Published in final edited form as:

Obstet Gynecol. 2013 January ; 121(1): .

The Utility and Management of Vaginal Cytology After Treatment For Endometrial Cancer

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Abstract

Objective—To estimate the accuracy of vaginal cytology in postoperative surveillance for detecting recurrent endometrial cancer and estimate the optimal management of squamous abnormalities detected in this setting.

Methods—This review included women who underwent hysterectomy for endometrial cancer between January 1, 2006 and December 31, 2010 and had at least one post-operative Pap test. Clinical and demographic data were collected and outcomes including abnormal vaginal cytology, results of colposcopic examination, and endometrial cancer recurrence were assessed. A multivariable logistic regression model to estimate the risk of abnormal cytology was created. Sensitivity, specificity and negative/positive predictive values of detecting vaginal recurrences were calculated.

Results—Four hundred thirty three women contributed 2,378 Pap tests. At least one abnormal cytology result was found during follow-up of 55 (13%) women, representing 3% of all Pap tests. No recurrent endometrial cancers were diagnosed on the basis of isolated abnormal cytology. No cases of recurrent cancer were diagnosed in women with atypical squamous cells of undetermined significance (ASC-US) or low-grade squamous intraepithelial lesion (LSIL) Paps. In multivariable analysis, abnormal cytology was highly associated with prior post-operative radiation therapy ($p < 0.001$). The sensitivity, specificity, positive and negative predictive values of an abnormal Pap test in detecting a local recurrence are 40%, 87.9%, 7.3% and 98.4%, respectively.

Conclusion—Vaginal cytology is of limited utility in detecting recurrent endometrial cancer. Pap tests read as ASC-US/LSIL can be followed without colposcopy.

Introduction

Surveillance after treatment for endometrial cancer has historically included Pap tests to assess for local recurrences, “to afford early detection of vaginal cuff recurrences [1].” Isolated local recurrences are highly curable with local control rates of 81–100% [2–5] and five year overall survival rates from 43–96% [2–6]. Performance of surveillance Paps continues despite data that assessment of patients’ symptoms and physical exam detect more than 80% of all recurrences [7–9]. Multiple retrospective studies have shown little efficacy [7–12] and lack of cost effectiveness of these tests [8,10] particularly in women with early

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The authors have no significant financial disclosures.

stage disease [11]. Still, the National Comprehensive Cancer Network recommends performance of vaginal cytology every six months for two years [13], and the American College of Obstetrician and Gynecologists (ACOG) recommendations imply the need for continued testing in women previously treated for endometrial cancer [14]. Most studies of vaginal cytology after hysterectomy for endometrial cancer were undertaken prior to the adoption of liquid-based cytology and the 2001 Bethesda system for cervicovaginal cytology reporting [15]; thus, the reporting rate of these abnormalities in endometrial cancer survivors is poorly understood. In addition, the risk for high-grade vaginal intraepithelial neoplasia in women with high-grade intraepithelial lesions (HSIL) is unclear. The appropriate management of abnormal cytology in endometrial cancer survivors remains uncertain.

The objectives of this study were to estimate the accuracy of liquid-based cytology reported using 2001 Bethesda terminology in detecting recurrent disease in a large cohort of endometrial cancer patients and estimate the rate and optimal management of these abnormalities, especially the utility of colposcopy.

Materials and Methods

This was a retrospective study evaluating all patients treated for endometrial cancer by the Division of Gynecologic Oncology at Washington University School of Medicine from January 1, 2006 – December 31, 2010. After obtaining Washington University School of Medicine Institutional Review Board approval, patients were identified through local cancer registries and patient databases. All women older than 18 years of age with a histologically confirmed diagnosis of endometrial cancer treated during this time period were evaluated for inclusion. Patients were included if they had at least one liquid-based cytology after total hysterectomy. Decisions on adjuvant treatment, surveillance, and management after abnormal cytology including colposcopy were made by the treating gynecologic oncologist. All Pap tests were evaluated by certified cytopathologists. When a vaginal recurrence was suspected the treating gynecologic oncologist performed biopsies and the specimens were reviewed by certified pathologists. The pathologists were not blinded to the patients' histories or prior specimens. Women treated with primary definitive radiation therapy (and not surgery) as well as those with incomplete follow-up data were excluded. All cases of uterine sarcoma were excluded.

