Pseudovascular Invasion: Minimally Invasive Surgery for Endometrial Cancer

Farinaz Seifi, MD, Vinita Parkash, MD, Mitchell Clark, MD, Gulden Menderes, MD, Christina Tierney, MD, Dan-Arin Silasi, MD, Masoud Azodi, MD

ABSTRACT

Background and Objectives: To determine if the use of an intrauterine manipulator is associated with an increased incidence of pseudovascular invasion on pathologic evaluation of hysterectomy specimens for endometrial cancer and to assess the possible implications of pseudovascular space invasion in the treatment of endometrial cancer.

Methods: We performed a retrospective cohort study of patients with early stage (I/II) endometrial cancer who underwent minimally invasive surgical staging. The following data were abstracted: race, body mass index, grade, age, stage, histology, presence or absence of lymphovascular space invasion (LVSI), peritoneal cytology, and adjuvant treatment. Slides were blindly reviewed by a gynecologic pathologist.

Results: Of the 104 patients meeting eligibility criteria, 74 cases were reviewed in detail (the study was terminated early based on the results of an interim analysis). Patients in the no-manipulator group were older ($P = .02$) and had a higher stage 1B/II ($P = .01$) than patients in the manipulator group. No difference was found in the incidence of pseudovascular invasion between the manipulator and the no-manipulator groups ($P = .86$). Subgroup analysis showed no association of pseudovascular invasion with tumor grade ($P = .79$). Five patients were identified to have pseudovascular invasion misdiagnosed as true LVSI—4 had endometrioid and 1 had serous histology. Of these, 3 were in the manipulator group. Two received adjuvant radiotherapy which they not have gotten, absent reported lymphovascular invasion.

Conclusion: The use of a uterine manipulator does not appear to increase the rate of pseudovascular invasion in our limited data set. Misdiagnosis of pseudovascular invasion as LVSI can result in risk migration of patients with potential for harm from unwarranted adjuvant therapy.

Key Words: Uterine manipulator, pseudovascular invasion, endometrial cancer, laparoscopy, hysterectomy.

Obstetrics/Gynecology Department, Division of Gynecology, Yale University, New Haven, CT (Dr Seifi).

Department of Pathology, New Haven Hospital, Yale University, New Haven, CT (Dr Parkash).

Department of Obstetrics/Gynecology, Yale New Haven Health, Bridgeport Hospital, Bridgeport, CT (Dr Clark).

Division of Gynecology Oncology, New Haven Hospital, Yale University, New Haven, CT (Drs Menderes, Silasi, and Azodi).

Division of Minimally Invasive Gynecology Surgery, Yale New Haven Health, Bridgeport Hospital, Bridgeport, CT (Dr Tierney).

INTRODUCTION

Endometrial cancer is the most common gynecologic malignancy in the developed world. Both the International Federation of Gynecology and Obstetrics system and the American Joint Committee on Cancer recommend surgical staging for primary management.[1,2] A minimally invasive approach has become increasingly popular because it achieves reduced surgical morbidity with similar oncological outcomes compared with traditional laparotomy.[3,4]

Laparoscopy and manipulator use are reportedly associated with "spill artifacts" in which tissue is displaced into vascular spaces (pseudovascular invasion)[5] or the peritoneal cavity.[6,7] Vascular displacement can mimic lymphovascular invasion (LVSI) histologically, which is among the factors considered during stratification of patients into risk groups for recurrence.[8] Therefore, inaccurately labeling pseudovascular invasion as LVSI has the potential to bump a patient from a low-intermediate-risk group to a high-intermediate-risk group and result in unwarranted adjuvant radiation therapy for the patient.[9–12] While original reports attributed the pseudovascular invasion artifact to the use of a uterine manipulator,[12] subsequent sug-

gested that this artifact was perhaps related to processing in the pathology laboratory.[13]

Uterine manipulator use is also reportedly associated with artifactual displacement of tumor cells into the peritoneal cavity. While not part of the endometrial cancer staging algorithm, there is suggestion that isolated positive peritoneal washings in the absence of extrauterine spread portend a somewhat poorer survival regardless of histology and tumor grade.[14,15] Therefore, artifactually positive peritoneal washings can present the same issue as pseudovascular invasion and result in an inappropriate recommendation for adjuvant therapy.

