Digital Assessment of the Reproductive Tract Versus Colposcopy for Directing Biopsies in Women With Abnormal Pap Smears

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Abstract
Objective. This study aimed to compare digital camera assessment of the reproductive tract (DART) to colposcopy for the evaluation of abnormal Pap smears.

Materials and Methods. Participants included 207 women with abnormal Pap smears. Colposcopy and DART were performed on each patient by separate examiners with the goal of lesion detection. Analysis was performed per patient and per biopsy.

Results. Patients had an average of 2.9 biopsies. Forty-two patients and 81 biopsies were positive for cervical intraepithelial neoplasia 2+. Both DART and colposcopy detected 41 (97.6%) of 42 patients (95% CI = 85.9%–99.9%). Digital camera assessment of the reproductive tract detected 66/81 (81.4%; CI = 70.7%–88.9%) and colposcopy detected 69/81 (85.2%; CI = 73.2%–92.4%) of biopsies that were cervical intraepithelial neoplasia 2+.

Conclusions. Digital camera assessment of the reproductive tract detects high-grade lesions of the cervix with similar sensitivity to colposcopy. It holds great promise to expand cervical cancer precursor lesion detection in areas with limited resources.

Key Words: visual inspection with acetic acid (VIA), colposcopy, Pap smear, digital assessment of the reproductive tract (DART), cervical intraepithelial neoplasia (CIN)

Cervical cancer kills more than 273,000 women worldwide per year [1]. Much of the mortality from cervical cancer occurs in the developing world [2]. The incidence of disease is higher, and risk of dying from this disease is greatly increased in low-resource areas. The cervical cancer death rate in El Salvador is 18.4 per 100,000 compared with 2.3 per 100,000 in the United States [1].

Although women in El Salvador are able to complete the first step of obtaining a Pap test, they frequently do not return for management by colposcopy when the result is abnormal. In 2006, 18,124 women in El Salvador had preinvasive lesions or invasive cancers detected by cytology. Of these, only 5,768 women (31.8%) received follow-up with colposcopy or surgery [3].

A major reason for poor follow-up is that colposcopy is not available in most rural areas, requiring rural
women to incur the cost of travel and lodging. Many patients never go for follow-up care. At a colposcopy center, the wait for an appointment can be up to 3 months. The use of a low cost, portable alternative to colposcopy could relieve both this underserved rural population, and this overburdened urban clinic system.

The purpose of this study was to assess whether examination of the cervix using a digital camera could replace colposcopy for the evaluation of women with abnormal cytology. This technology called digital assessment of the reproductive tract (DART) uses a regular digital camera connected to a television screen to enlarge and magnify a still image of the cervix. A pilot study by our group showed that DART had similar sensitivity to cytology in identifying cervical cancer precursors [4].

Digital camera assessment of the reproductive tract is an inexpensive, highly portable technology that could facilitate expansion of sites for secondary diagnostic confirmatory procedures after abnormal Pap smears.

**MATERIALS AND METHODS**

The project was approved by the institutional review board of the University of Southern California in conjunction with approval letters from the Cancer Institute of El Salvador and the Salvadoran Ministry of Health.

Consecutive patients with abnormal Pap smears referred to the Instituto de Cancer de El Salvador from July to November of 2006 for colposcopy were eligible to participate in the study. Inclusion criteria were as follows: age 18 to 70 years and an intact uterus and cervix. Exclusion criteria were as follows: history of any gynecological cancer, pregnancy, or inability to provide verbal informed consent. Two hundred sixteen women were offered participation. Two declined stating fear of the procedure as the reason. Demographic information was obtained including age, height, weight, educational status, occupation, and socioeconomic status. A complete history was taken including patients’ medical, reproductive, and sexual history.

All patients were examined by 2 Salvadoran gynecologists with expertise in colposcopy. These physicians were proctored during a single-day session on the use of DART for directing biopsies for the detection of cervical intraepithelial neoplasia (CIN). A process evaluation was performed the first day of the study for quality assurance. The first examiner placed 5% acetic acid on the cervix and performed DART. Detailed descriptions of this apparatus and how it is used have been previously published elsewhere [5]. This examination was performed by placing a disposable self-illuminated speculum into the vagina for cervical visualization. A Nikon CoolPix 5400 camera was placed on a monopod and used to obtain a still photograph of the cervix that was projected onto an ordinary 19-in. television screen.

