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Utility of extra biopsies during colposcopy: experience with a cervical imaging system at an academic center

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Abstract

Objective: Determine if additional non-random biopsies beyond clinician directed biopsy enhance the detection of high-grade cervical disease.

Methods: A cervical imaging system (CIS) was used as an adjunct to colposcopy in an academic colposcopy clinic between July 2008 and October 2010 in an IRB approved post-FDA approval study. A post hoc analysis explored if additional biopsies through the CIS added diagnostic value to the clinician's biopsies.

Results: Of 181 women with complete analysis, 50 (27.6%) were found to have CIN2+ disease. Clinician directed biopsy detected 45 of 50 (90%) of CIN2+. CIS directed biopsy detected an additional 5 of 50 (10%) of CIN2+.

Clinicians directed 180 total biopsies meaning that 1 of every 4 clinician biopsies detected CIN2+ disease, whereas CIS directed an additional 68 biopsies resulting in a yield of one case of CIN2+ disease for approximately 14 additional biopsies.

Conclusion: Additional non-random biopsies based on CIS increased the detection of high-grade disease in cases where clinicians did not identify high-grade disease. As noted by others, both random and non-random additional biopsies increase the sensitivity of traditional colposcopy. What is not clear is whether the additional cases identified represent clinically significant disease. Our study is particularly relevant as colposcopists explore standardizing high yield diagnostic techniques.

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Background

Colposcopy with biopsy and histologic evaluation has been the standard for evaluation of abnormal cervical cytology since the 1960s. Colposcopy with biopsy is undertaken in women with persistent cytological abnormalities or concerning cytology. This allows for further characterization of pre-cancerous or cancerous lesions and guides management. Detection of high-grade cervical disease through colposcopy has been estimated to range from 50-80%.[1-3]

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Improving sensitivity of colposcopy has been undertaken by taking additional biopsies; however the optimum technique is unknown. Recent studies have explored various strategies. Additional directed biopsies from unique, suspicious appearing lesions improved sensitivity of detecting CIN3+ from 68.3% (1 biopsy) to 81.8% (2 biopsies).[4] Others have found the accuracy of colposcopically directed biopsy to be higher with 3 biopsies (up to 95.6%).[5,6] Random biopsies at the squamocolumnar junction when no lesions are visible have been shown to detect 19.7% of CIN2+ disease with one biopsy,[7] and 25.7% of CIN3+ with four biopsies (one in each cervical quadrant).[8]

Further techniques to improve the sensitivity of cervical high-grade disease and cancer detection include the use of digital imaging technologies. We reviewed the use of a cervical imaging system (CIS) to determine its impact in identifying CIN2+ beyond initial clinician directed biopsy.

Methods

Participants included women 18 years of age or older who were referred to the colposcopy clinic at the University of Iowa Hospital and Clinics according to established guidelines for evaluation of abnormal cervical cytology (atypical squamous cells (ASC) or greater) between July 2008 and October 2010. The colposcopy clinic is a resident clinic staffed by 5 general gynecology attending physicians and one nurse practitioner during the study enrollment period. The nurse practitioner had greater than 15 years of colposcopy experience, 2 of the gynecologists had at least 10 years of colposcopy experience, and 3 of the gynecologists had less than 10 years of colposcopy experience. All resident colposcopy exams were completed with direct real-time supervision by a gynecology attending physician. A total of 195 women aged 20 years and older were enrolled in the Institutional Review Board approved study.

The LUMA Cervical Imaging System (SpectraScience, Inc) was approved by the US FDA as an adjunct to colposcopy to map the cervix and identify high risk lesions with spectroscopy to identify high-grade neoplastic lesions of 2 mm or more.[9] LUMA exploits the inherent differences of light reflectance and fluorescence between normal and neoplastic tissue to map the ectocervix and identify areas with high probability of being neoplastic with an increase of at least 25% in the true-positive biopsy rate in prior studies.[9-11] The FDA approved this device in March 2006, however the device lost funding in 2010 (concluding the study).