We sought to determine if the use of a uterine manipulator in laparoscopic staging of early stage endometrial cancer was associated with an increased rate of either pseudovascular space invasion or positive peritoneal cytology. We also attempted to quantify the incidence of an inaccurate reads of LVSI and a possible impact on adjuvant treatment decisions.

MATERIALS AND METHODS

The study was approved by the institutional review board. A retrospective chart review was performed to identify patients with stage I and II endometrial cancer who underwent laparoscopic/robotic staging at our institution from January 2012 to December 2016. Women were excluded if any part of surgical staging was done at an outside hospital, if there were missing data in the electronic medical records (EMRs), if uterine perforation occurred during insertion of the uterine manipulator, or if the patient had an additional synchronous primary malignancy.

All procedures were performed by 1 of 2 gynecologic oncologists in an academic-affiliated community hospital, one always used uterine manipulator with a balloon component and the other favored a sponge stick in the vagina to identify the cervicovaginal junction.

Peritoneal washings were collected at the beginning of the procedure after the uterine manipulator was placed.

Clinicopathologic characteristics that were abstracted from the EMR included age, race, body mass index, stage, histology, grade, presence or absence of LVSI, positive peritoneal cytology result, and type of adjuvant treatment. All patients were followed to May 2017 for oncologic outcomes.

Slides were blindly reanalyzed by an established gynecologic pathologist for assessment of pathologic variables, including assessment of vascular and pseudovascular invasion. A repeat review was done because pseudovascular invasion is not a required reporting parameter in pathology reports. Therefore, the pseudovascular rate could not be accurately assessed simply through retrospective review of pathology reports. Potential bias between groups was limited by blinding the pathologist to the surgical methodology of the cases in the data set.

Pseudovascular invasion was diagnosed if (1) large fragments of tumor were present in a vascular space that did not conform to the shape of the vessel, (2) multiple widely separated fragments of tumor were present in a single vascular space, (3) there was extensive crush artifact of intravascular tumor, (4) tumor was present in large dilated thick-walled vessels, (5) associated stroma or vascular structures were present within intravascular tumor, (6) necrotic debris was associated with intravascular tumor, (7) tumor was present in deep myometrial vascular spaces in a tumor with nominal myometrial invasion, (8) intravascular tumor similar to the displaced tumor was present in nonvascular myometrial clefts in the myometrium in proximity to tumor, or (9) there was an absence of tinctorial change to the cytoplasm of the intravascular tumor clusters (**Figure 1A and B**). Vascular invasion was diagnosed if intravascular tumor conformed to vascular outline, typically in a similar vascular channel in proximity to the advancing edge of the tumor. True intravascular tumor generally demonstrated a tinctorial cytoplasmic change relative to the main tumor, generally conformed to the shape of the vessel, was unassociated with necrotic debris, and was often associated with lymphocytic infiltrate around vessels containing tumor (lymphovascular-associated inflammatory changes) (**Figure 2**).[4, 13, 23, 29]

A sample size estimation was performed using a 2-sided Z test with pooled variance, assuming a 30% difference in occurrence of pseudovascular invasion between the manipulator and the no-manipulator group. This was the reported difference documented in a prior study.[13] With a significance level set to $P = .05$, the calculated sample sizes was 43 cases in each group, which afforded an 85% power to detect the hypothesized 30% difference between the 2 groups.

