

Diagnostic accuracy of colposcopy with dynamic spectral imaging for cytology-negative/high-risk HPV positive (failed test of cure) after large loop excision of the transformation zone (LLETZ) of the cervix

Results of the DySIS colposcopy 1 study

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Abstract

After treatment for cervical intraepithelial neoplasia (CIN), in the UK women who are cytology-negative, high-risk (HR) human papilloma virus (HPV) positive are referred to colposcopy. This pilot study assessed the incidence of residual/recurrent CIN and the diagnostic accuracy of colposcopy with dynamic spectral imaging (DSI) mapping in their detection.

This was a prospective service evaluation carried out in a UK National Health Service (NHS) colposcopy clinic. All women, referred with negative cytology/HR-HPV positive result following treatment for CIN from March 2013 until November 2014, who were examined with the DSI digital colposcope were included. We excluded 3 cases because of poor-quality imaging from user errors. Everyday clinical practice was followed. Initial colposcopic impression, DSI map indication, and biopsy site selections were recorded. CIN2+ was considered the primary outcome and CIN of any grade a secondary outcome.

A total of 105 women were included of which 5 (4.8%) had CIN2+ histology and 24 (22.9%) had CIN1. Pre-DSI map colposcopy suggested normal/low grade in all 5 of the CIN2+ cases and DSI suggested high-grade (HG) CIN in 4 of the 5 cases. Sensitivity of standard colposcopy for CIN2+ was 0%, improving to 80% with the incorporation of the DSI map.

The CIN burden in this population is higher than previously expected. Colposcopic identification of HG CIN appears to improve significantly with DSI in this cohort leading to refinement in patient management. A larger, multicentric prospective study (DySIS colposcopy 2) is planned to confirm these initial findings.

Abbreviations: CIN = cervical Intraepithelial neoplasia, DSI = dynamic spectral imaging, HG = high-grade, HR = high-risk, HPV = human papilloma virus, LLETZ = large loop excision of the transformation zone, LG = low-grade, NHS = national health service, NPV = negative predictive value, NHSCSP = NHS cervical screening programme, NGOC = northern gynecological oncology centre, PPV = positive predictive value, TOC = test of cure.

Keywords: cervical intraepithelial neoplasia, colposcopy, dynamic spectral imaging, test of cure, treatment

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1. Introduction

The UK national health service (NHS) Cervical Screening Programme recently implemented changes including the use of cotesting for high-risk human papilloma virus (HR-HPV) to triage women with negative cytology after treatment for cervical intraepithelial neoplasia (CIN) as a test of cure (TOC).^[1] The driving force for this change has been the results of the Sentinel Sites study, assessing the impact of HR-HPV triage in the cervical screening system. The results for the TOC population are to date unpublished; however, their economic analysis assisted by the use of predictive models, demonstrated improved effectiveness both in harvesting disease and cost.^[2] Women treated for CIN are now tested 6 months after treatment and if found HR-HPV positive, they are referred for colposcopy even with negative cytology. Those with a negative colposcopy/biopsy are then discharged to routine 3-yearly screening.

This population constitutes a newly introduced cohort and published data are limited, predominantly coming from a prospective study by Kitchener et al^[3] in which of the 75 women with a negative cytology/HR-HPV positive result, 5 (6.7%) were found to have CIN2+ lesions and 4 (5.3%) CIN1 during a 2-year period. Notably, neither this, nor the Sentinel Sites study were

designed to assess the performance of colposcopy in this cohort, but rather to investigate the disease incidence and management options.

Colposcopy is a subjective examination with great variability, and there is abundant evidence that it suffers from poor sensitivity and low inter/intraobserver agreement to identify high-grade (HG) disease.^[4,5] Albeit prospective studies have shown that incorporating the dynamic spectral imaging (DSI) map in colposcopy improves the sensitivity to detect CIN2+ lesions significantly^[6–8] and even more so for patients who are HPV16 positive,^[9] no evidence has been presented so far on its use for post-treatment women.

The aim of the results presented here is to provide an initial assessment on the diagnostic accuracy of colposcopy and its potential improvement with utilization of DSI mapping in detecting CIN2+ and CIN of all grades on post-treatment patients referred for colposcopy with a negative cytology and HR-HPV positive result. These results will be used for the design of a multicentre prospective clinical study.

2. Methods

The DySIS colposcopy 1 (DyS-CO1) study was a prospective service evaluation performed in the Northern Gynaecological Oncology Centre, Queen Elizabeth Hospital, Gateshead, UK between March 2013 and November 2014. It was registered with the Trust's audit department. The need for a study-specific patient consent was waived.

