Dynamic Spectral Imaging Colposcopy Versus Regular Colposcopy in Women Referred With High-Grade Cytology: A Nonrandomized Prospective Study

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Objective: The aim of the study was to evaluate the sensitivity of dynamic spectral imaging (DSI) colposcopy compared with regular colposcopy in women referred with high-grade cervical cytology.

Methods: In a prospective, nonrandomized, multicenter study, we included women referred for colposcopy at hospital gynecology clinics with high-grade cytology. Women were examined using either a regular or DSI colposcope. In both groups, colposcopists located 1 area viewed as most suspicious. In the DSI group, this was done before viewing the DSI map. Subsequently, an area was chosen based on the worst color of the DSI map, and further additional biopsies were taken. All women had 4 cervical biopsies taken, all analyzed separately. The main outcome was sensitivity to find cervical intraepithelial neoplasia grade 2 or worse (CIN2+).

Results: A total of 261 women were examined using DSI colposcopy, and 156 women were examined using regular colposcopy. The sensitivity for finding CIN2+ when using the DSI technology as an adjunctive technology was found to be 82.2% (95% CI = 75.9–87.4), based on an average of 1.4 biopsies. This was corresponding in sensitivity to 2 biopsies taken using regular colposcopy (80.3%; 95% CI = 72.3–86.8). There was no difference in sensitivity for CIN2+ between the groups when 3 or more biopsies were taken.

Conclusions: We found that the DSI colposcope may help direct biopsy placement; however, the improvement is based on small differences in needed biopsies and the clinical significance of this may be small. Multiple biopsies were still superior.

Key Words: cervical intraepithelial neoplasia, colposcopy, sensitivity

Colposcopy is the cornerstone of cervical intraepithelial neoplasia (CIN) diagnosis and an important link between cervical cancer screening programs and the prevention of cervical cancer development. However, the sensitivity of colposcopy has been found to be as low as 55%.1 It is therefore important to improve colposcopy performance, especially in light of future human papillomavirus (HPV)–vaccinated populations and primary HPV screening. This situation will decrease the number of colposcopy procedures2 and make it increasingly difficult for colposcopists to gain and maintain clinical experience.

Colposcopists confident in their colposcopic abilities may only perform biopsies from visible lesions. In 2017/2018, no biopsies were performed for 42% of new colposcopy referrals in the United Kingdom.3 However, studies have shown that CIN grade 2 or worse (CIN2+) is often found in areas that colposcopists did not consider abnormal,4 and sensitivity could be increased by taking more biopsies.5,6 Therefore, Danish national guidelines recommend that 4 biopsies be taken from every woman undergoing colposcopy examination.7

The sensitivity of colposcopy might be improved when using dynamic spectral imaging (DSI), which measures the intensity of acetowhite changes that may occur after the application of acetic acid.8–16 The gain in diagnostic accuracy may be highest when this technology is used by colposcopists with less experience.17 In 2018, the National Institute for Health and Care Excellence and the National Institute for Health Research concluded that further research is needed to determine the potential gain from this adjunctive colposcopy technology.18,19 The gold standard is histological findings in conization specimens,20 but most previous studies have evaluated colposcopic impressions in comparison with histological biopsy results. This is a good method for evaluating the skills of individual colposcopists, but not for evaluating the performance of the colposcopy procedure itself.21 Furthermore, it is unclear whether the improvement in sensitivity when using DSI is a consequence of the system prompting the colposcopists to take more biopsies.

Denmark offers a unique opportunity to evaluate the sensitivity of colposcopy because 4 cervical biopsies are taken, and we have previously shown that 4 biopsies correspond to conization...
diagnosis in 95% of cases. The objectives of this study were to evaluate the sensitivity of DSI colposcopy compared with regular colposcopy in women referred with high-grade cervical cytology and to evaluate the number of cervical punch biopsies needed to maintain high diagnostic performance.

