The prognostic significance of lymphovascular space invasion in laparoscopic versus abdominal hysterectomy for endometrioid endometrial cancer

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Summary

Introduction: Recent reports have suggested that uterine manipulators can induce lymphovascular space involvement (LVSI) by endometrial cancer in laparoscopic hysterectomy specimens. The prognostic significance of this phenomenon known as "vascular pseudo invasion" remains elusive. *Materials and Methods:* The authors conducted a retrospective, single institution study of patients who underwent initial surgery for grade 1 and grade 2 endometrioid endometrial cancers with LVSI. Cases were stratified by surgical approach (laparoscopy vs laparotomy). Clinicopathologic and procedure characteristics as well as outcome data were analyzed. Univariate and multivariate analyses were performed. Disease-free survival (DFS) was analyzed using the Kaplan-Meier product limit method. *Results:* A total of 104 cases (20 laparoscopic, 84 laparotomy) were analyzed. Mean age (65 vs 64 years, respectively), stage distribution, mean number of lymph nodes sampled (18 vs 21, respectively) and use of adjuvant therapy was similar for both groups ($p > 0.05$). Mean body mass index (BMI) was 30 vs 35 kg/m^2, respectively ($p = 0.002$). Mean follow up was 24 months (range 0.1–102). Univariate analysis demonstrated that LVSI in the laparoscopic setting was associated with worse DFS ($p = 0.002$). After adjusting for grade the risk of recurrence remained higher for laparoscopic cases (HR: 15.7, 95% CI 1.7–140.0, $p = 0.014$). *Conclusions:* Adjusted risk of recurrence associated with LVSI is higher in cases approached laparoscopically arguing against the concept of "vascular pseudo invasion" associated with the use of uterine manipulators and balloons. LVSI should be regarded as a serious risk factor and taken into account for triage to adjuvant therapies, even in laparoscopically treated early-stage endometrial cancer.

Key words: Endometrial cancer; Lymphovascular space invasion; Pseudo invasion.

Introduction

A laparoscopic approach to the staging of endometrial cancer has become an accepted alternative to the traditional exploratory laparotomy[1-4]. Benefits of laparoscopy include fewer short term complications and shorter hospital stays. The laparoscopic approach as originally described and whether performed with or without robotic assistance, usually involves the use of a uterine manipulator. These devices have a shaft and balloon that is inserted into the uterine cavity and then used throughout the procedure to manipulate the uterus in order to facilitate exposure and complete removal of the surgical specimen. Logani *et al.* [5] and Kitahara *et al.* [6] have recently suggested a phenomenon of "vascular pseudo invasion". It has been postulated that closed positive pressure or mechanical manipulation of the specimen can cause cancer cells to be mechanically forced into the lymphovascular spaces, creating the artifactual appearance of cancer cells in capillary and lymphatic spaces without inherent risk for regional or distant metastasis [5, 6]. Several pathologic characteristics have been proposed in an attempt to distinguish true from artifactual lymphovascular space invasion (LVSI). Unfortunately, despite best efforts at sub-classification of true versus "pseudo-invasion" such pathologic differentiation remains inaccurate [7, 8].

Triage to adjuvant therapies for patients with endometrioid endometrial cancer is currently based not only on stage but also on the presence of certain clinicopathologic risk factors. These include the age of the patient, depth of myometrial invasion, and importantly LVSI as described in Gynecologic Oncology Group (GOG 99). The prognostic significance of "vascular pseudo invasion" and thus the implications of such diagnosis on therapeutic decisions have not been defined. Initial studies, described and focused on the specific features of this phenomenon in cases of grades 1 and 2 endometrioid endometrial cancer [5, 6].

The authors sought to determine the prognostic significance of LVSI associated with the use of uterine manipulators at the time of minimally invasive surgery for endometrial cancer in the above described patient population.