A χ^2 or Fisher's exact test was used to assess the association between categorical variables. Parametric (t test) and nonparametric (Wilcoxon rank sum test) tests were used, as appropriate, for normally and non-normally distributed variables. Statistical significance was set at an α level (Type I) of .05.
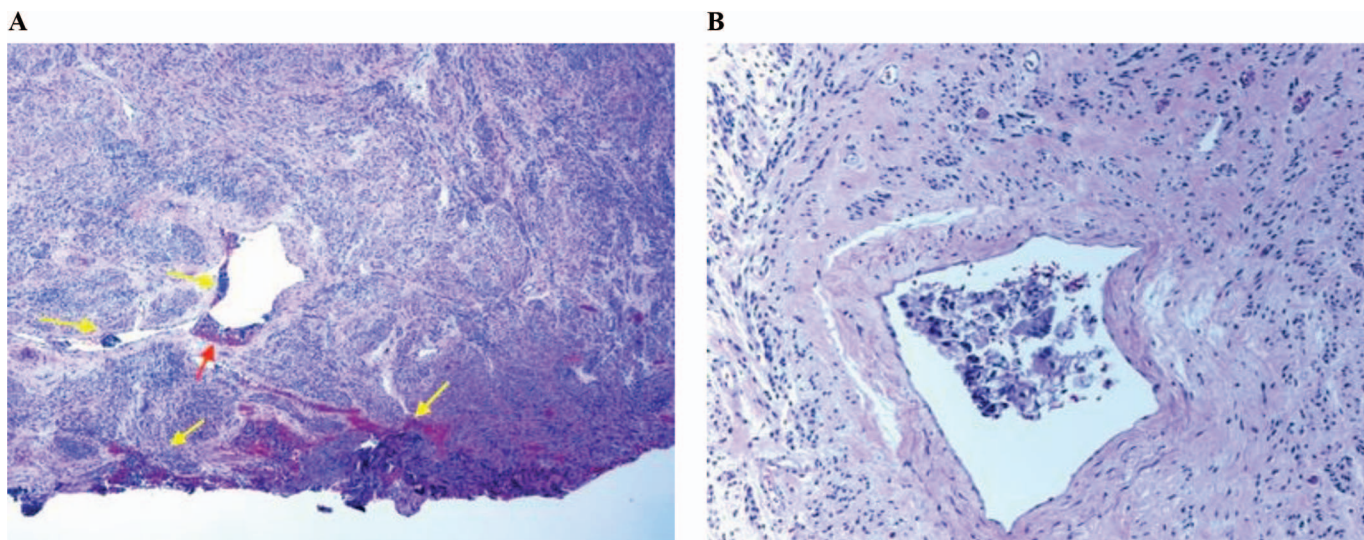
A

B

Figure 1. (A) Pseudovascular invasion. Multiple widely separated tumor fragments (yellow arrowheads) are present in a single dilated vascular structure, associated with debris (red arrowhead). Vessel is present at the edge of a section where there is smeared/fragmented tumor (yellow arrows). **(B)** Higher-power view of different case with crushed tumor fragments that do not conform to the shape of a thick-walled large-caliber vessel. This was interpreted as pseudovascular invasion.
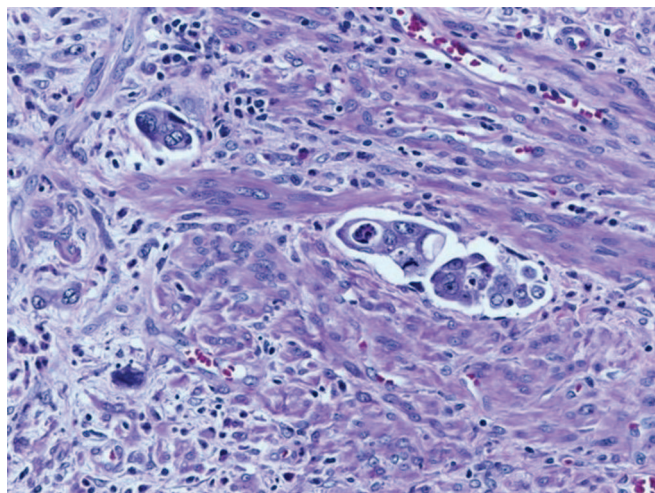

Figure 2. True lymphovascular invasion. Tumor is present in 2 small-caliber vessels and conforms to the shape of the vessel. The cytoplasm showed subtle tinctorial difference from the tumor. A sprinkling of inflammatory cells associated with stromal changes surrounds the vessels.

