of Invasion, and Pelvic Node Metastasis of Endometrioid Adenocarcinomas

	Grade		
Depth of Invasion	**G1 N=20**	**G2 N=9**	**G3 N=6**
Endometrium Only N=11	0 (0%)	0 (0%)	0 (0%)
Inner N=8	0 (0%)	0 (0%)	0 (0%)
Middle N=8	0 (0%)	0 (0%)	1 (100%)
Deep N=8	0 (0%)	1 (25%)	1 (100%)

Grade, Depth of Invasion, and Pelvic Node Metastasis of Non-Endometrioid Adenocarcinomas

	Grade		
Depth of Invasion	**G1 N=0**	**G2 N=0**	**G3 N=15**
Endometrium Only N=5	0 (0%)	0 (0%)	0 (0%)
Inner N=5	0 (0%)	0 (0%)	0 (0%)
Middle N=3	0 (0%)	0 (0%)	1 (33%)
Deep N=2	0 (0%)	0 (0%)	1 (50%)

A correlation between increasing depth of invasion and positive lymph nodes was demonstrated. No patients with tumor confined to the endometrium or inner myometrium (less than 50% myometrial invasion) had nodal metastasis. 23% of patients with pelvic node disease and 25% of patients with para-aortic disease had tumors with at least 50% myometrial invasion.

Thirteen patients (26%) had positive cytology. Those with non-endometrioid histologies had positive cytology 47% of the time, compared to 17% with patients with endometrioid adenocarcinoma. Overall, 15% of patients with positive cytology also had positive lymph nodes. All patients in this study with positive washings were affected with pelvic and para-aortic nodal disease.

Adnexal involvement was present in 2 patients (4%). Regardless of histology, adnexal involvement was not related to nodal disease.

Intraperitoneal spread was highly correlated to metastasis to the pelvic and para-aortic lymph nodes. In the one patient with intraperitoneal spread, both the pelvic and para-aortic nodes were affected. However, the absence of intraperitoneal spread does not exclude nodal disease. In 49 patients with negative intraperitoneal spread, 4 patients (8%) were affected by positive nodal disease. This trend was seen in endometrioid adenocarcinoma tumors and high-risk tumors.

Lymphovascular space invasion (LVSI) was present in 17% and 13% of endometrioid and high-risk tumor histologies, respectively. Non-endometrioid tumors affected by LVSI had positive pelvic and para-aortic lymph nodes 50% of the time. Endometrioid adenocarcinoma with LVSI was seen to have positive pelvic and para-aortic lymph nodes in thirty-three percent of cases.

Grade and depth of invasion were evaluated in the correlation of nodal disease. Even though both are risk factors, depth of invasion is more influential. Deep invasion of any histology of tumor was correlated with nodal disease. No patients with superficial invasion were affected by positive lymph nodes. All five patients with nodal disease were noted to have at least 50% myometrial invasion (Tables 6 and 7).

Table 7: *Grade, Depth of Invasion, and Aortic Node Metastasis*

Grade, Depth of Invasion, and Aortic Node Metastasis of Endometrioid Adenocarcinomas

	Grade		
Depth of Invasion	**G1 N=20**	**G2 N=9**	**G3 N=6**
Endometrium Only N=11	0 (0%)	0 (0%)	0 (0%)
Inner N=8	0 (0%)	0 (0%)	0 (0%)
Middle N=8	0 (0%)	0 (0%)	0 (0%)
Deep N=8	0 (0%)	1 (20%)	1 (100%)

Grade, Depth of Invasion, and Aortic Node Metastasis of Non-Endometrioid Adenocarcinomas

	Grade		
Depth of Invasion	**G1 N=0**	**G2 N=0**	**G3 N=15**
Endometrium Only N=5	0 (0%)	0 (0%)	0 (0%)
Inner N=5	0 (0%)	0 (0%)	0 (0%)
Middle N=3	0 (0%)	0 (0%)	1 (33%)
Deep N=2	0 (0%)	0 (0%)	1 (50%)

DISCUSSION AND CONCLUSION

GOG 33 was a landmark trial to instill the reform for uterine cancers to become a surgically staged disease. Our primary objective was to compare the trends from GOG 33 to the surgical-pathologic trends noted in this retrospective study of patients who underwent robot-assisted laparoscopic staging of uterine cancers. The two cohorts of patients analyzed were those with endometrial

endometrioid adenocarcinomas and those with non-endometrioid uterine adenocarcinomas.