Pap test results were read according to the Bethesda system for cervicovaginal cytologic diagnosis as normal, atypical squamous cells of uncertain significance (ASC-US), atypical squamous cells of uncertain significance with high-risk HPV positivity (ASC-US +HPV), atypical squamous cells favor high-grade (ASC-H), low-grade squamous intraepithelial lesions (LSIL), high-grade squamous intraepithelial lesions (HSIL), atypical glandular cells not otherwise specified (AGC-NOS), and AGC favor neoplasia [15].

Demographic and clinical characteristics were summarized with contingency tables. The association between abnormal Pap tests and other clinical variables was assessed using chi-square, Fisher's exact tests or Student's t-test, as appropriate. To account for varying amount of follow-up time Cox regression models were developed to assess the impacts of abnormal Pap tests on recurrent disease and of adjuvant radiation therapy on the development of an abnormal Pap after controlling for stage and grade. Test performance characteristics for Pap test, including sensitivity, specificity and positive / negative predictive values for cytology in detecting vaginal recurrences were calculated. A p-value <0.05 was considered statistically significant. All statistical analyses were performed using StataIC v9.2 (College Station, TX).

Results

We identified 433 women meeting inclusion criteria who contributed 2,378 vaginal cytology results. The median age at the time of diagnosis was 61.6 years (range: 23.8 to 89) and the mean number of Pap tests per patient was 5.5 (range: 1–18) during a median follow-up time of 36 months (range: 2 to 100 months). Seventy nine (18%) women reported a history of abnormal Pap test prior to the diagnosis of endometrial cancer. Demographic and clinical characteristics of these patients are reported in Table 1.

A summary of the Pap test results, management, and outcomes for the whole cohort are shown in Figure 1. Overall, 51 (12%, 95% CI: 8.7–14.8%) women were diagnosed with recurrent endometrial cancer. Most (41, 80% 95% CI: 69.1–91.7%) presented as pelvic or distant recurrences, with the remaining being isolated vaginal recurrences (8, 16% 95% CI: 5.4–26.0%) or vaginal + pelvic/distant recurrences (2, 4% 95% CI: 0–9.4%). To account for variable follow-up times a Cox regression model was developed. After accounting for the effects of stage and grade, there was no significant difference in the hazard ratio of recurrence between women who had an abnormal Pap test and those who did not (HR 0.82, 95% CI: 0.34–1.96, $p=0.65$). We further evaluated each Pap test individually using a generalized mixed model approach to take into account the clustering effect of the individual patient. Similarly, in this analysis, there was no significant association between abnormal Pap and disease recurrence.

Fifty-five (13%, 95% CI: 9.6–15.8%) women had at least one abnormal cytology result, representing 3% (68/2,378, 95% CI: 2.2–3.6%) of all Pap tests. The overall rate of abnormal Pap tests was 5.4 per 100 woman-years of follow-up. Six women had two abnormal Paps, 2 had 3 abnormal Paps and one woman had four abnormal Pap tests. In the cases of multiple abnormal Paps the highest grade lesion for each woman was considered for further analyses. ASC-US/LSIL were the most common Pap abnormalities, accounting for 67% of all abnormal cytology results. (Table 2).

Nineteen (35%, 95% CI: 21.9–47.1%) women with abnormal Pap tests underwent colposcopy. Patients with ASC-US/LSIL Paps only rarely underwent colposcopic examination. (Table 2). No woman (0/37) with ASC-US or LSIL Pap tests had a vaginal recurrence. Seventeen (89%) of the colposcopies demonstrated no visible lesions or had negative biopsies. One woman, with 1c papillary serous uterine carcinoma, had an AGC Pap with negative colposcopic findings and was diagnosed with a liver recurrence on CT scan ordered for an elevated CA-125. The remaining sixteen women with negative colposcopy remain recurrence-free.