We included women referred with negative cytology and testing positive for HR-HPV either 6 months after treatment or in the context of the catch-up programme (i.e. had been treated for CIN in the past and were still on yearly follow-up with cytology when the new guidelines were introduced) and who underwent colposcopy with the DSI colposcope (DYSIS by DYSIS Medical, Edinburgh, UK). There was no further selection process and women were recruited consecutively.

The DSI digital colposcope allows the performance of standard/conventional colposcopy enhanced by additional digital imaging tools and offers the adjunctive use of the DSI map. Acetic acid is applied using an integrated applicator system standardizing quantity, coverage, and timing. The acetowhitening changes are quantified by the device software and the color-coded DSI map of the cervix is calculated; before reviewing the DSI map, the colposcopist performs a thorough examination (i.e. standard colposcopy) to form their colposcopic opinion and select biopsy sites, which is entered on the system and locked in the on-board database.

In the current data, before the DSI map was displayed, colposcopists selected biopsy sites (if any) according to their assessment. After the map was reviewed, additional biopsy sites could be selected at the colposcopist's discretion. The upper part of the acetowhitening mapping scale of DSI (red/yellow/white colors) was interpreted as suggestive of HG disease.

A detailed record of each examination was kept on the on-board database, including colposcopic assessment (entered by the colposcopist pre/post reviewing the DSI map), images captured throughout the acetowhitening process, the DSI map, and images indicating annotated biopsy sites. All cases were reviewed by the primary investigator (CF) to exclude those of poor-quality imaging because of user errors. After their colposcopic examination, all patients were managed according to national and departmental guidelines.

Additional to colposcopic findings and histology of biopsy samples, data collected included basic demographics (age,

smoking, parity, and contraception), cytology history, year of treatment, degree of histological abnormality, and marginal status on treatment specimen. For a small percentage of our population demographic information and/or details of previous loop were not available (e.g. when the treatment record could not be located, or when patients had the original treatment at a different hospital).

Histologically confirmed CIN2+ disease was the primary outcome measure, and CIN (any grade) a secondary outcome, as these are the threshold outcomes that according to current guidelines determine subsequent patient management.^[1]

Colposcopic identification of lesions as recorded before reviewing the DSI map was used as internal control and compared to the interpretation of the map, using histology as verification to calculate the corresponding sensitivity, specificity, positive and negative predictive values (PPV, NPV). The difference in sensitivity for detection of CIN before and after using the DSI map, at 2 different thresholds (any grade CIN and CIN2+), was assessed by calculating its 95% confidence interval (CI) and by using McNemar's test^[10] (significance level 0.05), accepting the limitation of small numbers of CIN2+ cases. Analyses were performed using NCSS 11 Statistical Software (2016, NCSS, Limited Liability Company, Kaysville, Utah, ncss.com/software/ncss).

For all women found with CIN lesions, treatment outcomes, and follow-up results were collected; this includes histology for those that received further treatment and follow-up outcomes (cytology and any subsequent colposcopy with biopsies) for the rest.

3. Results

After the exclusion of 3 patients from analysis because of user errors at the time of colposcopy, a total of 105 women were included; patient demographics are presented in Table 1.

Details regarding previous excisional treatment were analysed and are presented in Table 2. CIN2 was considered the threshold of marginal involvement. For 22 (21%) women the referral cytology was at 6 months after their treatment, whereas the remainder belonged to the catch-up population. The median period since their treatment was 4 years.

Table 1
Baseline characteristics of the study population.

Characteristic	N = 105
Age (years)	
Mean (range)	37.3 (25–72)
Median	34.0
Smoking status	
Yes	40 (38%)
No	60 (57%)
Unknown	5 (5%)
Parity (number of births)	
Mean (range)	1.41 (0–5)
Median	1.00
Unknown	5 (5%)
Contraceptive method*	
None	38 (38%)
Combined oral contraceptive pill	18 (18%)
Progestogens	27 (27%)
Other	11 (11%)
Unknown	6 (6%)

Data is N, unless otherwise specified.

* Five postmenopausal women are not included (5% of total population).

Table 2
Detailed information on the patient's previous LLETZ, regarding excisional treatment margins, time, and histology.

Characteristic	N=105
Treatment margins	
Clear	59 (56.3%)
Only ecto involved	14 (13.3%)
Endo and/or deep lateral involved	16 (15.2%)
Unknown	16 (15.2%)
Years since LLETZ	
Mean (range)	5.1 (0–27)
Median	4.00
LLETZ histology	
No CIN	2 (1.9%)
CIN1	8 (7.6%)
CIN2	33 (31.4%)
CIN3	58 (55.3%)
Unknown/inadequate	4 (3.8%)

Data refers to number and proportion of patients, unless otherwise specified.
CIN=cervical intraepithelial neoplasia, LLETZ=large loop excision of the transformation zone.