Once the cervix was visualized, the first examiner indicated areas suspicious of a lesion on a schematic diagram of the cervix derived from the digital photograph. The second physician who was unaware of the results of the first examination then performed a standard colposcopic examination and took biopsies of all colposcopically detected lesions. Immediately ensuing the colposcopically obtained biopsies, the second physician was made aware of the DART results and ensured that a biopsy of all sites found suspicious by DART was performed. If DART was positive at sites not sampled as a result of colposcopy, a biopsy of those sites at that time was performed. If no lesions were indicated by either DART or colposcopy, biopsies were taken at 2 o’clock and 10 o’clock [6]. An endocervical curettage was completed on all patients. Samples were placed in separate marked containers and labeled with the area of the clock where the specimen was obtained.

The examinations were done in 2 different examination rooms, and the patient switched from the “DART room” to the “Colpo room” after her DART examination. The acetic acid was reapplied by the colposcopist. The colposcopic examination was always performed second because colposcopically directed biopsy is the gold standard in management of abnormal Pap smear. Pathology specimens were processed in El Salvador and read by an expert gynecologic pathologist in the United States.

Data were analyzed using a per-patient and per-biopsy diagnosis. Per-patient diagnosis was based on the most severe lesion by biopsy at any site. For example, if a patient had 2 biopsies, one with CIN 1 and another with CIN 3, her final per-patient diagnosis was CIN 3. Per-biopsy diagnosis was based on the diagnosis at the particular site. For example, the patient with CIN 1 and CIN 3 had the 2 biopsies counted separately with separate diagnosis. The biopsy was considered to be true diagnosis when comparing DART versus colposcopy.

There were 207 patients and 593 biopsies. Because the samples were separated and labeled by the area of the clock, it was possible to analyze the results both by patient and by biopsy. For the patient analysis, the comparison test was considered positive if any site was positive on the examination. For the per biopsy analysis, each site was considered separately and the confirmatory test was defined as positive if a lesion was present in...
the area of the clock ±2 hours. The endocervical curet-
tage was included in the patient analysis but not in the
biopsy analysis because it does not correspond to a col-
poscopically assessable site.

Analyses were conducted using SAS statistical soft-
ware, version 9.1 (SAS Institute, Cary, NC). Sensitivity,
specificity, and positive and negative predictive values
were calculated using standard formulas for binomial
proportions. Corresponding 95% CIs for “per patient”
estimates of accuracy were calculated assuming a binom-
ial distribution [7], p values in Tables 2 and 3 for “per
patient” analyses were calculated using McNemar test
with Yates correction following the method of Hawass
[8]. To account for the correlation resulting from multi-
ple lesions per patient, generalized estimating equations
were used to construct CIs and obtain p values for “per
biopsy” analyses [9]. p values less than .05 were con-
sidered statistically significant.

## RESULTS

Two hundred fourteen patients were initially enrolled in
the study. Seven were excluded: 2 charts were missing, 2
patients were missing US pathology diagnosis, 2 patients
had no biopsies taken, and colposcopy data were
missing from 1 chart. A total of 207 patients and 593
biopsies were included in the final analysis. An average
of 2.9 biopsies were taken per patient (range, 2
6).

Pertinent demographics and reproductive history are
shown in Table 1. Most subjects were nonsmokers and
had an average of 2 lifetime sexual partners. As a group,
the women studied had a relatively low level of education,
with an average number of 3 school years, and a reported
average of 4 pregnancies per person. Women in the study
were referred for colposcopy for a variety of cytological
abnormalities. Seventy-five percent (155/207) were re-
ferred for low-grade intraepithelial neoplasia, whereas
21% (44/207) were referred for high-grade intraepithelial
neoplasia or carcinoma, and approximately 4% (8/207)
were referred for a lesion of undetermined grade.

There were a total of 68 (32.9%) of 207 patients and
125 (21.1%) of 593 biopsies with lesions of CIN 1 or
greater (CIN 1+). A pairwise comparison of the data is
shown in Table 1, and the breakdown of the biopsy
results is shown in Table 2. A comprehensive compari-
son of the 2 methods is shown in Tables 3A, B. Table 3A
is a breakdown of the data using CIN 2 as a cutoff, and
Table 3B uses a cutoff of CIN 1. Colposcopy was better
than DART at detecting CIN 1+, both per patient
(94.1% vs 88.2%; p = .95) and per biopsy (81.6% vs
73.6%; p = .14), although the differences between the 2
methods were not statistically significant (Table 3B).