RESULTS

A total of 104 consecutive endometrial cancer cases met eligibility criteria, with 59 patients in the uterine manipulator group and 45 patients in the no-manipulator group. The clinical and pathologic characteristics of the patients as abstracted from the pathology reports are presented in **Table 1**. The patients in the no-manipulator group were

on average older (62 versus 66 years; $P = .02$). There was no significant difference in recurrence rate between 2 groups in terms of race and body mass index. The mean follow-up was 26 (range 7.4 to 37.5) months. Two patients in the manipulator group had a recurrence during the follow-up period. None of the patients in the no-manipulator group did. There was no significant difference in recurrence rate between the 2 groups ($P = .19$).

Overall, 84% of patients had endometrioid histology. A serous subtype was slightly more common in the manipulator group: 11.9% (7/59) versus 6.7% (3/45) ($P = .046$). Of note, the no-manipulator group included 4 cases of carcinosarcoma. Tumors in the no-manipulator group had greater absolute depth of invasion (23% vs 33%, $P = .02$) but on average invasion was still within the inner half of the myometrium. There was no significant difference in positive peritoneal washing between the 2 groups. Peritoneal washing was positive in 15.5% (9/59) of patients in the manipulator group and 13% (6/45) in the no-manipulator group ($P = .76$) (**Table 1**). Positive LVSI was initially reported in 6 patients (10%) in the manipulator group and 9 (20%) in the no-manipulator group ($P = .37$).

An interim analysis was performed at the request the pathologist after review of a total of 74 cases. The pathologist reported frequent occurrence of pseudovascular invasion and identified 17 cases with only minimal residual with none

Table 1.
Demographic and Pathologic Characteristics

	Manipulator (n = 59)	No Manipulator (n = 45)	Total (n = 104)	*P* value
Age, mean y (SD)	61.6 (9.2)	66.5 (10.9)	63.7 (10.2)	.02
Race, n				
White	40 (67.8%)	34 (75.6%)	74 (71.2%)	.30
African American	11 (18.6%)	5 (11.1%)	16 (15.4%)	
Hispanic	2 (3.4%)	0 (0.0%)	2 (1.9%)	
Asian	2 (3.4%)	0 (0.0%)	2 (1.9%)	
Other	4 (6.8%)	6 (13.3%)	10 (9.6%)	
BMI, mean (SD)	35.5 (10.2)	34.9 (10.4)	35.3 (10.3)	.76
Histological type, n				
Endometrioid	50 (84.7%)	38 (84.4%)	88 (84.6%)	.046
Serous	7 (11.9%)	3 (6.7%)	10 (9.6%)	
Mixed	2 (3.4%)	0 (0.0%)	2 (1.9%)	
Carcinosarcoma	0 (0.0%)	4 (8.9%)	4 (3.8%)	
LVSI status, n				
Negative	51 (86.4%)	35 (77.8%)	86 (82.7%)	.37
Positive	6 (10.2%)	9 (20.0%)	15 (14.4%)	
Indeterminate/suspected	2 (3.4%)	1 (2.2%)	3 (2.9%)	
Grade, n				
1	31 (62%)	19 (38%)	50 (56.8)	.17
2	16 (51.6%)	15 (48.4 %%)	31 (35.2%)	
3	3 (42.8%)	4 (57.2%)	7 (8%)	
Stage, n				
IA	51 (86.4%)	29 (64.4%)	80 (76.9%)	.01
IB	8 (13.6%)	14 (31.1%)	22 (21.2%)	
II	0 (0.0%)	2 (4.4%)	2 (1.9%)	
Washing, n				
Negative	49 (84.5%)	39 (86.7%)	88 (85.4%)	.76
Positive	9 (15.5%)	6 (13.3%)	15 (14.6%)	
Invasion				
Mean (SD)	19.2 (22.6)	33.1 (34.1)	25.2 (28.9)	.02
Median (IQR)	5.0 (0.0 to 38.0)	23.0 (0.0 to 70.0)	17.0 (0.0 to 43.5)	.04
Pseudoinvasion, n				
Negative	18 (30.5%)	13 (28.9%)	31 (29.8%)	.86
Positive	16 (27.1%)	10 (22.2%)	26 (25.0%)	
Not determined	9 (15.3%)	8 (17.8%)	17 (16.3%)	
Not reviewed	16 (27.1%)	14 (31.1%)	30 (28.8%)	