In total, 74% of the patients were biopsied. The remaining were considered negative in our analyses, acknowledging the underlying verification bias.

A total of 29 (27.6%) patients were found to have (histologically confirmed) CIN; of these, 24 (22.8%) had CIN1 and 5 (4.8%) had CIN2+ (Table 3).

Among the 5 CIN2+ cases, one would not have been biopsied at all without the DSI map (colposcopy was considered normal and no biopsy was indicated before reviewing the map); in 3 cases the DSI map indicated HG but the colposcopist suspected a low-grade (LG) lesion and in 1 case the DSI map did not suggest abnormal acetowhitening but was colposcopically considered as LG and biopsied. Overall, the DSI map predicted HG disease in 4 of the 5 (80%) CIN2+ cases and colposcopy was LG in 4 and normal in 1 (Table 3).

Among the 24 CIN1 cases, the colposcopic impression was normal for 4 (16.6% of them), LG for 18 (75%), and HG for 2 (8.4%) and the DSI map was considered normal in 3 (12.5%), LG in 9 (37.5%), and HG in 12 (50%). However, if we look at the combined prediction (i.e. at least 1 of the 2, colposcopic prediction and/or DSI map were abnormal thus leading to a decision for biopsy) results show that in all women with CIN1 in histology and normal colposcopy the DSI map was abnormal and

Table 3
Number of patients predicted as normal, low grade, or high grade, stratified by biopsy outcome. Results are presented separately for standard colposcopy and colposcopy including the DSI map to allow comparisons.

	Histology result				
	No biopsy	Unsatisfactory	No CIN	CIN1	CIN2+
Standard colposcopy prediction					
Normal	13	6	31	4	1
Low grade	6	0	16	18	4
High grade	1	1	2	2	0
Standard colposcopy and DSI map prediction					
Normal	6	3	11	0	0
Low grade	10	2	21	11	1
High grade	4	2	17	13	4

Data is number of patients.
CIN=cervical intraepithelial neoplasia, DSI=dynamic spectral imaging.

Table 4
Clinical performance of standard colposcopy and colposcopy with DSI in predicting high-grade neoplasia. Results and 95% confidence intervals are presented for high-grade CIN (CIN2+) and also for any grade of CIN.

Measure	Standard colposcopy	Standard colposcopy and DSI map
Prediction of CIN2+		
Sensitivity (95% CI)	0% (0–52%)	80% (28–99%)
Specificity (95% CI)	94% (86–97%)	64% (54–73%)
NPV (95% CI)	95% (88–98%)	98% (91–100%)
PPV (95% CI)	0% (0–48%)	10% (3–25%)
Prediction of any-grade CIN		
Sensitivity (95% CI)	83% (64–94%)	100% (88–100%)
Specificity (95% CI)	66% (54–76%)	26% (17–38%)
NPV (95% CI)	91% (80–97%)	100% (80–100%)
PPV (95% CI)	48% (34–63%)	34% (24–45%)

CI=confidence interval, CIN=cervical intraepithelial neoplasia, DSI=dynamic spectral imaging, NPV=negative predictive value, PPV=positive predictive value.

vice versa. The 2 acted complementary, and so all CIN1 cases were predicted as abnormal. Of note, for the cases with normal colposcopy, biopsy/ies were performed from the areas indicated as abnormal by the DSI map.

The sensitivity, specificity, PPV, and NPV of standard colposcopy alone and combined with the DSI map, for any grade CIN and for CIN2+, are presented in Table 4. For CIN2+ the sensitivity increased from 0% (95% CI: 0–52.18%) to 80% (95% CI: 28.36–99.49%), with the 95% CI of this 80% difference being 24.9–100% ($P=.0455$ McNemar test). For any grade of CIN, the sensitivity increased from 82.8% (95% CI: 64.23–94.15%) to 100% (95% CI: 88.05–100%), and the 95% CI of this 17.2% difference is 0.05–34.44% ($P=.0253$ McNemar test). The 95% CI of the differences do not include 0, and the P values are $<.05$, suggesting that the increase in sensitivity with the addition of the DSI map is statistically significant at both disease thresholds. The increased sensitivity is accompanied by a decrease in specificity as expected.

