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Lymphovascular Space Invasion in Robotic Surgery for Endometrial Cancer

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ABSTRACT

Background: Minimally invasive surgery has become a standard treatment for endometrial cancer and offers significant benefits over abdominal approaches. There are discrepant data regarding lymphovascular space invasion (LVSI) and positive peritoneal cytology with the use of a uterine manipulator, with previous small-scale studies demonstrating an increased incidence of these prognostically important events. We sought to determine if there was a higher incidence of LVSI in patients who underwent robot-assisted surgery for endometrial cancer.

Methods: We performed a single-institution review of medical records for patients who underwent open abdominal or robot-assisted hysterectomy for endometrial cancer over a 24-month period. The following data were abstracted: age, tumor grade and stage, size, depth of invasion, LVSI, and peritoneal cytology. For patients with LVSI, slides were reviewed by 2 pathologists for confirmation of LVSI.

Results: Of 104 patients identified, LVSI was reported in 39 (37.5%) and positive peritoneal cytology in 6 (4.8%). Rates of peritoneal cytology were not significantly different between the 2 groups (odds ratio, 0.55; 95% confidence interval, 0.10–3.17; $P = .50$). LVSI was reported in significantly fewer robot-assisted hysterectomies than open procedures (odds ratio, 0.39; 95% confidence interval, 0.17–0.92; $P = .03$). In subgroup analyses restricted to early-stage disease (stage ≤ II), there was no significant difference in LVSI between open and robot-assisted hysterectomies (odds ratio, 0.64; 95% confidence interval, 0.22–1.85; $P = .43$).

Conclusion: In this retrospective study, we found that use of a uterine manipulator in robot-assisted surgery did not increase the incidence of LVSI.

Key Words: Cytology, Endometrial cancer, Robotic hysterectomy, Total abdominal hysterectomy, Lymphovascular space invasion.

INTRODUCTION

Endometrial cancer is the most common gynecologic malignancy, with 49,560 projected new cases in 2013 and 8,190 projected deaths.[1] Hysterectomy, bilateral salpingo-oophorectomy, and lymphadenectomy remain the primary surgical treatments.[2] Over the past decade, minimally invasive techniques, including laparoscopic and robot-assisted approaches, have largely overtaken abdominal hysterectomy as the surgical method of choice for these operations. The Gynecologic Oncology Group (GOG) LAP2 trial showed that compared with traditional laparotomy, laparoscopy has shorter recovery times, similar intraoperative complication rates, and decreased postoperative complications.[3] Robot-assisted surgery for endometrial cancer has further been shown to reduce blood loss, while maintaining the benefits of laparoscopic techniques.[4–6]

Lymphovascular space invasion (LVSI) has been found to be an independent predictor of nodal disease, recurrence, and survival in endometrial cancer.[7–9] Guntupalli et al[7] suggested that the presence of LVSI could be used as a surrogate marker for lymphadenectomy in clinical decision making, thus making reliable identification of this histologic feature paramount to optimal management. The GOG 99 trial used the presence of LVSI, in addition to moderate or poorly differentiated histology and deep myometrial invasion, to stratify patients into a "high-intermediate risk" group, for which they demonstrated a significant reduction in recurrence after adjunctive radiation therapy.[10] Thus, LVSI is increasingly being used in clinical decision making, and the ability to reliably determine the presence or absence of LVSI is critical to determining treatment.

A number of studies have suggested that laparoscopic surgical techniques might introduce cancer cells into the

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lymphovascular space artificially, thereby erroneously qualifying a patient as at high-intermediate risk and indicating adjuvant therapy.[11–13] This has been theorized to be due to the use of a uterine manipulator (inserted through the cervix into the endometrial cavity) to assist the surgeon in the removal of the uterus. Kitahara et al[11] suggested that the use of a uterine manipulator creates a closed pressure system that results in an initial release of cancer cells into the surrounding lymphovascular space, with a secondary mechanical force further displacing the cells during gross examining and sectioning. However, a series of retrospective studies have contradicted these results, showing no relationship between the incidence of LVSI and minimally invasive surgical techniques.[14,15] Laparoscopic surgery has further been implicated in possibly spreading cancerous cells into the peritoneal cavity, resulting in positive peritoneal cytology.[16,17] These findings remain exceedingly controversial.[18] Similarly, the use of a uterine manipulator has been implicated in introducing cancer cells into the peritoneal cavity. As with LVSI, evidence suggests that positive peritoneal cytology is predictive of worse outcomes in patients with endometrial cancer.[19,20] As such, knowing with greater certainty that peritoneal cytology is representative of disease status and not an artifact of the surgical modality is important to treatment planning. In this study, we sought to determine if robot-assisted laparoscopic techniques increase the rates of reported LVSI as well as peritoneal cytology in patients undergoing surgery for endometrial cancer.