METHODS

In Denmark, women aged 23–65 years are invited to undergo a cervical smear at their general practitioner to screen for cervical cancer. All women can be screened, diagnosed, and treated free of charge. This study took place in the eastern part of the Central Region of Denmark. Women were referred for colposcopy if they had an abnormal cervical smear (atypical squamous cells of undetermined significance or greater). Independently of the study, the central visitation center randomly mailed out timeslots for colposcopies at a specialist gynecology department in a hospital based on the women’s main place of residence. Women could also choose, at no extra cost, to be referred for colposcopy at a private gynecology clinic. Study participants were prospectively included between January 2017 and September 2019 at Randers Regional Hospital, Horsens Regional Hospital, and a private gynecological clinic in Aarhus.

Women older than 18 years were eligible to participate if they were referred for colposcopy because of either a follow-up after initial diagnosis of CIN2 or were newly referred because of high-grade cytological changes defined as follows: atypical squamous cells, favoring high grade; high-grade squamous intraepithelial lesion; atypical glandular cells; adenocarcinoma in situ; adenocarcinoma; and squamous cell carcinoma. Women could not participate if they had cervical biopsies taken within the previous 6 months, were currently pregnant or had been pregnant within the last 3 months, had undergone conization previously, or had received pelvic radiation therapy. Eligible women were identified by the examining colposcopists in the outpatient clinics and were informed about the study. Participants were required to understand and speak Danish and to give verbal and written consent before participating. They filled out a short questionnaire regarding height, weight, smoking habits, previous pregnancies, contraception use, and HPV vaccination status.

Women included at Randers Regional Hospital were examined using a DSI (DySIS, V3) colposcope (study group). Women included at Horsens Regional Hospital and the private gynecological clinic, Aarhus, were examined using regular colposcopy (control group), a Leisegang colposcope, and an Olympus colposcope, respectively. All women had 4 biopsies taken, and most used the forced coughing method for pain relief.

Colposcopists using the DSI coloscope performed a regular colposcopy examination during the analysis time of the DSI technology. Before the DSI map was revealed, the colposcopists marked their first biopsy choice from the most abnormal-looking area on the cervix (i.e., the colposcopic-directed biopsy [CDB]). The second biopsy was marked based on the worst area of the DSI map. If these 2 areas were the same, the colposcopists recorded this. Two to 3 additional cervical biopsies were taken from other cervical quadrants, for a total of 4 biopsies per woman.

During regular colposcopies, acetic acid (3%) was applied and a standard procedure was performed. Colposcopists were instructed to take 4 cervical punch biopsies, as usual, but the first biopsy had to be from what they perceived to be the most abnormal-looking area of the cervix (i.e., CDB). Colposcopists were not asked to grade the additional biopsies in order.

Cervical biopsies were taken with 3-mm forceps (Baby Tischler), placed in formalin in individual containers all marked with corresponding numbers, and examined by pathologists separately. They were analyzed by gynecological pathologists who were blinded to the origin of the biopsy (i.e., CDB, DSI-directed biopsy, or additional biopsy). All biopsies from Randers Regional Hospital and Horsens Regional Hospital were examined by the same 2 pathologists at the Department of Pathology, Randers Regional Hospital, and they were not blinded to the hospital of origin. Biopsies from the private gynecology clinic were examined in the Department of Pathology, Aarhus University Hospital, and this corresponded to 8.4% of all women included (35/417).

The histological diagnosis for each biopsy was recorded separately and categorized into less than CIN2 or CIN2+. The histological end point was defined as the worst histological diagnosis based on all 4 biopsies. Thus, individual biopsies would directly influence the chosen gold standard for all 4 biopsies.

The clinical background of the colposcopist (i.e., trained colposcopy nurse, resident doctor, or consultant) was noted along with whether the squamous columnar junction was fully, partly, or not visible; the visible signs of dysplasia (i.e., acetowhite changes, mosaic vessel patterns, punctuations, atypical vessels, or none); and the colposcopists’ own colposcopic impressions (i.e., normal, low grade, or high grade). Only women with partially or fully visible squamous columnar junctions were included, and all 4 biopsies had to be suitable for pathological diagnosis. Only cervical lesions were assessed in the study; we did not obtain data on vaginal or endocervical lesions.