to minimal myometrial invasion. This made the evaluation of pseudovascular invasion unfeasible (cases labeled "undetermined" in **Table 3**). The interim analysis demonstrated both groups with an incidence of pseudovascular invasion in the 30% range with no statistically significant difference between the 2 groups. Because the original ascertainment for the sample size was based on a much higher difference in occurrence of pseudovascular invasion between the 2 groups, the study was terminated early. The group size was insufficiently powered to accurately assess any differences at such a high level of occurrence.

Of the 74 cases reviewed, 34 were in manipulator group and 23 were in no-manipulator group. In addition, 37.2% were in manipulator group and 32.2% in the no-manipulator group ($P = .69$) had pseudovascular invasion. Analysis performed by subtype and grade indicated no differences between the 2 groups (**Table 3**). Subgroup analysis based on histologic grades 1, 2, and 3 also did not demonstrate differences in presence or absence of LVSI, pseudovascular invasion, or positive peritoneal cytology between the manipulator and the no-manipulator groups (**Table 2–3**). Logistic regression analysis did not reveal significant differences be-

tween the 2 groups after adjusting for grade and histology ($P = .75$) or in unadjusted models for each of 3 variables (**Table 4**).

Five cases with an original diagnosis of LVSI, were reclassified as pseudovascular invasion (6.8% of cases). Four cases had endometrioid histology, and 1 had serous type; 3 had use of uterine manipulator. Adjuvant radiation therapy was recommended to 3 of these patients. Absent LVSI, 2 would not have been offered adjuvant radiation therapy in accordance with the usual protocol at our institution (**Table 5**). In an additional 3 patients (2 in the manipulator group and 1 in the no-manipulator graoup), areas labeled as LVSI were deemed to represent tumor in artifactual spaces rather than in vessels and as such could not be labeled either vascular or pseudovascular invasion (**Table 1**).

DISCUSSION

The aim of this study was to determine whether using a uterine manipulator in the staging of endometrial cancer could cause a higher rate of pseudovascular invasion. In addition, our goal was to identify the incidence of an

Table 2.
Pelvic Washing Status Comparison Within Grades

	Washing Positive	Washing Negative	Total	*P* value
Stage IA/IB/II				
All grades				
Manipulator	8 (13.5%)	51 (86.5%)	59	.71
No manipulator	5 (11.1%)	40 (88.9%)	45	
Nonendometrioid				
Manipulator	3 (33.3%)	6 (66.6%)	9	.21*
No manipulator	0 (0%)	7 (100%)	7	
Endometrioid				
Grade 1				
Manipulator	3 (9.6%)	28 (90.4%)	31	.66*
No manipulator	3 (15.8%)	16 (84.2%)	19	
Grade 2				
Manipulator	2 (12.5%)	14 (87.5%)	16	>.99*
No manipulator	2 (13.3%)	13 (86.7%)	15	
Grade 3				
Manipulator	0 (0%)	3 (100%)	3	>.99*
No manipulator	0 (0%)	4 (100%)	4	

*Fisher exact test used (low expected cell counts).