METHODS

After institutional review board approval was obtained, a chart review of patients with endometrial cancer who underwent surgery at the University of Colorado Hospital between February 2010 and June 2012 was conducted. All women >18 years of age with confirmed diagnoses of endometrial cancer who underwent surgical staging at this institution were included. Women were excluded if all or part of their surgery or treatment was conducted elsewhere, if an additional synchronous primary malignancy was found, or if outcomes data were not available. All patients underwent total hysterectomy and bilateral salpingo-oophorectomy either via open laparotomy or by robot-assisted laparoscopic hysterectomy. Beginning in 2009, robotics began to replace standard laparotomy for the treatment of apparent early-stage endometrial cancer; patients whose preoperative imaging and clinical examination results were consistent with disease confined to the uterus were offered this approach. Patients with significant comorbidities that precluded tolerance of pneumoperitoneum (significant pulmonary or cardiac disease) or clinical examination consistent with a significantly enlarged or fixed uterus were offered traditional laparotomy. Additionally, patients with apparent extrauterine disease (stage ≥ III) as confirmed by imaging or clinical examination were treated with laparotomy. In patients who underwent lymphadenectomy, standard dissection techniques and borders were used.[7] Staging was assigned using the International Federation of Gynecology and Obstetrics 2009 staging system.[21] Data were abstracted from electronic medical records and reviewed for the following data: patient age, presurgical diagnosis, tumor grade, stage, histologic type, size, depth of myometrial invasion, LVSI, peritoneal cytologic results, and lymph node status. LVSI was defined as the presence of any adenocarcinoma in endothelial-lined channels of uterine specimens extracted at the time of surgery, as described by GOG Protocol 99.[10] Positive peritoneal cytology was defined as the presence of malignant cells in a prehysterectomy washing of the pelvis and adnexal structures, with ≥50 mL of fluid obtained. For cases that were reported as positive for LVSI, slides were independently reviewed by 2 pathologists (M.D.P. and A.M.R.) for the presence of "pseudo-LVSI," as described in previous publications: disaggregated tumor cells in thick-walled vessels with similar cytomorphology to the main tumor mass **(Figures 1a and 1b)**, lack of attachment to the vessel wall and absent perivascular lymphocytic response **(Figures 1c and 1d)**, lack of admixed fibrin within tumor cell clusters, presence of intraluminal inflammatory debris, tumor cells within lymphovascular spaces adjacent to the main tumor mass with retraction artifact, presence of stromal component along with tumor cells, and concomitant artifactual changes (eg, endomyometrial clefts and benign glands in lymphovascular spaces).[11–14]

Power was estimated using a baseline rate of LVSI (from previous studies) of approximately 20%, with a difference of a 30% increase over baseline deemed clinically significant. Eighty percent power to detect a difference of ≥5% between LVSI in open versus robotic surgery would require 45 patients in each arm using a 2-tailed χ^2 test, with significance defined as $P < .05$. Associations between surgical type (open vs robotic) and the presence of LVSI or positive peritoneal cytology were then analyzed using χ^2 tests for categorical or dichotomous variables and Student t tests for continuous data in bivariate analysis. All tests were performed with 95% confidence intervals. For all tests, P values $< .05$ were considered significant.