Statistical Methods

Based on prior studies, we expected that 70% of the women referred for a potential high-grade disease would be diagnosed with CIN2+ based on the CDB. As additional biopsies were taken, we predicted that detection would increase by 5%. For the DSI technology to be clinically relevant, we decided that it should be 20% more effective than regular colposcopy for detecting CIN2+ changes. With a power of 0.9 and an α level of 0.05, we determined that a sample size of 162 women was needed in each arm of the study.

Sensitivity was calculated based on the ability of different biopsies to correctly identify CIN2+ compared with the combined histological diagnosis of all 4 biopsies, assuming this to be the closest approximation of the true cervical dysplasia grade. In a previous study, we found 95% agreement between the 4 biopsies and conization diagnoses.

A χ² test was used to compare sensitivities between control and study groups. A p value of .05 or less was considered to be statistically significant. Stata 16.0 (Stata Corp LP, College Station, TX) was used for analysis. All 2 × 2 tables can be seen in the appendix (http://links.lww.com/LGT/A198).

Ethics

The Central Denmark Region Committees on Biomedical Research Ethics concluded that the project was exempt from approval, as it is a quality improvement study (r.nr. 1-10-72-262-16). The study was approved by the Danish Data Protection Agency (r.nr. 1-16-02-534-16).

Role of the Funding Source

No sponsors had any role in the study design, data collection, data analysis, data interpretation, or writing of the manuscript.

RESULTS

A total of 547 women were included in the study, 417 (76.2%) of whom fulfilled the study inclusion criteria. Of these, 261 women were examined using DSI colposcopy and 156 women were examined using regular colposcopy (see Figure 1).

The median age was 30 years (range = 19.2–71.5) in both groups (see Table 1). Most women used oral contraceptives, were
nulliparous, and were vaccinated against HPV. They were also more likely to be new referrals for colposcopy, especially in the control group. Compared with the control group, colposcopists in the DSI group reported more acetowhite reactions on the cervix based on colposcopy alone. See Table 1 for more detailed characteristics of the participants.

In both colposcopy groups, sensitivity increased with each additional biopsy. The CDB yielded diagnostic sensitivity of 64.6% (95% CI = 55.6–72.8) for CIN2+ detection in the regular colposcopy group compared with 73.5% (95% CI = 66.5–79.7) in the DSI colposcopy group (p = .06). When adding the DSI-directed biopsy to the CDB, the sensitivity increased to 82.2% (95% CI = 75.9–87.4). This was calculated based on 1 biopsy in 63.6% of the cases and 2 biopsies in 36.4% of cases, for a mean of 1.4 biopsies per woman (median = 1). When adding the DSI technology, the sensitivity to detect CIN2+ was increased by 27.2% compared with the CDB in the regular colposcopy group (64.6% versus 82.2%; p < .001) or 11.8% compared with the CDB in the DSI group (73.5% versus 82.2%; p = .02). When analyzing 2 biopsies in both groups, the sensitivity to detect CIN2+ between regular colposcopy increased by 12.4% (80.3% versus 72.3–86.8) compared with DSI colposcopy (90.3%; 95% CI = 85.1–94.1; p = .004). When adding the third biopsy, no difference between the 2 colposcopy groups was observed (see Table 2).

The results were further stratified by examiner. The sensitivity of the CDB alone was 75.4% (95% CI = 67.1–82.5) for trained colposcopy nurses. This was not significantly different from trained nurse colposcopists in the regular colposcopy group (68.0%; 95% CI = 45.5–85.1; p = .4). Resident doctors achieved a sensitivity of 77.4% (95% CI = 58.9–90.4) for the CDB in the DSI group, compared with 66.7% (95% CI = 47.2–82.7) in the control group (p = .3). For the CDB, consultants in the DSI group