Table 3.
Pseudoinvasion Comparison Within Grades

	Pseudoinvasion Positive	Pseudoinvasion Negative	Pseudoinvasion Undetermined	Total	P value
Stage IA/IB/II					
All cases					
Manipulator	16 (37.2%)	18 (41.9%)	9 (20.9%)	43	.69*
No manipulator	10 (32.2 %)	13 (41.9%)	8 (25.9%)	31	
Nonendometrioid					
Manipulator	1 (14.2%)	4 (57.1%)	2 (28.7%)	7	.85*
No manipulator	1 (25%)	1 (25%)	2 (50%)	4	
Endometrioid Grade 1					
Manipulator	10 (43.4%)	9 (39.1%)	4 (17.5%)	23	.29*
No manipulator	5 (29.4%)	6 (35.3%)	6 (35.3%)	17	
Endometrioid Grade 2					
Manipulator	5 (41.6%)	5 (41.6%)	2 (16.8%)	12	**
No manipulator	3 (37.5%)	5 (62.5%)	0 (0%)	8	
Endometrioid Grade 3					
Manipulator	0 (25.0%)	0 (75.0%)	1 (100%)	1	**
No manipulator	1 (50.0%)	1 (50.0%)	0	2	

*P value from χ^2 for trend.

**0 value; cannot calculate trend.

Table 4.
Logistic Regression—Pseudoinvasion (n = 57, Pseudoinvasion Positive vs Negative)

	Unadjusted	P value	Adjusted*	P value
Manipulator, yes vs no	1.16 (0.40 to 3.35)	0.79	1.19 (0.40 to 3.53)	.75
Grade, 2 and 3 vs 1	0.69 (0.24 to 1.96)	0.48	0.84 (0.27 to 2.63)	.76
Histology, endometrioid vs nonendometrioid	2.31 (0.41 to 13.03)	0.34	2.13 (0.33 to 13.91)	.43

*Adjusted model includes manipulator, grade, and histology.

Values given as odds ratio (95% confidence interval).

inaccurate pathology read of LVSI and its effect on the course of treatment. Our result showed that there was no significant difference in pseudovascular invasion rate with the use of a uterine manipulator.

Laparoscopic and robotic-assisted hysterectomy has become the preferred approach for endometrial cancer staging. Uterine manipulators are often used to improve the exposure of the cervicovaginal junction to prevent ureteral injuries even though the advantage of using uterine manipulators is unproved.[16] Uterine manipulator use supposedly confounds pathologic evaluation by causing histological artifacts. The 2 most consequential artifacts are "pseudovascular invasion," a mimic of lymphovascular invasion, and peritoneal spill, a mimic of positive peritoneal cytology. Both of these, if inaccurately assessed to be positive, have the potential to upstage the patient to a higher risk stratum, subjecting them to unwarranted adjuvant therapy and attendant risk for complications.[6,13]

LVSI is a documented independent prognostic risk factor in early stage endometrial cancer.[9,17,18] The reported prev-

Table 5.
Characteristics of Cases with False-Positive LVSI

Patient	Age, y	Manipulator	Stage	Myometrial Invasion (%)	Histology (Grade)	Adjuvant Radiation
8	54	No	II	95	Endometrioid (1)	No
26	76	No	IA	23	Endometrioid (2)	Yes
54	52	Yes	IA	0	Serous	No
73	73	Yes	IB	55	Endometrioid (1)	Yes
57	57	Yes	IA	33	Endometrioid (2)	Yes

alence is 10% to 12% in early stage endometrial carcinoma.[10,19,20] In the current study, LVSI was found in 14% of cases, which is more or less in agreement with previously reported numbers. We did not quantify the volume of LVSI or pseudovascular invasion in our cases.