Two women were found to have high-grade vaginal intraepithelial neoplasia (VAIN) after HSIL cytology. No women were found to have squamous cancer. One 47-year-old with an apparent Stage Ia, grade 1 endometrioid endometrial cancer was diagnosed with VAIN3 35 months after hysterectomy. Diagnosis was made only on the second colposcopy after Paps read as HSIL and LSIL. A 53-year-old with a grade 1, stage IIIC1 endometrioid endometrial cancer treated with adjuvant chemotherapy and intensity-modulated pelvic radiotherapy had an abnormal Pap test but negative colposcopy 5 years after hysterectomy and was diagnosed with VAIN2 8 months later, after subsequent HSIL Pap. No cases of VAIN were diagnosed in women with normal Pap tests.

Among the thirty-six (66%) women who had abnormal Pap tests but did not undergo colposcopy, eight endometrial cancer recurrences were diagnosed. Three women had AGC Pap tests and lesions noted on speculum exam that were biopsied confirming recurrent adenocarcinoma; all were salvaged with radiation therapy. Cytology for one woman returned adenocarcinoma and she was diagnosed with both local and distant recurrences.

The remaining four women had AGC or ASC-US Pap tests and were diagnosed with distant recurrences after workups prompted by patient symptoms or physical exam findings. None of the remaining 29 women were diagnosed with recurrent endometrial cancer. Twenty-five (86%) had at least one subsequent negative Pap test while 4 (14%) had no subsequent cytologic follow-up.

Forty-two women without any abnormal surveillance Pap tests were diagnosed with recurrent endometrial cancer. Of these 88% (37/42) had a normal Pap test within six months of their recurrence. Five women had vaginal cuff recurrences within four months of a negative Pap test (mean: 2.3 months, SD 1.3 months, median 1.6 months, range: 0.4–3.3 months) and all were diagnosed after presenting with vaginal bleeding. All these vaginal recurrences were salvaged with radiation therapy.

We sought to estimate the liquid-based Pap test performance characteristics for the detection of vaginal recurrences during surveillance for endometrial cancer. The sensitivity and specificity of abnormal vaginal cytology in detecting vaginal recurrences are 40% (95% C.I.: 12.2%–73.8%) and 87.9% (95% C.I.: 84.5–90.9%), respectively. The positive and negative predictive values are 7.3% (95% C.I.: 2.0–17.6%) and 98.4% (95% C.I.: 96.6–99.4%), respectively.

Univariable analyses demonstrated that high stage, grade and adjuvant radiation therapy were all associated with higher rates of abnormal cytology. Histology, smoking history, age and history of prior abnormal Pap tests were not associated with abnormal cytology detected during follow-up (Table 3). A Cox regression model was fit to estimate the effect of adjuvant radiation on the development of an abnormal cytologic finding. After controlling for stage grade and follow-up time, the use of adjuvant radiotherapy remained significantly associated to the development of abnormal cytologic findings (HR: 2.51, 95% CI: 1.36–4.64, $p < 0.001$). After controlling for adjuvant radiation therapy, stage and grade were no longer significantly associated with abnormal Pap tests.

Discussion

Evaluation of vaginal cytology has traditionally been used in the surveillance of patients after treatment for endometrial cancer despite the lack of evidence of its efficacy. Perhaps because of this lack of demonstrated efficacy, clinicians' management of abnormal cytology is variable, potentially leading to invasive procedures with minimal yield and questionable benefit. Thus, determining optimal management of abnormal cytology is important. In our study ASC-US and LSIL Pap tests did not lead to the diagnosis of any cases of recurrent endometrial cancer or VAIN. Only two women with any these cytologic abnormalities recurred, both with concomitant distant recurrences diagnosed after symptoms prompted a radiologic workup.