FIGURE 1. Participant flow diagram. SCJ, squamous columnar junction.
TABLE 1. Baseline Demographic and Clinical Characteristics of Participants

|                  | Dy/SIS colposcopy | Regular colposcopy |
|------------------|-------------------|--------------------|
|                  | n = 261           | n = 156            |
| Age, median (range) | 30.3 (20.0–67.8) | 29.9 (19.2–71.5)  |
| BMI, median (range) | 23.3 (17.4–49.5) | 23.1 (17.6–44.1)  |
| Smoking           |                   |                    |
| No               | 126 (48.3%)       | 73 (46.8%)         |
| Current          | 67 (25.7%)        | 51 (32.7%)         |
| Previous         | 68 (26.0%)        | 31 (19.9%)         |
| Unknown          | 0                 | 1 (0.6%)           |
| Contraception use|                   |                    |
| Oral             | 103 (39.5%)       | 68 (43.6%)         |
| IUD              | 43 (16.5%)        | 22 (14.1%)         |
| Condom           | 13 (5.0%)         | 8 (5.1%)           |
| Other            | 4 (1.5%)          | 2 (1.3%)           |
| None             | 98 (37.5%)        | 56 (35.9%)         |
| Parity           |                   |                    |
| No previous pregnancies | 103 (39.5%) | 81 (51.9%) |
| Previous births  | 89 (34.1%)        | 44 (28.2%)         |
| Previous abortions (spontaneous and provoked) | 21 (8.0%) | 9 (5.8%) |
| Both             | 48 (18.4%)        | 22 (14.1%)         |
| HPV vaccination status |             |                    |
| Not vaccinated   | 97 (37.2%)        | 54 (34.6%)         |
| Vaccinated       | 155 (59.4%)       | 97 (62.2%)         |
| Ongoing          | 6 (2.3%)          | 3 (1.9%)           |
| Unknown          | 3 (1.1%)          | 2 (1.3%)           |
| New referral     | 191 (73.2%)       | 141 (90.4%)        |
| ASC-H            | 51 (26.7%)        | 47 (33.3%)         |
| AGC              | 4 (2.1%)          | 1 (0.7%)           |
| HSIL             | 136 (71.2%)       | 92 (65.3%)         |
| CIS              | 0                 | 1 (0.7%)           |
| Follow-up        | 70 (26.8%)        | 15 (9.6%)          |
| CIN2             | 53 (75.7%)        | 12 (80.0%)         |
| CIN3             | 3 (4.3%)          | 2 (13.3%)          |
| Ungradable CIN   | 14 (20.0%)        | 1 (6.7%)           |
| Colposcopist     |                   |                    |
| Trained colposcopy nurse | 172 (65.9%) | 35 (22.4%) |
| Resident         | 45 (17.2%)        | 35 (22.4%)         |
| Consultant       | 44 (16.9%)        | 86 (55.1%)         |
| Visible SCJ      |                   |                    |
| Yes, fully       | 199 (67.3%)       | 145 (92.9%)        |
| Yes, partially   | 62 (23.7%)        | 11 (7.1%)          |
| Visible cervical changes |         |                    |
| Acetowhite       | 233 (89.3%)       | 93 (56.6%)         |
| Atypical vessels | 31 (11.9%)        | 19 (12.2%)         |
| Punctuations     | 50 (19.2%)        | 36 (23.1%)         |
| Mosaic           | 59 (22.6%)        | 42 (26.9%)         |
| No visible changes | 14 (5.4%)      | 42 (26.9%)         |

AGC indicates atypical glandular cells; AIS, adenocarcinoma in situ; ASC-H, atypical squamous cells, favoring high grade; HSIL, high-grade squamous intra-epithelial lesion; IUD, Intrauterine device; SCJ, squamous columnar junction.

achieved a sensitivity of 58.3% (95% CI = 36.6–77.9) and those in the control group achieved 62.5% (95% CI = 50.3–73.6; p = .6). The sensitivity of the DSI-directed biopsy alone was 80.0% (95% CI = 72.1–86.5) for trained colposcopy nurses and 74.2% (95% CI = 55.4–88.1) for resident doctors (p = .4). However, this was not the case for consultants, for whom the sensitivity of the DSI-directed biopsy was found to be 50.0% (95% CI = 29.1–70.9). This value was significantly lower than that achieved by nurses (p < .001) and residents (p = .02). See Table 2 for the sensitivities of the different groups and biopsies.