Table 3A shows both per-patient and per-biopsy
analysis for lesions with a diagnosis of CIN 2 or higher
(CIN 2+). According to the per-patient analysis, 42
(20.1%) of 207 patients had at least 1 positive biopsy for
CIN 2+. Digital assessment of the reproductive tract
detected 41 (97.6%) of 42 patients with CIN 2+ (95% CI =
85.9%–99.9%). Colposcopy also detected 41 (97.6%)
of 42 patients with CIN 2+ (95% CI =
85.9%–99.9%). The two tests were also similar in
terms of specificity: DART specificity was 23.6% (95%
CI = 17.5%–31.0%), and colposcopy specificity was
20.6% (95% CI = 14.9%–27.7%; p = .33).

When analyzed by total number of positive biopsy
sites, 81 (13.6%) of 593 biopsies were positive for CIN

### Table 1. Participant Demographics in Study Comparing Colposcopy With DART for Directing Biopsies in Women With Abnormal Pap Smears

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>Mean</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>207</td>
<td>41.6</td>
<td>11.7</td>
<td>20–77</td>
</tr>
<tr>
<td>No. pregnancies</td>
<td>206</td>
<td>4.1</td>
<td>2.75</td>
<td>0–14</td>
</tr>
<tr>
<td>No. living children</td>
<td>206</td>
<td>3.5</td>
<td>2.2</td>
<td>0–11</td>
</tr>
<tr>
<td>Age at first intercourse, y</td>
<td>205</td>
<td>17.6</td>
<td>3.7</td>
<td>9–39</td>
</tr>
<tr>
<td>No. lifetime sexual partners</td>
<td>202</td>
<td>2.4</td>
<td>1.86</td>
<td>1–21</td>
</tr>
<tr>
<td>Years of education</td>
<td>207</td>
<td>3.7</td>
<td>3.6</td>
<td>0–12</td>
</tr>
</tbody>
</table>

| Smokers (current)             | 206| 5/206| 2.4%|
| Smokers (past)                | 206| 15/206| 7.3%|
| Smokers (never)               | 206| 186/206| 90.3%|

DART, digital camera assessment of the reproductive tract.

### Table 2. Histology Results “Per Patient” and “Per Biopsy” for Results ≥CIN 1+

<table>
<thead>
<tr>
<th>Histological diagnosis</th>
<th>DART recognized</th>
<th>Colposcopy recognized</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive histology results “per patient” diagnosis (n = 68)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>32/139 (23%)</td>
<td>31/139 (22%)</td>
<td>.62</td>
</tr>
<tr>
<td>CIN 1</td>
<td>19/26 (73%)</td>
<td>23/26 (88%)</td>
<td>.22</td>
</tr>
<tr>
<td>CIN 2</td>
<td>11/12 (92%)</td>
<td>11/12 (92%)</td>
<td>ND</td>
</tr>
<tr>
<td>CIN 3</td>
<td>21/21 (100%)</td>
<td>21/21 (100%)</td>
<td>ND</td>
</tr>
<tr>
<td>Carcinoma in situ</td>
<td>2/2 (100%)</td>
<td>2/2 (100%)</td>
<td>ND</td>
</tr>
<tr>
<td>Microinvasive</td>
<td>1/1 (100%)</td>
<td>1/1 (100%)</td>
<td>ND</td>
</tr>
<tr>
<td>Invasive cancer</td>
<td>6/6 (100%)</td>
<td>6/6 (100%)</td>
<td>ND</td>
</tr>
<tr>
<td>Positive histology results “per biopsy” diagnosis (n = 125)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>213/468 (46%)</td>
<td>163/468 (35%)</td>
<td>.003</td>
</tr>
<tr>
<td>CIN 1</td>
<td>26/44 (59%)</td>
<td>33/44 (75%)</td>
<td>.13</td>
</tr>
<tr>
<td>CIN 2</td>
<td>14/19 (74%)</td>
<td>16/19 (84%)</td>
<td>.45</td>
</tr>
<tr>
<td>CIN 3</td>
<td>38/48 (79%)</td>
<td>41/48 (85%)</td>
<td>.45</td>
</tr>
<tr>
<td>Carcinoma in situ</td>
<td>2/2 (100%)</td>
<td>1/2 (50%)</td>
<td>ND</td>
</tr>
<tr>
<td>Microinvasive</td>
<td>2/2 (100%)</td>
<td>1/2 (50%)</td>
<td>ND</td>
</tr>
<tr>
<td>Invasive cancer</td>
<td>10/10 (100%)</td>
<td>10/10 (100%)</td>
<td>ND</td>
</tr>
</tbody>
</table>

CIN, cervical intraepithelial neoplasia; DART, digital assessment of the reproductive tract; ND, p value could not be calculated for the difference between positive results recognized by DART and colposcopy.
2+. When evaluated against lesion location by the hour of the clock, ±1 hour, both DART detected 66 (81.4%; 95% CI = 70.7%–88.9%) of 81 and colposcopy detected 69 (85.2%; 95% CI = 73.2%–92.4%) of 81 lesions (p = .58). The specificity of DART was 45.1% (95% CI = 39.7%–50.7%) and that of colposcopy was 34.0% (95% CI = 28.9%–39.4%) (p = .0045).