The incidence of VAIN in the general population is extremely low [16–18]. Because of the rarity of the disease routine surveillance for VAIN and vaginal cancer is not recommended. The rate of VAIN after hysterectomy for benign conditions is even lower [19] leading to recommendations against routine screening after hysterectomy for benign indications [14]. Only two cases of VAIN (0.4%) were diagnosed in this cohort, with no cases of vaginal cancer seen. Cytology surveillance for recurrent endometrial cancer cannot be justified based on yield of high-grade VAIN.

The utility of colposcopy in identifying women with vaginal recurrences of endometrial cancer in this study was limited. No cases of recurrent disease were diagnosed on colposcopic examination. Two cases of VAIN were diagnosed on colposcopic examination, both in women with HSIL Pap tests.

Our study supports previous studies demonstrating the significant limitation of Pap tests in diagnosing recurrent endometrial cancer. We found no cases of salvageable local recurrence diagnosed after abnormal cytology in the absence of patient symptoms or physical exam findings. Recent literature suggests that the prevalence of vaginal recurrences has decreased with the use of pelvic radiotherapy or vaginal brachytherapy [20,21]. This decrease in prevalence impacts negatively on the positive predictive value of abnormal vaginal cytology in detecting local recurrences.

The false negative rate of vaginal cytology cannot be ignored. Five cases of recurrent endometrial cancer were diagnosed shortly after a normal Pap test. These could represent true false negatives, incomplete testing of the entire vaginal cuff, or development of the recurrence between the time of the Pap test and the time of the biopsy. This highlights the need for thorough inspection and palpation of the vaginal cuff and vault to detect asymptomatic recurrences.

These results are similar to the results of prior studies, suggesting limited benefit to Pap tests in diagnosing recurrent endometrial cancer [7–12]. Our study is the first to limit evaluation to women screened using liquid based cytology and to use the 2001 Bethesda terminology. Our results support the most recent recommendation by the Society of Gynecologic Oncologists stating: “Because most recurrences at the vaginal cuff can be found on examination, vaginal cytologic evaluation adds only significant healthcare costs without added benefit [22].”

This study is limited by its retrospective nature and the absence of comprehensive colposcopy for cytologic abnormalities. We cannot exclude the possibility that VAIN was missed in women with ASC-US/LSIL. However, the absence of squamous cancers in these women during follow-up suggests that Pap tests are unlikely to improve survival in endometrial cancer survivors through early diagnosis of second squamous cancers of the vagina. Additionally, some patients were eventually referred back for continued follow up by their primary gynecologists. However, it is unlikely that recurrences occurred in these extremely low risk as most would have been referred back for evaluation by their gynecologic oncologist had an abnormality been noted.

Despite these limitations, we propose that performance of vaginal cytology in patients treated for endometrial cancer is of low-yield and therefore unnecessary. Thorough inspection of the vaginal cuff is integral in the follow-up of these patients as most local recurrences will present with a visible lesion. For clinicians who elect to perform cytology surveillance for women with treated endometrial cancer, serial cytology rather than colposcopy should follow ASC-US/LSIL Pap test results. Patients may be counseled that the risk of missing a recurrent endometrial cancer or VAIN is extremely low. Discontinuing surveillance is also an option. Since duration of follow-up in this study is limited, colposcopy may be helpful if only for reassurance after multiple ASC-US/LSIL Pap tests.

These recommendations do not apply to women with a history of high grade cervical intraepithelial neoplasia (CIN). According to recommendations from ACOG, ongoing cytologic surveillance is recommended for such women, though not for women with prior CIN1 or abnormal cytology but not high grade CIN. [14]

Women with AGC Paps should undergo careful examination of the vaginal cuff and vault and close follow-up for recurrent disease. As only two women had ASC-H Paps in our cohort, we are unable to make recommendations as to the optimal follow-up for these patients. Though both cases of ASC-H in our series were benign, these women should likely be followed as if they had HSIL cytology to avoid missing recurrent endometrial cancer or VAIN. HSIL cytology may indicate VAIN and colposcopic abnormalities may be minimal.