Conization was performed in 133 women in the DSI group and 101 women in the control group. In the DSI group, 3.8% of women (n = 5) were found to have CIN1 or less in the cone when biopsy histology had been CIN2+, this was 2.0% of women (n = 2) in the CC group. In 96.2% (n = 128) women, the conization histology was equal to or worse than the histology found on the cervical biopsies in the DSI group, this was 98.0% (n = 99) in the control group. In Appendix 2, (http://links.lww.com/LGT/A199) the sensitivity reached when using the loop electrosurgical excision procedure diagnosis as the gold standard is presented. The sensitivities of colposcopy to detect CIN2+ when 4 biopsies were taken were 99.2% (95% CI = 95.6–99.9) in the DSI group and 100% (95% CI = 96.3–100.0) in the control group. This supports our assumption of using 4 biopsies as the criterion standard as a close approximation of the true gold standard (conization diagnosis).

DISCUSSION

Main Findings

In women referred with high-grade cervical cytology, using DSI as an adjunctive technology based on an average of 1.4 biopsies provided equal sensitivity for detection of CIN2+ compared with 2 biopsies taken with regular colposcopy (82.2% vs 80.3%). In both colposcopy groups, when 2 biopsies were taken, the sensitivity in the DSI colposcope group was 12.4% higher than that in the regular colposcopy group (p = .004). Furthermore, the sensitivity when 2 biopsies were taken in the DSI group was equal to that when 3 biopsies were taken in the regular colposcopy group. No difference was observed between the 2 groups when a third biopsy was taken. A proposed potential function of adjunctive colposcopy technologies is to reduce the number of biopsies that needs to be taken and thus lower the potential discomfort experienced by women without lowering the sensitivity of the examination. Although we found a statistically significant improvement in sensitivity when using the DSI colposcope, the improvement is based on small differences in biopsy numbers and the clinical significance of this may be small.

Strengths and Limitations

The lack of randomization between the groups should be taken into considerations when interpreting the results. There is no national accreditation program for colposcopists in Denmark, and therefore, it is possible that the results were due to differences in training between the colposcopists. In addition, most colposcopy examinations using the DSI colposcope were performed by trained colposcopy nurses, whereas in the regular colposcopy group, more examinations were performed by consultants. There was no difference in type of cervical disease examined by different colposcopists. A strength of the current study was that the pathologists did not know the origins of the 4 biopsies taken from each woman (i.e., CDB, DSI-directed, or additional). However, they were not blinded to the hospital of origin where the biopsies derived from and thus knew which colposcope had been used to examine the women. Verification bias was minimized by taking 4 biopsies, and thus knew which colposcope had been used to examine the women. Verification bias was minimized by taking 4 biopsies, and thus knew which colposcope had been used to examine the women.
yielded a false positive, as the final histological diagnosis was based on the worst of the 4 biopsies. The study design limits statistical comparison of sensitivities within the same group due to the high influence of 1 biopsy on the gold standard. However, this limitation does not exist for comparisons between the control and study group. Moreover, colposcopists were not blinded to the referral cytology, which may have influenced their colposcopy procedure; nevertheless, the current study reflects a real clinical setting. Interpretation of the DSI map was performed by the colposcopists. We also chose to include women referred for colposcopy based on a follow-up for a previous high-grade diagnosis. These cases represent a large proportion of the total number of colposcopies due to the conservative management of CIN2 in fertile women. Therefore, our numbers represent all colposcopies and not just new referrals. However, this did provide pathologists with previous dysplasia history on some women, which might have influenced their results. Additional biopsies were not graded in order, and we can therefore not conclude whether these biopsies were truly random or whether they were additional directed biopsies. A further limitation is that our data are based on high-grade referrals, and therefore, the results cannot be transferred to women referred with low-grade cytology.