Materials and Methods

The authors conducted a retrospective, single institution study of patients with grades 1 or 2 endometrial cancer with docu-

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mented LVSI in hysterectomy specimens. All cases underwent primary surgery for management of newly diagnosed endometrioid endometrial cancer. Surgeries were performed by members of the Division of Gynecologic Oncology of Washington University School of Medicine at Barnes Jewish Hospital / Siteman Cancer Center. Patients treated at the institution between January 2000 and March 2010 were identified from the Department of Pathology database. All cases were reviewed by experienced gynecologic pathologists at the institution and had histologically confirmed FIGO grade 1 or grade 2 endometrioid adenocarcinoma of the endometrium with documented LVSI. For the purposes of this study, LVSI was broadly defined as presence of tumor cells inside vascular spaces lined by endothelium. FIGO 1988 surgical staging was used. Clinicopathologic characteristics and outcome data were obtained from outpatient and inpatient medical records. Cases without LVSI as well as those with non-endometrioid histologies, grade 3 tumor, Stage IV disease, and laparoscopic surgeries converted to laparotomy were excluded. Cases were stratified by surgical approach (laparoscopy – including laparoscopically assisted vaginal, total laparoscopic, and robotic hysterectomies – vs laparotomy).

Descriptive statistics were used to characterize the study cohort. The primary outcome was disease free survival (DFS), defined as the time from surgery to the date of recurrence or progression. Recurrence free subjects were censored at the date of last contact. Associations between categorical variables and DFS were described using the Kaplan-Meier product limit method and compared by log-rank test. The effects of continuous variables on survival were assessed using univariate Cox proportional hazard model. Multivariate Cox model was also fit to assess the association between surgical approach and DFS while adjusting the confounding effects of other demographic and clinical characteristics. Given the small number of events, however, a variable-by-variable approach was employed in the multivariate analysis including those variables of interest that approached significance in the univariate analysis. All analyses were two-sided, and significance was set at a p-value of 0.05. Statistical analyses were performed using SAS.

This study was approved by the Human Research Protection Office at Washington University in St. Louis (HRPO#10-0451).

Results

A total of 113 grades 1 and 2 endometrioid endometrial cancer cases with documented LVSI on their final histologic specimen were identified during the study period. Nine patients were excluded, eight for Stage IV disease and one for conversion to laparotomy from a laparoscopic attempt. Of the remaining 104 patients, 84 underwent a laparotomy and 20 underwent laparoscopic surgery.

Demographic and disease characteristics are presented in Table 1. Mean age was 65 years (range 5673) for the laparoscopic cases and 64 years old (range 53–76) for the laparotomy group. Mean body mass index (BMI) was 30 kg/m^2 for the laparoscopy group vs 35 kg/m^2 for the laparotomy group. Pelvic and para-aortic lymphadenectomy was not performed systematically in 20 out of 104 cases (three in the laparoscopy group and 17 in the laparotomy group). Of the three incompletely staged laparoscopic cases, one did undergo pelvic lymphadenectomy without para-aortic dissection. Similarly, six of the 17 incompletely staged cases in the laparotomy group underwent pelvic lymphadenectomy without para-aortic dissection. The mean number of lymph nodes was similar for laparotomy and laparoscopy cases (21 and 18 respectively). In the laparoscopy group, a variety of uterine manipulators were used.

Table 1. — *Demographics and disease characteristics.*

	Laparoscopy (n = 20)	Laparotomy (n = 84)	p value
Age (years) *	65.1 ± 8.3	64.5 ± 11.3	N.S.
BMI (kg/m^2)*	29.9 ± 4.3	34.9 ± 11	0.002
	N (%)	N (%)	
Stage (FIGO 1988)			N.S.
IA	2 (10)	2 (2.4)	
IB	13 (65)	32 (38.1)	
IC	1 (5)	23 (27.4)	
IIA	0 (0)	1 (1.2)	
IIB	2 (10)	2 (2.4)	
IIIA	1 (5)	5 (5.9)	
IIIB	0 (0)	0 (0)	
IIIC	1 (5)	19 (22.6)	
Histologic grade			N.S.
Grade 1	6 (30)	45 (53.4)	
Grade 2	14 (70)	39 (46.4)	
Lymph node count (mean)	18	21	N.S.

* BMI: body mass index; Mean ± standard deviation: FIGO: International Federation of Gynecology and Obstetrics; N.S.: Not significant.