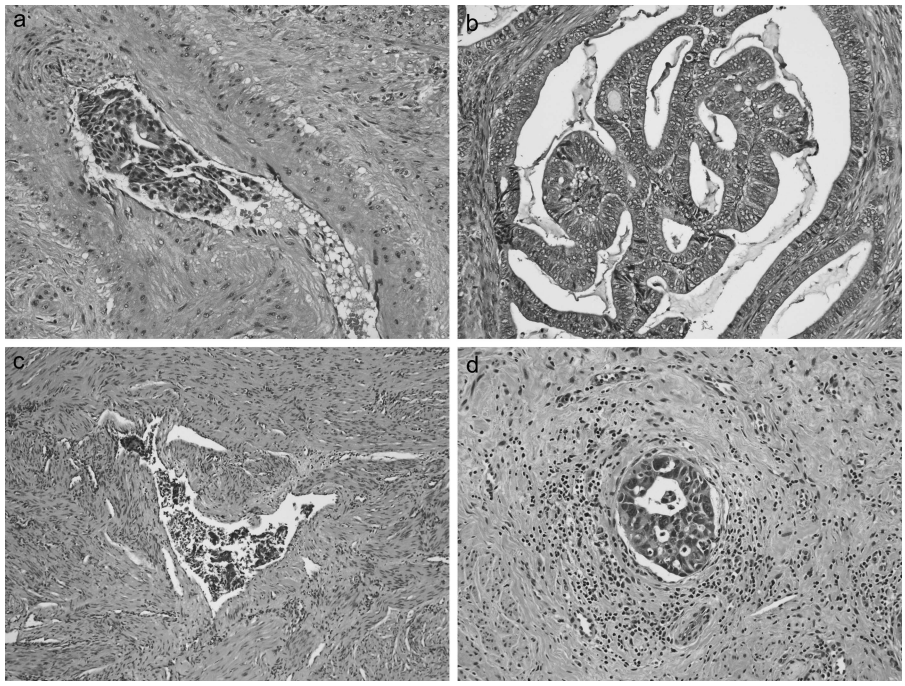

Figure 1. Characteristics of pseudo-LVSI include disaggregated fragments within thick-walled vessels **(a)** with identical cytomorphology to tumor **(b)**. They lack mural attachment and have admixed inflammatory debris **(c)**. Tumor cells conforming to vessel shape with perivascular inflammatory response **(d)** represent true LVSI. (Hematoxylin and eosin, [a], [b], and [d], 200×; [c], 100×.)

RESULTS

A total of 105 patients with endometrial cancer were reviewed **(Table 1)**, of whom 104 had reported presence or absence of LVSI and/or peritoneal cytology. Among these were 54 robot-assisted surgeries, 45 total abdominal surgeries, and 5 surgeries in which a uterine manipulator was inserted in preparation for a robotic hysterectomy that was subsequently converted to an open procedure because of poor visualization (n = 3), excessive bleeding (n = 1), or perforation of the uterus by the manipulator (n = 1). The demographic and clinicopathologic characteristics for each surgical modality are shown in **Table 2**. Patient age was similar between the 2 groups (robotic vs open, 59.4 vs 61.7 years, $P = .33$). Open surgeries had larger average tumor size (4.9 vs 3.5 cm, $P < .01$) and greater depth of invasion (40.1% vs 22.6%, $P < .01$), whereas robotic procedures had a lower percentage of high-grade tumors (30.6% vs 66.7%; odds ratio [OR], 0.22; 95% confidence interval [CI], 0.10–0.51; $P < .01$) and more advanced stage (40.7% vs 10.0%; OR, 0.16; 95% CI, 0.06–0.47; $P < .01$).