Women referred for colposcopy underwent a CIS scan prior to undergoing a standard colposcopic evaluation. The results of the CIS scan were revealed after the colposcopist had completed colposcopy and committed to any colposcopically directed biopsy sites. After sites for colposcopically directed biopsies had been annotated on the CIS computer screen, the results of the CIS scan were unmasked and any additional biopsy sites were identified based on the CIS result. Colposcopists were instructed to take at least one biopsy from any area identified as a high probability for CIN 2+ based on the CIS result in addition to areas

identified during standard colposcopy. Biopsy was not required in cases where the colposcopic impression was normal or low-grade squamous intraepithelial lesion (LSIL) corresponding to cervical intraepithelial neoplasia (CIN) I or less. In every case the clinician was asked to complete endocervical sampling (endocervical Pap smear or endocervical curettage). All biopsy specimens were reviewed by Pathologists at the University of Iowa Hospital and Clinics according to standard institutional protocol. All patients were informed of the results and management recommendations based on the American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines at that time and underwent further excisional procedure if clinically indicated.

Results were collected and categorized according to presence and level of cervical dysplasia; CIN 2, CIN 3 adenocarcinoma in-situ (ACIS) and invasive cancer were considered CIN2+ disease. Additional information including age, self-identification as a current tobacco smoker, and referral Pap smear was collected by chart review.

Exclusion criteria included pregnancy through 6 weeks post-partum, previous hysterectomy, history of diethylstilbestrol exposure, cervical biopsy or therapeutic procedure since the referral cervical cytology, cervical cytology test within the prior seven days, use of vaginal medications within the last 48 hours or photosensitizing agents within 72 hours, history of photosensitivity or other diseases affected by UV radiation, or an observable and untreated gynecological infection.

Results

195 women were enrolled in the study. There were 14 (7.2%) women where the CIS was not utilized during the exam, including: device unable to focus (n=6), device failure (n=5), withdrew consent (n=2), and bleeding (n=1). Thus there were 181 subjects eligible for comparison.

The median age of women in the study was 27 years old (range 20 to 66); the majority were 30 years old or less 118 of 181 (65%), with 20 women age 40 to 49 years old, and 9 women age 50 years old or greater. Review of Pap smear results preceding colposcopy identified 44 of 181 (24%) women were referred for high-grade intraepithelial lesions (HSIL). However, the most common indication for colposcopy was for low-grade intraepithelial lesions (LSIL) 91 of 181 (50%) (Table 1).

Fifty women were found to have CIN2+ including 2 women with invasive squamous cell carcinoma. Clinician directed biopsy detected 45 (90%) of the CIN2+ identified. Additional CIS directed biopsy identified CIN2+ in 5 women which were not detected by clinician annotation; including CIN 2 in 3 women and CIN 3 in 2 women (Table 2). Referral Pap smears included 3 for ASC, and 1 each for LSIL and HSIL.

The CIS identified CIN2+ in many cases also noted by the clinician; however it did not detect disease in nearly half, 24 of 50 (48%) of cases identified by the clinician. Clinician and CIS identified one case of invasive cancer that was diagnosed with biopsy.

Table 1. Cases, by Age, smoking status and referral Pap smear

Age years	
20-24	64
25-29	54
30-39	36
40-49	18
50 or older	9
Current Smoker	
Yes	58
No	123
Referral Pap Smear	
ASC: atypical squamous cells	36
ASC-H: atypical squamous cells, cannot exclude high grade	10
LSIL: low grade intraepithelial lesion	91
HSIL: high grade intraepithelial lesion	44

Table 2. CIN2+ cases detected by clinician, CIS, or both

Pathology	Clinician directed biopsy (n)	CIS directed biopsy (n)	Clinician and CIS directed biopsy (n)
CIN 2	11	3	6
CIN 3	13	2	14
Invasive CA	0	0	1
Totals	24	5	21

CIS: cervical imaging system
CIN: cervical intraepithelial neoplasia
n: number

However, only the clinician took a biopsy of the CIN3+ in a patient with invasive cancer detected on subsequent loop electrical excision procedure (LEEP).

Two hundred and forty-eight total biopsies were taken (Figure 1). Clinician directed biopsy collected 180 total biopsies (0 to 5 biopsies directed by clinician for each patient) (Table 3). Thus, one case of CIN2+ was identified for every 4 clinician biopsies.