Repeated Pap tests and colposcopies may be required to diagnose high-grade VAIN in these women.

Acknowledgments

Gongfu Zhou for his statistical assistance.

The Siteman Cancer Center is supported by NCI Cancer Center Support Grant P30 CA91842.

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Figure 1.
Follow-up for 433 Patients

Table 1**Patient Demographic and Clinical Characteristics**

Age (years)		n (%)
	18–40	15 (3.5)
	41–50	44 (10.2)
	51–60	139 (32.1)
	61–70	154 (35.6)
	Older than 70	81 (18.7)
History of Prior Abnormal Pap Test	No	348 (80.4)
	Yes	79 (18.2)
	Unknown	6 (1.4)
Smoking History	None	323 (74.6)
	Former	73 (16.9)
	Current	32 (7.4)
	Unknown	5 (1.2)
FIGO 2009 Stage		
	I	331 (76.4)
	II	16 (3.7)
	III	58 (13.4)
	IV	28 (6.5)
Histology		
	Endometrioid	350 (80.8)
	Clear cell	6 (1.4)
	Serous	27 (6.2)
	Mixed	31 (7.2)
	Carcinosarcoma	18 (4.2)
	Other histology	1 (0.2)
Grade		
	1	241 (55.7)
	2	88 (20.3)
	3	98 (22.6)
	Ungraded	6 (1.4)
Adjuvant Therapy	None	267 (61.7)
	Chemotherapy	64 (14.8)
	VB	24 (5.5)
	PRT + VB	9 (2.1)
	Chemotherapy + VB	18 (4.2)
	Chemotherapy + PRT	7 (1.6)
	Chemotherapy + PRT + VB	42 (9.7)
	Other	2 (0.5)

PRT = pelvic radiotherapy, VB = vaginal brachytherapy

Table 2

Distribution of Abnormal Pap Tests and Colposcopic Examination

	# of abnormal Pap tests	# undergoing colposcopy (% , 95% CI)	# of cases of VAIN	# of cases of recurrent cancer
ASC-US	27	2 (7.4, 0–17.3%)	0 (0%)	2 (7%)
LSIL	10	6 (60, 29.6–90.4%)	1 (10%)	0 (0%)
ASC-H	2	2 (100)	0 (0%)	0 (0%)
AGC	12	6 (50, 21.7–78.3%)	0 (0%)	6 (50%)
HSIL	3	3 (100)	1 (33%)	0 (0%)
Adenocarcinoma	1	0 (0)	0 (0%)	1 (100%)

Table 3

Association Between Clinical Factors and Abnormal Pap Tests*

		No abnormal cytology - n (%)	Abnormal cytology - n%	P
Age				
	(Mean $\pm$ SD)	61.7 $\pm$ 10.8	60.6 $\pm$ 11.0	0.47
Stage	Stage I/II	310 (82.0)	37 (67.3)	0.01
	Stage III/IV	68 (18.0)	18 (32.7)	
Grade	I	208 (55.0)	33 (60.0)	0.03
	II	84 (22.2)	4 (7.3)	
	III	82 (21.7)	16 (29.1)	
	Ungraded	4 (1.1)	2 (3.6)	
Adjuvant Radiation				
	No	303 (80.2)	28 (50.9)	<0.001
	Yes	75 (19.8)	27 (49.1)	
Histology				
	Endometrioid	307 (81.2)	43 (78.2)	0.59
	All others	71 (18.8)	12 (21.8)	
History of prior				
Abnormal Pap	No	305 (81.8)	43 (78.2)	0.74
	Yes	67 (18.0)	12 (21.8)	
Smoking History				
	Never	281 (75.3)	42 (76.4)	0.87
	Current/Former	92 (24.7)	13 (23.6)	

* Totals may not add up to 433 because of missing information