A significantly greater proportion of patients who underwent open abdominal procedures (48.1%) had reported LVSI on final pathology compared with those who underwent robot-assisted surgery (27%) (OR, 0.39; 95% CI, 0.17–0.916; $P = .03$). Cytologic results were available for 90 patients, and positive peritoneal cytology (n = 6) was more common in patients who underwent open procedures (8.3% vs 4.8%), although the difference was not statistically significant (OR, 0.55; 95% CI, 0.10–3.17; $P = .50$). With both LVSI and cytology, significance was not affected by the inclusion of patients converted into either the robotic or the open group. Of the 38 cases reported as positive for LVSI, 36 had slides available for review. Of these, 26 were determined to be true LVSI, and 8 showed features of pseudo-LVSI; the remaining 2 were reported initially and on subsequent review as "indeterminate for LVSI." The cases suspected of being pseudo-LVSI were subsequently reviewed to determine if the presence of pseudo-LVSI could have affected patient management. Three cases had positive lymph node metastases, and 1 had peritoneal metastases, indicating that genuine LVSI was present somewhere but possibly not sampled. An additional 2 cases had cervical stromal involvement, which although not necessarily directly linked to LVSI, indicates a more aggressive tumor that increases the likelihood of genuine LVSI being present. This leaves 2 cases of pseudo-LVSI originally reported as genuine LVSI in otherwise uncomplicated patients, with 1 case each in the robotic and open groups. Exclusion of these 2 cases did not change the significance of either positive peritoneal cytology or LVSI.

Table 1.
Demographic and Clinicopathologic Characteristics

Characteristic	Value
Age, y, mean ± SD	59.5 ± 12.0
Race, n (%)	
White	87 (83.7)
Other	17 (16.7)
Stage, n (%)	
IA	58 (58.6)
IB	8 (8.1)
II	7 (7.1)
III	19 (20)
IV	7 (7.1)
Grade, n (%)	
1	48 (46.2)
2	16 (15.4)
3	31 (29.8)
Unspecified	9 (8.7)
LVSI positive, n (%)	39 (37.5)
Washings negative, n (%)	84 (80.8)
Washings positive, n (%)	6 (5.8)
Washings not reported, n (%)	14 (13.5)

Abbreviation: LVSI, lymphovascular space invasion.

In an attempt to eliminate the presence of a surgical bias of larger tumor size and depth of myometrial invasion in the open group, patients with stage I or stage II disease were analyzed separately **(Table 3)**. In this subgroup, tumor size remained significantly different between open and robot-assisted procedures (2.5 vs 3.6, $P = .04$), as did the prevalence of high-grade histology (grade II or III) (27.3% vs 54.8%; OR, 0.31; 95% CI, 0.12–0.81; $P = .02$). However, the rate of LVSI was no longer significant (20% vs 28%; OR, 0.64; 95% CI, 0.22–1.85; $P = .43$), and peritoneal cytology remained insignificant.

DISCUSSION

Robot-assisted hysterectomies have surpassed total abdominal and traditional laparoscopic procedures at many institutions as the surgical modality of choice in the treatment of uncomplicated endometrial cancer. Outcomes have been shown to be similar between both modalities.[4,5] However, several studies have raised concerns that the use of a manipulator could cause intraoperative tumor disturbances by displacing tumor cells into lymphatic space, creating "pseudoinvasion" that can be misidentified as genuine LVSI.[11–13] The presence of LVSI has been incorporated into clinical decision making largely on the basis of the recommendations of the GOG 99 trial, which used LVSI as a criterion for classifying a patient as at high-intermediate risk.[10] Thus, the ability to reliably assess the presence of LVSI is crucial to determining the correct clinical course and avoiding unnecessary adjuvant therapy, likely in the form of vaginal brachytherapy.

In this study, we reviewed 104 patients with endometrial cancer of all stages and grades treated in the past 2 years at our institution and examined rates of LVSI and positive peritoneal cytology between open and robotic groups. We found that LVSI was significantly more frequent in the open group compared with the robotic-assisted group when all stages of disease were considered; however, it was likely that this comparison was confounded by a preference to treat patients with less advanced cancer with robotic surgery at our institution. Further analysis of the subgroup of early-stage patients (stage ≤ II) who were treated primarily with a robot-assisted approach did not show a significant difference in the rate of LVSI. This agrees with methodologically similar studies conducted by Folkins et al[14] and Momeni et al,[15] who found no significant relationship between surgical technique and an increased rate of reported LVSI. The rate of positive peritoneal cytology was found to be similar between the 2 groups in both the original data set and the limited set. This agrees with the conclusions of Eltabbakh et al,[18] who conducted a prospective study that showed cytology results were not affected by laparoscopic surgery.