CIS directed biopsy collected 68 additional biopsies (additional 0 to 2 directed by CIS for each patient) to identify the 5 additional cases of CIN2+. Thus, approximately 14 biopsies directed by CIS were required to find each additional case of CIN2+ disease not identified by clinician directed biopsy.

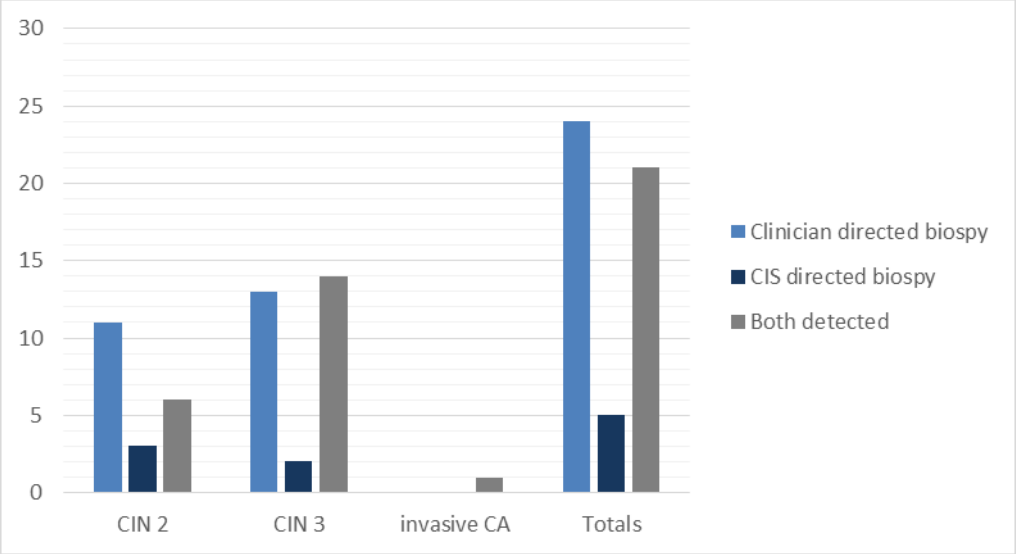

Figure 1. CIN2+ detected by biopsy from clinician, cervical imaging system (CIS) or both

Table 3. Clinician directed biopsies

Provider years of colposcopy experience	0 biopsy	1 biopsy	2 biopsy	3 biopsy	4+ biopsy
20 years nurse practitioner	64 patients	39 patients	2 patients	0	0
10 or greater years 2 gynecology attendings	15 patients	21 patients	16 patients	9 patients	2 patients (1 each with 4 and 5 biopsies)
Less than 10 years 3 gynecology attendings	13 patients	9 patients	3 patients		

Among the additional 5 cases of CIN2+ identified by CIS, 0 to 1 clinician directed biopsies were performed and 1 to 2 additional CIS directed biopsies were performed. The additional 5 cases were identified with 1 to 3 total biopsies performed for each patient (Table 4).

Total biopsies for each patient (clinician directed and additional CIS directed) range from 0 (endocervical sampling only) to 5. No cases of CIN2+ were identified based on endocervical sampling only. The majority of patients had 0 to 2 biopsies performed; 29 patients had 3 or more biopsies.

Table 4. Additional 5 patients with CIN2+ identified by CIS

	Provider experience	Clinician Biopsies (n)	Additional CIS biopsies (n)	Total Biopsies (n)
CIN 2	Less than 10 years	1	2	3
CIN 2	20 years	1	1	2
CIN 2	20 years	0	1	1
CIN 3	20 years	1	1	2
CIN 3	20 years	0	1	1

CIS: cervical imaging system
CIN: cervical intraepithelial neoplasia
n: number

All of the patients with CIN 2 were less than 50 years old: 6 were 21 to 24 years old, 8 were 25 to 30 years old, and 6 were 31 to 41 years old. Subsequent LEEP was performed in 17 patients of which 1 was normal, 4 revealed CIN I, 5 revealed CIN 2, 6 revealed CIN 3, and 1 revealed ACIS. Two of the remaining patients were treated with ablation therapy (1 cryotherapy, 1 laser) and 1 patient was followed with serial colposcopy. All three had return to normal cytology at 12 months.