There were 29 (14.1%) of 207 patients with negative examination results on both DART and colposcopy. Biopsies were taken at 10 o’clock and 2 o’clock on these patients because a study by Richart [6] showed that these are the areas that are most likely to have abnormalities. Of the 29 controls, 3 were positive (2 CIN 1 and 1 CIN 2).

**DISCUSSION**

We demonstrate that DART is an effective method to detect high-grade cervical cancer precursor lesions in women with abnormal cytology. It demonstrated equivalent sensitivity in both per-patient and per-biopsy analysis for the detection of CIN 2+ compared with colposcopy. It has the potential both to ease the burden of overwhelmed urban colposcopy clinics and to provide rural women with easier access to follow-up care. Because it is inexpensive compared with colposcopy, DART equipment can be added to colposcopy clinics to increase the volume of patients seen. This equipment is also easily transporable to remote areas where women may not have the time or resources to visit urban colposcopy clinics.

A major strength of this study was that it was conducted in a group of high-risk patients who were referred to colposcopy clinic after abnormal Pap smears. Of the abnormal Pap smears, 74.8% were low-grade lesions, 21.18% were high-grade lesions, and 4.4% were unspecified dysplasia. Another strength of the study was the split sample design, which allowed each patient to serve as her own control. In addition, we obtained biopsies in all patients so that the likelihood of approaching true diagnoses in each patient is extremely high. The use of local Salvadoran physicians rather than those trained in the United States made it more likely that the results would be reproducible in El Salvador.

Our study also demonstrated that DART is easy to learn in a clinical setting. The Salvadoran colposcopists in our trial mastered the techniques and overcame the challenges of digital photography. They also accrued more than 200 patients in 4 months, excluding none of the consecutively consented patients from the study because of technical difficulties. Examination of the images produced by DART in a clinical setting proved to be a relatively seamless process with a steep learning curve. Images projected onto an ordinary television screen were clear and bright. Areas of interest could be easily magnified for closer evaluation and clinical

### Table 3. Sensitivity, Specificity, and Positive and Negative Predictive Value for DART and Colposcopic Impression

<table>
<thead>
<tr>
<th></th>
<th>DART</th>
<th>Colposcopy</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. CIN 2+</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>95% CI</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>41/42</td>
<td>97.6</td>
<td>85.9–99.9</td>
</tr>
<tr>
<td>Specificity</td>
<td>39/165</td>
<td>23.6</td>
<td>17.5–31.0</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>41/167</td>
<td>24.6</td>
<td>18.4–31.9</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>39/40</td>
<td>97.5</td>
<td>85.3–99.9</td>
</tr>
<tr>
<td><strong>Per-biopsy diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>66/81</td>
<td>81.4</td>
<td>70.7–88.9</td>
</tr>
<tr>
<td>Specificity</td>
<td>231/512</td>
<td>45.1</td>
<td>39.7–50.7</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>66/347</td>
<td>19.0</td>
<td>13.8–25.6</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>231/246</td>
<td>93.9</td>
<td>89.5–96.5</td>
</tr>
<tr>
<td><strong>B. CIN 1+</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>95% CI</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>60/68</td>
<td>88.2</td>
<td>80.6–95.9</td>
</tr>
<tr>
<td>Specificity</td>
<td>32/139</td>
<td>23.0</td>
<td>16.0–30.0</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>60/167</td>
<td>35.9</td>
<td>28.9–43.2</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>32/40</td>
<td>80.0</td>
<td>67.6–92.4</td>
</tr>
<tr>
<td><strong>Per-biopsy diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>92/125</td>
<td>73.6</td>
<td>64.6–81.0</td>
</tr>
<tr>
<td>Specificity</td>
<td>213/468</td>
<td>45.3</td>
<td>40.3–50.9</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>92/347</td>
<td>26.5</td>
<td>22.0–31.5</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>213/246</td>
<td>86.6</td>
<td>81.1–90.7</td>
</tr>
</tbody>
</table>

DART, digital assessment of the reproductive tract; CIN, cervical intraepithelial neoplasia; ND, p value could not be calculated for the difference in sensitivity between DART and colposcopy.
decision making. Because the DART examiner did not instrument the cervix in any way, there is no reason to believe that consistently performing colposcopy after the DART influenced the results in any significant manner.