Table 2. — *Characteristics of recurrent cases.*

Case	Surgical approach	Stage	Adjuvant therapy	Location of recurrence
1	LSC	IB	VBT	Regional
2	LSC	IB	None	Vaginal
3	LSC	IB	None	Distant
4	LSC	IB	None	Vaginal
5	LAP	IIIC	RT	Distant
6	LAP	IIIC	Chemo/RT	Distant

LSC: Laparoscopy; LAP: Laparotomy; VBT: vaginal cuff brachytherapy; RT: radiotherapy; Chemo/RT: combined chemotherapy and radiotherapy.

Less than half (n = 45, 43%) of the patients received some sort of adjuvant therapy. Of those, 20 received radiotherapy (either vaginal brachytherapy and/or external beam), 16 received both chemotherapy and radiotherapy, and four received chemotherapy only. In five cases the type of adjuvant therapy used was not documented.

Mean follow up was 24.1 months (range 0.1–102.4). There was a significant difference in recurrence rate between cases in the laparoscopy and the laparotomy group. Four patients (20%) in the laparoscopy group recurred and two patients (2.4%) had a recurrence in the laparotomy group (p = 0.002, Figure 1). The authors did not find differences in frequency of use of adjuvant therapies between the study groups (p = 0.45). Of the four patients with recurrence in the laparoscopy group, one received adjuvant vaginal brachytherapy and three did not

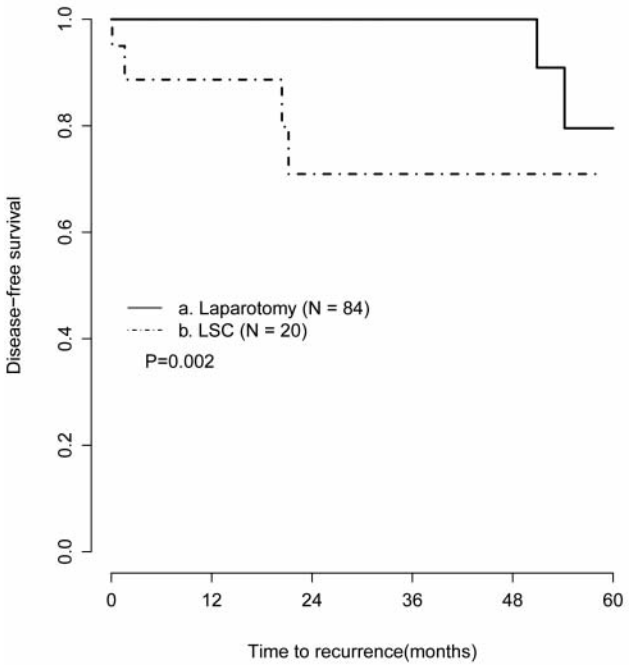

Figure 1. — Kaplan-Meier disease-free survival plot stratified according to surgical approach. Numerals indicate the number of survivors in each group (a. laparotomy, b. LSC: laparoscopy) at each censor point.

receive adjuvant therapy. In the laparotomy group, two patients had a recurrence. Of those, one had adjuvant radiation and the other had both adjuvant radiation and chemotherapy (Table 2).

On univariate analysis age, BMI, stage, and nodal count were not associated with DFS. Histologic grade was the only factor that appeared marginally associated with DFS on univariate analysis ($p = 0.06$). After adjusting for grade, the risk of recurrence remained higher for laparoscopic cases (HR: 15.7, 95% CI 1.7–140.0, $p = 0.014$).