The 29 patients with CIN 3 were 21 to 54 years old, with 8 patients age 31 years old or greater. Twenty-five of 29 patients with CIN 3 were treated with LEEP of which 2 revealed CIN I, 7 revealed CIN 2, 14 revealed CIN 3, 1 revealed invasive squamous cell cancer, and 1 revealed HSIL with extensive cautery (unable to grade further). Two of the remaining patients were treated with ablation therapy (1 cryotherapy, I laser). One patient was scheduled for laser but was pregnant when she presented for treatment and transferred care to her local provider, and 1 patient underwent a hysterectomy concurrent with bowel resection for Crohn's disease with residual CIN I identified on pathology.

Discussion

Comparing the overall effectiveness of screening and diagnostic paradigms that incorporate different strategies is difficult. To insure the CIS was used as an adjunct to colposcopy, the results of the CIS scan were not displayed until after the colposcopic examination was complete and the colposcopist had committed to sites for colposcopically directed biopsies. Additional CIS directed biopsies increased the detection of cervical high-grade disease by 10% among women referred to colposcopy for abnormal cytology compared to colposcopy alone, with approximately 14 additional biopsies required for each additional CIN2+ detected. Specifically reviewing the 5 cases of CIN2+ identified by CIS, 1 to 3 total biopsies were performed for each patient.

Forty-five patients in this study received endocervical sampling only - without biopsy at the time of colposcopy which may have resulted in decreased detection of CIN2+ as a subsequent excision procedure was not required as a gold standard. As identified by others, both random and directed additional biopsies increase the sensitivity of

traditional colposcopy.[4-8]

What is not clear is whether the additional cases identified represent clinically significant disease. We agree with Huh et al. that colposcopy misses clinically significant (as well as clinically insignificant) disease.[7] We did not further evaluate patients with diagnostic procedures to determine if underlying cervical disease missed by the clinician with or without additional biopsies per the CIS was present. We suspect that the sensitivity of the clinicians in our department is similar to other academic departments. Furthermore, we did not confirm the histological diagnosis of CIN 2 as the use of biomarkers including p16 was not the standard of care at the time of this study. Thus, cases may have been misclassified. However, these dilemmas reflect the overall clinical challenge of risk based assessment and improving the sensitivity of colposcopy.

Our study evaluated a generally young patient population with a significant number of patients aged less than 30 years; with only 29 patients age 40 years old or greater. Given that most cervical cancer is diagnosed in patients in the fourth decade,[12] we suspect the overall sensitivities of clinician and CIS directed biopsy would have been higher if the population in our study was older.

Additional limitations of this study include the CIS was not reliable and not adaptable to various cervical evaluations. The CIS is limited to scan and analyze a 2D plane.[9] In our series, 12 (of 195) of women were unable to undergo evaluation with CIS due to machine malfunction or limitation (additionally 2 withdrew – for a total of 14 exclusions). Furthermore, while the CIS agreed with the clinician directed biopsy in many cases, it did not identify CIN2+ in 24 of 50 (48%) cases where the clinician biopsy confirmed CIN2+. This is lower than previous reports for the CIS.[9-11]

While, colposcopy and biopsy are the standard methods of diagnosing high-grade lesions of the cervix, it is not without limitations. Even highly experienced colposcopists can vary greatly in their colposcopic interpretations. Thus, histology obtained by biopsy is paramount in the detection of cervical dysplasia. Based on the data in this study, the use of a CIS does not appear to be better than performing additional random biopsies. Our study is particularly relevant as practitioners develop best practice guidelines including implementation of standards to identify optimal diagnostic techniques and adjunct technology to improve upon current practice.

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References

1. American College of Obstetricians and Gynecologists. Practice Bulletin No. 140: management of abnormal cervical cancer screening test results and cervical cancer precursors. Obstet Gynecol. 2013 Dec;122(6):1338-67. https://doi.org/10.1097/01.AOG.0000438960.31355.9e PubMed PMID: 24264713.