Whether manipulator use is associated with pseudovascular invasion continues to be debated. While some investigators have documented an increased occurrence of pseudovascular invasion in laparoscopic surgery, others have not.[10,14,21,22] Logani et al. found epithelial tissue in vascular spaces in both benign and malignant uteri where a manipulator was used and attributed this finding to the use of the manipulator.[10] Krizova et al. also reported a significant association of pseudovascular invasion with robotic surgery and manipulator use.[21] However, Hopkins et al.[22] and Folkins et al.[23] found no difference in the incidence of pseudovascular invasion between open cases and robotic hysterectomies. In our limited study set, we were unable to document a significant difference in the occurrence of pseudovascular invasion in surgeries with manipulator use and those without manipulator use, even after adjusting for grade and histology. While it is possible that we were not able to demonstrate a differential occurrence because our study was insufficiently powered to detect lower-level differences, demonstrating a significant difference at a such high occurrence rate would not be clinically meaningful.

Our study confirmed that the distinguishing vascular invasion from pseudovascular invasion can be challenging for pathologists. In this study, we found 5 cases where pseudovascular invasion was originally labeled as true vascular invasion, and in 2 cases, this resulted in overtreatment. A similar finding was that LVSI were reclassified as pseudovascular invasion.[22] The assessment of LVSI is purely a histologic assessment. There is little role for immunohistochemistry in helping to make this distinction. The tumor is in a vascular space, albeit artifactually transported rather than biologically transported to that site. The recent recommen-

dation to stratify volume of LVSI for risk assessment in endometrial carcinoma may offset the clinical impact of this potential misclassification[20,24]; however, we were not able to evaluate this possibility as we did not quantify the volume of either pseudovascular invasion or LVSI in our study. Distinction between pseudovascular invasion and true LVSI is further complicated by the co-occurrence in a subset of cases.[23]

LVSI have been shown to be an independent prognostic factor in early stage endometrial cancer.[9,17,18] LVSI has been reported at a prevalence of 10% to 12% in early stage endometrial carcinoma.[10,19,20] The use of a uterine manipulator did not make any difference in the rate of LVSI in our study. We did not quantify the volume of LVSI or pseudovascular invasion in our cases. This may be of importance as the PORTEC 1 and 2 trials demonstrated strong risk stratification based on number of foci of LVSI identified.[20] Further studies may be warranted to assess the role of manipulator use in that setting.

Positive peritoneal washings in endometrial cancer has been variably attributed to occur due to transtubal transport, multifocal disease in peritoneal mesothelium, or spread through lymphatic circulation.[25] Pressure from the intrauterine manipulator is suggested to result in intraoperative exfoliation of malignant cells with attendant increase in positive peritoneal cytology rate in laparoscopic cases.[5] That a significantly higher rate of tubal contaminants are found in robot-assisted hysterectomies lends some support to this hypothesis.,[26] and some studies report a significantly higher rate of positive peritoneal cytology for surgeries using a uterine manipulator,[16,21] while others do not.[27,28] Our study also did not demonstrate a significant increase of positive peritoneal washings in patients with manipulator use.

Our study has several limitations. The mean follow-up period was 26 months, which is relatively short and may be insufficient to assess the recurrence risk, if any, from

pseudovascular invasion. We did not control for the type of surgery—laparoscopy or robotic assisted, and that may have obscured or confounded observations. That said, our study was tightly controlled with only 2 surgeons performing all surgeries and only 2 types of balloon manipulators used for all surgeries. In addition, we controlled for interobserver variability between pathologists. A single gynecologic pathologist reassessed all the cases to obviate confounding from differential reporting practices among pathologists. There is inconsistency between pathologists with respect to reporting elements considered to be procedural artifacts, which could result in inaccurate estimation of occurrence rates.

In conclusion, use of a uterine manipulator did not increase the rate of pseudovascular invasion or positive peritoneal washing in this study. Pseudovascular invasion is a relatively common artifact, and distinguishing it from true vascular invasion can be challenging for the pathologist. Occasionally, this can result in overtreatment for the patient. A high level of suspicion for misclassification is especially warranted in cases.

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