We also examined the role of "pseudo-LVSI" in 8 patients with endometrial cancer whose LVSI met the previously described definition on subsequent review by 2 pathologists.[11–14] Of these, 4 were found in patients with distant metastases, and 2 were found in patients with cervical stromal invasion, indicating aggressive disease in which the lack of reported LVSI would have minimal impact on clinical decision making. The remaining 2 cases were otherwise uncomplicated. These patients were classified as at "high-intermediate risk" and received adjuvant brachytherapy and may have undergone additional unnecessarily aggressive therapy per GOG 99 recommendations.

Weaknesses of our study include the inherent selection bias seen at large, tertiary referral centers, which receive patients with large tumor volumes and advanced stages, which may have biased our patient population to more

Table 2.
Demographic and Clinicopathologic Characteristics by Surgery Type

Characteristic	Robotic (n = 45)	Open (n = 54)	*P* Value[a] or OR[b] (95% CI)
	Value	Value	
Age, y, mean ± SD	59.4 ± 12.0	61.7 ± 11.4	.33
Race, n (%)			
White	39 (87)	44 (81.5)	.49
Other	6 (13)	10 (18.5)	
Tumor size, cm, mean ± SD	2.5 ± 1.7	4.9 ± 3.3	<.001
Depth of invasion, %, mean ± SD	22.6 ± 26.8	40.1 ± 32.8	.007
Stage, n (%)			
I or II	41 (91)	32 (59.3)	6.19 (2.12–18.07)
>II	4 (8.9)	22 (40.7)	0.16 (0.06–0.47)
Grade, n (%)			
1	29 (64)	17 (33.3)	
2 or 3	13 (29)	34 (66.7)	0.22 (0.10–0.51)
LVSI positive, n (%)	12 (27)	26 (48)	0.39 (0.17–0.92)
Positive peritoneal cytology, n (%)	2 (4.4)	4 (8.3)	0.55 (0.10–3.17)

Abbreviations: CI, confidence interval; LVSI, lymphovascular space invasion; OR, odds ratio.
[a] Student *t* test.
[b] Chi-square test.

Table 3.
Demographic and Clinicopathologic Characteristics of Patients With Stage ≤ II Disease by Surgery Type

Characteristic	Robotic (n = 40)	Open (n = 32)	*P* Value[a] or OR[b] (95% CI)
	Value	Value	
Age, y, mean ± SD	59.8 ± 11.3	60.9 ± 11.1	.69
Tumor size, cm, mean ± SD	2.5 ± 1.7	3.6 ± 2.4	.04
Depth of invasion, %, mean ± SD	22.8 ± 27.1	28.6 ± 26.0	.55
Grade, n (%)			
1	32 (72.7)	14 (45.2)	
2 or 3	12 (27.3)	17 (54.8)	0.31 (0.12–0.81)
LVSI positive, n (%)	9 (20)	9 (28)	0.64 (0.22–1.85)
Positive peritoneal cytology, n (%)	0	0	

Abbreviations: CI, confidence interval; LVSI, lymphovascular space invasion; OR, odds ratio.
[a] Student *t* test.
[b] Chi-square test.

complicated cases, and our relatively small sample size compared with other methodologically similar retrospective reviews. Additionally, there were significantly more patients with larger tumor sizes and deep myometrial invasion in the open group compared with the robotic group, which limits the comparison of the 2 groups. This is mitigated by our subgroup analysis of early-stage patients, and we have previously described that LVSI is

strongly associated with depth of myometrial invasion. Because this was not the case in the robotic group, we believe that our results have statistical merit.

Strengths of our study include a single-institutional sample with consistent surgical techniques and pathologic review by a board-certified pathologist with expertise in gynecologic pathology (M.D.P.). Additionally, slides reported as positive for LVSI were independently re-reviewed by 2 pathologists (A.M.R. and M.D.P.) to ensure a correct diagnosis of genuine LVSI as opposed to pseudo-LVSI, which has previously been reported in the gynecologic literature.

This study shows that the use of robot-assisted surgical techniques may not be associated with increased rates of LVSI and positive peritoneal cytology. Sufficiently large-scale research in a prospective manner is warranted to evaluate the true rate of these phenomena to ensure optimal adjuvant care for patients with early-stage, intermediate-risk endometrial cancers.

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