One potential disadvantage of DART is that it requires the use of an illuminated speculum, which is not widely available in developing countries. In El Salvador, it is available only in the capital city but can also be ordered online and shipped. One way to implement this new method would be to have these systems available in a limited number of central areas as an alternative to the colposcope. The widespread implementation of DART across developing countries would depend on the development of low-cost alternatives to these specula. There is the potential that if an illuminated speculum was not available, a practitioner may attempt to perform DART with a suboptimal light such as a gooseneck lamp. Using a simple gooseneck lamp, it is impossible to generate a clear visible image. If the practitioner were to get a clear image, there is no reason to believe that this image could not be used to direct biopsies.

Another potential disadvantage of DART is that it requires the use of a television screen, which is bulky to carry into a remote area. Many communities in El Salvador and throughout Central America have electricity. In every community with electricity, there is typically at least 1 television that could be used for this purpose. Colposcopy is not only bulky but also hard to repair. Repairs to camera and television equipment are available in virtually all major Central American cities.

A limitation of this study was that it was done by gynecologists already trained in colposcopy. To make this technology widespread and beneficial, it would also have to be taught to generalist physicians practicing in rural areas. The advantage of DART is that it creates a lasting image that could be used for training purposes, whereas the generalist is learning this technology. These generalist physicians are the ones performing cytology in their communities and are responsible for having these specimens processed in urban centers. They could easily have the biopsies from DART processed as well. They are also already connected to referral systems so any positive findings or complicated patients can be referred to a gynecologist.

The cost of a video colposcope from Welch Allyn is $8,750. The cost of the digital camera used in this study was approximately $150. Nineteen-inch color televisions can be purchased in San Salvador for less than $150. The Welch Allyn speculum illumination system is now available in Central America for approximately $200. A case of 25 reusable disposable specula is approximately $70. The initial costs of DART are $570 compared with an $8,750-worth colposcope. Even if multiple specula needed to be purchased, the DART would likely be more cost-effective. Furthermore, if DART was more accessible, it would enable women to have treatment of precancer rather than invasive cancer, which is far more expensive. There are inexpensive fiber optic speculums that can be used with a handheld flashlight. To increase the availability of this new technology, future studies need to assess the use of these specula for this purpose.

The sensitivity of DART was lower than that of colposcopy for the detection of low-grade lesions (CIN 1) on a per-lesion analysis. However, when analyzed on a per-patient basis, DART was equivalent to colposcopy in detecting even CIN 1. We believe that the clinical benefit of expanding the detection of true high-grade cervical cancer precursor lesions (CIN 2 and 3) to areas where colposcopy is unavailable would outweigh the risk of failing to detect a small number of low-grade lesions of the cervix. The clinical importance of underdetecting CIN 1 is minimal because low-grade lesions of the cervix regress in more than 90% of instances [10] and seldom, if ever, progress to higher-grade lesions or carcinoma [11].

Several recent studies have questioned the sensitivity of colposcopy. Belinson et al. [12] reported a sensitivity of 81% for the detection of CIN 2, 3 or invasive cancer. Findings from the ASCUS and low grade triage study (ALTS) trial reported a sensitivity of 55.9% in their series [13]. The discrepancy between our study (93.0%) and these 2 reports may be explained by the fact that the patients were in a colposcopy clinic, so the physicians may have been more likely to call examinations positive. This likely led to a greater number of cervical biopsies being taken. The small percentage of examinations called negative by the physicians most certainly accounts for the excellent sensitivity. This also accounts for the poor specificity of both DART and colposcopic impression, albeit at the expense of more biopsies.

The specificity of both the DART and colposcopy was poor (<30%) even in this high-risk population. There are many possible explanations for this. As stated above, because these women were presenting to a colposcopy clinic, the physicians may have been more likely to diagnose women with a lesion even if the examination results were not highly suspicious. There is also a high incidence of inflammation in this population, which may lead to false-positive visual tests.

In summary, we report a new, low-cost method for the detection and diagnosis of cervical cancer that seems
to rival the detection rates obtained with the current gold standard of diagnosis, colposcopy. Areas for further investigation include expanding the study to achieve greater statistical power and attempting to implement DART in remote areas, where the technology would be most useful.

REFERENCES