Discussion

Considerable effort has gone into developing approaches to better identify endometrial cancer patients at risk for disease progression and recurrence. In the 1980s, the GOG undertook a systematic approach to surgical staging demonstrating that clinical staging missed metastatic disease in ~25% of cases [10]. Given the inadequacy of clinical staging, the International Federation of Gynecologists and Obstetricians (FIGO) approved a revised surgical staging classification for uterine cancer in 1988. Despite complete surgical staging, many women with "early stage" endometrial cancer still experience progression or recurrence and ultimately die from their disease. Multiple algorithms for better prediction of recurrence and progression have been proposed. Those include other prognostic features (such as LVSI, grade, and age) that were not part of the 1988 staging system [9]. Furthermore, recent debate regarding the therapeutic effect of lymphadenectomy for patients with endometrial cancer has renewed interest in recognition of pathologic factors for risk stratification [11, 12]. To this regard, the present group has recently reported on the independent prognostic value of LVSI. Lymphovascular invasion in patients with endometrioid endometrial cancer is associated with significantly worse DFS (HR 2.19, 95% CI: 1.62–2.96, $p < 0.0001$) and overall survival (HR 2.04, 95% CI: 1.49–2.79, $p < 0.0001$) [11].

Minimally invasive approaches have become well-accepted for the management of patients with endometrial cancer. Initial concern led to extensive debate and became the leitmotif for LAP2; a randomized controlled trial designed to compare outcomes after laparotomy versus laparoscopy for the initial management of patients with endometrial cancer [4]. While primary outcome data from this study is not yet mature, initial reports indicate that the laparoscopic approach appears to be feasible and safe [4].

Uterine manipulators are often used to improve exposure and surgical access and to potentially prevent genitourinary injuries during laparoscopic and robotically assisted hysterectomies. These instruments consist of an intracavitary shaft with or without an intrauterine balloon and cervico-vaginal ring. As a result, it is possible that such instrumentation could result in mechanical disruption of the tumor leading to artifacts at the time of pathologic evaluation. Logani *et al.* coined the term "pseudo invasion" in 2008 to refer to presumed artifactual presence of tumor in capillary and lymphatic spaces [5]. After review of 37 laparoscopic hysterectomy specimens (seven for endometrial carcinoma / hyperplasia and 30 for benign disease) these authors were able to identify intravascular tumor in 71% of pre-malignant/malignant cases and benign endometrial glands in 13% of cases with benign pathology. They postulated that the creation of a closed pressure system was responsible for the newly reported phenomenon [5]. Kitahara *et al.* reported on 21 cases of laparoscopically treated low risk endometrial cancer and 28 cases of low risk endometrial cancer treated by laparotomy [6] . The incidence of vascular space invasion appeared significantly higher in the laparoscopic when compared to the cases approached by laparotomy (33% vs none, $p = 0.001$). This group attempted to characterize these cases of vascular invasion and noted occasional lack of perivascular inflammatory infiltrate and detachment from the vessel wall as some of the most notorious characteristics. These authors proposed mechanical transport of tumor to lymphatic spaces during pathologic processing of the specimen as the potential causative factor in those cases [6]. Two subsequent studies have confirmed a higher incidence of vascular space involvement associated with laparoscopic procedures [7, 8]. Despite the reported higher

incidence of LVSI in cases managed laparoscopically, recent studies acknowledged the lack of consistent findings to allow for accurate pathologic sub-classification of true as opposed to pseudo-invasion. More importantly the uncertainty regarding the clinical implications of such phenomenon is well recognized [7, 8].

In this study the authors sought to evaluate for the first time the outcome differences related to LVSI occurring in endometrioid endometrial cancer cases managed laparocopically when compared to those managed via laparotomy. In keeping with the potential artifactual occurrence of "pseudo invasion", the authors originally hypothesized that after controlling for confounding variables, LVSI in cases managed laparoscopically would be associated with better DFS. Contrary to what had been proposed, the present authors found that the adjusted risk for recurrence was significantly higher in cases approached laparoscopically (adjusted HR: 15.7, 95% CI 1.7–140.0, $p = 0.014$).

The present study is limited by its retrospective nature and the inherent inability to determine whether tumor identified in lymphatic vessels and capillaries was present before the actual surgical procedure. However, its findings suggests that LVSI, as traditionally defined and as described by previous studies, represents a poor prognostic factor whether found after laparoscopic or open surgery. As such, LVSI should be regarded as a serious risk factor even when identified in laparoscopically treated early stage and apparently "indolent otherwise" endometrioid endometrial cancer. Until further understood, the authors strongly advise clinicians against considering "pseudo invasion" as a causative entity of pathologic LVSI at the time of making treatment recommendations for patients with endometrial cancer.

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