Overall, several trends noted in our data paralleled the findings from GOG 33 regarding the frequency of nodal involvement and depth of tumor invasion. As expected, the non-endometrioid cohort contained high-risk uterine subtypes, and this group demonstrated an increased rate for metastatic spread outside of the uterus with involvement of the adnexa, pelvic, and para-aortic lymph nodes. All uterine subtypes also showed a positive correlation between lack of tumor differentiation and an increased incidence of lymph node spread. None of the patients with well-differentiated tumors were noted to have nodal spread. Conversely, all of the patients with pelvic or para-aortic lymph node metastasis were seen to have poorly differentiated grades of tumor, regardless of histology. There was one patient with a moderately differentiated tumor grade who had spread to the pelvic and para-aortic lymph nodes. Lastly, all of the patients with positive pelvic and para-aortic nodal metastases had greater than 50% myometrial invasion.

Our results show two important differences between GOG 33 and other contemporary trials. The results from GOG 33 show a 2% rate of isolated positive para-aortic nodes without pelvic nodal involvement. In a contemporary trial from 2008, Mariani et al describe a 16% isolated positive para-aortic rate in those patients with deeply invasive, high grade tumors.[7] Our study, on the other hand, shows a 0% isolated positive para-aortic lymph node rate with robot-assisted surgery, in both endometrioid and non-endometrioid tumors. We show that all patients with positive para-aortic lymph nodes also had positive pelvic lymph nodes.

A second difference between our results and GOG 33 is the concomitant rate of positive aortic nodes when the pelvic nodes harbor metastatic disease. GOG 33 showed approximately one-third of aortic nodes will be positive with pelvic nodal disease.[3] Instead, our results show a higher rate with 80% aortic involvement. It is possible that our study is underpowered to make the same observations as previous studies. Another explanation may be that the magnification present during robotic surgery allows the surgeon to better visualize enlarged lymph nodes, leading to their removal, with fewer reported instances of isolated para-aortic tumor spread. Further studies with robot-assisted surgical staging are needed to evaluate this possibility.

Our data is significant in that it parallels the results of previous landmark studies, providing further validation for robot-assisted laparoscopic surgical staging of endometrial carcinoma. Previous research has evaluated conventional laparoscopic surgical staging. The GOG LAP 2 trial compared conventional laparoscopy to laparotomy and demonstrated decreased hospital inpatient stays and blood loss with low rates of recurrence.[8] Additionally, other publications have compared the outcomes of robotic surgery to conventional laparoscopy. Corrado et al examined the surgical and oncological outcomes in robotic surgical staging in obese patients with endometrial cancer. The authors demonstrated the safety, feasibility, and reproducibility of robotic surgical staging.[9] Nieto et al examined the rates of robotic-assisted procedures, as well as survival, in non-endometrioid endometrial cancers. The authors report that 75% of all minimally invasive surgeries were performed robotically without adversely impacting survival.[10] Additional studies have evaluated other outcomes, such as blood loss, nodal counts, and post-operative complications in laparoscopic surgical staging.[11,12]

Despite the work previously performed from the above studies, no other study has evaluated the surgical-pathological trends in robot-assisted surgical staging for uterine cancers as did GOG 33. In summary, the results of this study validate the trends previously known from GOG 33, in a population undergoing robot-assisted surgical staging for uterine carcinomas.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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