2. Ferris DG, Litaker M; ALTS Group. Interobserver agreement for colposcopy quality control using digitized colposcopic images during the ALTS trial. J Low Genit Tract Dis. 2005 Jan;9(1):29-35. https://doi.org/10.1097/00128360-200501000-00007 PubMed PMID: 15870519.

3. Jeronimo J, Massad LS, Castle PE, Wacholder S, Schiffman M; National Institutes of Health (NIH)-American Society for Colposcopy and Cervical Pathology (ASCCP) Research Group. Interobserver agreement in the evaluation of digitized cervical images. Obstet Gynecol. 2007 Oct;110(4):833-40. https://doi.org/10.1097/01.AOG.0000281665.63550.8f PubMed PMID: 17906017.

4. Gage JC, Hanson VW, Abbey K, Dippery S, Gardner S, Kubota J, Schiffman M, Solomon D, Jeronimo J; ASCUS LSIL Triage Study (ALTS) Group. Number of cervical biopsies and sensitivity of colposcopy. Obstet Gynecol. 2006 Aug;108(2):264-72. https://doi.org/10.1097/01.AOG.0000220505.18525.85 PubMed PMID: 16880294.

5. Wentzensen N, Walker JL, Gold MA, Smith KM, Zuna RE, Mathews C, Dunn ST, Zhang R, Moxley K, Bishop E, Tenney M, Nugent E, Graubard BI, Wacholder S, Schiffman M. Multiple biopsies and detection of cervical cancer precursors at colposcopy. J Clin Oncol. 2015 Jan 1;33(1):83-9. https://doi.org/10.1200/JCO.2014.55.9948 Epub 2014 Nov 24. PubMed PMID: 25422481; PubMed Central PMCID: PMC4268255.

6. Müller K, Soergel P, Hillemanns P, Jentschke M. Accuracy of colposcopically guided diagnostic methods for the detection of cervical intraepithelial neoplasia. Geburtshilfe Frauenheilkd. 2016 Feb;76(2):182-187. https://doi.org/10.1055/s-0041-111504 PubMed PMID: 26941452; PubMed Central PMCID: PMC4771495.

7. Huh WK, Sideri M, Stoler M, Zhang G, Feldman R, Behrens CM. Relevance of random biopsy at the transformation zone when colposcopy is negative. Obstet Gynecol. 2014 Oct;124(4):670-8. https://doi.org/10.1097/AOG.0000000000000458 PubMed PMID:25198268.

8. Pretorius RG, Belinson JL, Burchette RJ, Hu S, Zhang X, Qiao YL. Regardless of skill, performing more biopsies increases the sensitivity of colposcopy. J Low Genit Tract Dis. 2011 Jul;15(3):180-8. https://doi.org/10.1097/LGT.0b013e3181fb4547 PubMed PMID: 21436729.

9. Kendrick JE, Huh WK, Alvarez RD. LUMA cervical imaging system. Expert Rev Med Devices. 2007 Mar;4(2):121-9. https://doi.org/10.1586/17434440.4.2.121 PubMed PMID: 17359219.

10. Huh WK, Cestero RM, Garcia FA, Gold MA, Guido RS, McIntyre-Seltman K, Harper DM, Burke L, Sum ST, Flewelling RF, Alvarez RD. Optical detection of high-grade cervical intraepithelial neoplasia in vivo: results of a 604-patient study. Am J Obstet Gynecol. 2004 May;190(5):1249-57. https://doi.org/10.1016/j.ajog.2003.12.006 PubMed PMID: 15167826.

11. Alvarez RD, Wright TC; Optical Detection Group. Effective cervical neoplasia detection with a novel optical detection system: a randomized trial. Gynecol Oncol. 2007 Feb;104(2):281-9. Epub 2006 Dec 14. https://doi.org/10.1016/j.ygyno.2006.08.056 PubMed PMID: 17173959.

12. Surveillance, Epidemiology, and End Results Program. Cancer Statistics Review: Median age of cancer patients at diagnosis, 2009-2013 by primary cancer site, race, and sex. Table 1.12. 1975-2013. https://seer.cancer.gov/csr/1975_2013/results_single/sect_01_table.12_2pgs.pdf (accessed January 4 2017).