**Interpretation**

Louwers et al. found that the performance of DSI colposcopy was superior to that of regular colposcopy, with a sensitivity increase from 60% for colposcopists alone to 70% for DSI alone and 79% for both combined in cases of high-grade cytological referrals. Similar increases in sensitivity for CIN2+ detection were observed in the current study, from 73.5% for colposcopists alone (in the study group) to 75.1% for DSI alone and 82.2% for both combined. However, it is not possible to directly compare these studies, as Louwers et al.13 analyzed the performance of the DSI colposcope based on comparison of colposcopic impressions to histological diagnosis of cervical punch biopsies. Furthermore, Louwers et al.14 did not take multiple biopsies from all participants; for some women, only 1 biopsy was taken. This makes it unclear whether the improvement is due solely to the use of the technology or to the increased number of biopsies. In the current study, colposcopists and the DSI map did not agree on the most visibly abnormal area of the cervix in 36.4% of women; in these women, the DSI map assisted in the guidance of a second biopsy.

When sensitivity for CIN2+ was stratified by the clinical setting, no statistical difference was found between the control and study group. This difference might be explained by Wentzensen et al.5 previously published a study in which the histological diagnosis of 4 biopsies was also assumed to represent the true grade of dysplasia. They showed that for regular colposcopy in women referred with high-grade cytology, the sensitivity to detect CIN2+ increased from 67.8% for 1 biopsy to 89% for 2 biopsies, to 98.4% for 3 biopsies, and to 100% for 4 biopsies.5 The results in the present study are similar, but slightly lower in the regular colposcopy group. This difference might be explained by the higher number of biopsies in the present study due to the prioritization of biopsies.

When sensitivity for CIN2+ was stratified by the clinical background of the colposcopists, the results were similar, with an increase in sensitivity demonstrated among both trained colposcopy nurses and resident doctors when CDB and DSI-directed biopsies were combined (as compared with 1 CDB taken using a regular colposcope). However, consultant doctors performed poorly when using the DSI colposcope. The most interesting results were seen when looking at the DSI-directed biopsy alone: a sensitivity of 80.0% was found for trained colposcopy nurses, whereas a sensitivity of 74.2% was found for resident doctors, with no statistical difference between these 2 groups (p = .4). For consultant doctors,
however, the sensitivity of the DSI-directed biopsy was 50.0%, which was significantly lower than that for the nurse group (p < .001) and the resident group (p = .02). Because the DSI colposcope should not perform differently for different colposcopists, user error may have occurred in the consultant group. Accordingly, all consultant examinations from the DSI database were checked for error, but no systematic errors were found. The trained colposcopy nurses who performed colposcopies at the outpatient clinic of Randers Regional hospital do so weekly. However, both the residents and consultants typically perform colposcopies less frequently because of schedule rotations. Thus, the results could indicate that the DSI colposcope has a learning curve and that regular use is important for gaining and maintaining experience. As most colposcopies assessed in this study were performed by trained nurses, comparative data concerning the colposcopies performed by residents and consultants were based on small numbers and therefore should be interpreted with caution.

In the past, clinical trials on colposcopy have lacked clearly defined standards, including requirements for biopsies. Based on the present results as well as those reported elsewhere, it is recommended that future studies intending to evaluate colposcopy should be based on several biopsies, as it has been clearly demonstrated that CIN2+ cases are missed if only 1 biopsy is taken. However, it is acknowledged that taking 4 biopsies is not possible in all settings for economic reasons and may have implications on pathology workload. It is also recommended that small biopsy forceps be used, as this has been reported to be less painful.

**Conclusions**

The current study suggests that a DSI colposcope may be able to provide additional assistance to colposcopists and help direct biopsy placement compared with a regular colposcopy. However, a high detection rate is needed for colposcopy, and multiple biopsies were still superior in both colposcopy groups. The impact of DSI colposcope and multiple biopsies on women with indications for colposcopy less than high-grade cytology remains to be determined.

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