Based on UK national guidelines, patients with CIN1 should have cytology sampling repeated in 12 months in the community. Of the 24 patients in our cohort who had CIN1 in their biopsy, 10 have had their follow-up by cytology at time of data analysis. Of these, 2 were LG/HR-HPV positive and 1 of them had CIN2 in a directed biopsy.

Regarding follow-up of patients with CIN2+ biopsy results, out of the 5 women, 1 has had a large loop excision of the transformation zone (LLETZ) showing CIN2, 3 have had LLETZ showing CIN1, and 1 is on conservative management and has so far been seen in clinic once at which point colposcopy was negative and a cytology sample collected was also negative.

4. Discussion

Women who fail their TOC (negative cytology, HR-HPV positive) after treatment for CIN are a new colposcopy population and there is concern among colposcopists that an inability to assess them adequately increases their risk to develop an invasive lesion in the following 3 years. These are the first data incorporating colposcopy with DSI into the management algorithm of this cohort. Consistent with previous results for mixed colposcopy referral groups,^[6,7,8] we found an improved sensitivity to identify women with HG CIN compared with

standard colposcopy, which is of significant clinical importance as, under current guidelines in England,^[1] missing HG CIN destines these women to no surveillance for 3 years.

Although in 4 of the 5 cases found with HG CIN, standard colposcopy did suggest LG CIN and therefore these women might have undergone a biopsy thereby possibly detecting the HG CIN, one can comment on 2 points. First, the poor diagnostic ability of standard colposcopy is emphasized and for this population in particular, however, its role in deciding whether to perform a biopsy and selecting the most appropriate site, suggests that improvements should be sought. Second, in contrast to the general population where colposcopic suspicion for LG CIN does not warrant a biopsy,^[1] this is a specific cohort, where tissue sampling of suspected LG CIN may be essential.

Our data also demonstrate a higher than expected detection rate of LG CIN, with 22.9% of cases found to have CIN1 lesions. This is significantly higher than seen by Kitchener et al^[3] where CIN1 was found in 5.3% of cases, and compared to the Sentinel Sites study unpublished data where CIN1 was found in 2.3% of the population.^[11] Accepting that LG CIN is generally of low risk for progressing to invasive cancer, it is worth noting that women in this cohort are HR-HPV positive and have previously developed a HG lesion as a result of persistent infection, which constitutes the primary pathophysiology behind their well-documented future high risk (HR).^[12–14] Failure to detect those that already have or may subsequently develop HG CIN and subject them to no surveillance for 3 years raises some concern and requires further investigation.

A major strength of this study is that patients were their own controls, as standard colposcopy findings were recorded prior to assessment with the DSI map. This minimizes selection bias and other confounding factors. In addition, it is reinforced by the fact that the DSI map assessment is objective and formed by an integrated software system unaffected by patient/clinician factors.

Although the sample size can be considered a limitation, it should be noted that the single previous publication on TOC cases included only 75 women who were cytology negative/HR-HPV positive,^[3] and the Sentinel Sites study (results unpublished) included 259 cases.^[11] Consequently, this is the largest publication of TOC cases and additionally provides data on the improvement of colposcopy with DSI for this specific population. That said, DyS-CO1 should be considered a pilot as a prelude to DyS-CO2, which will examine TOC cases with the use of DSI in a larger cohort of women, in a prospective multicentre setting. The results of DyS-CO1 will also allow power calculations in the development of the DyS-CO2 study.

The primary objective of this work was to determine the diagnostic ability of colposcopy with DSI in this population. Although we have identified sensitivity and NPV for standard colposcopy, and colposcopy with the DSI map as an adjunct, we are unable to determine the true sensitivity or NPV as this would require the full histological assessment (i.e. excisional biopsy/treatment) of all cases. Alternatively, random biopsies could have been obtained from the cases showing no abnormality on either standard colposcopy or the DSI map, and random biopsies in addition to directed biopsies in those cases showing an abnormality in an attempt to reduce or eliminate verification bias.^[15,16] This was not performed as it is not current standard practice, and whereas this was also the case with the previous publication by Kitchener et al,^[3] it is intended for additional/random biopsies to be obtained following normal or abnormal colposcopy within the design of the DyS-CO2 study. These data

are, therefore, at risk of over estimating the sensitivity and NPV of colposcopy with DSI, however, 74% of the women did undergo histological assessment with directed biopsies, which is a higher proportion than in Kitchener et al.^[3]

Data on the performance of colposcopy specifically on the regenerated post-treatment cervical epithelium are limited. Soutter et al^[17] published a retrospective study in 2006 showing that colposcopy improves the accuracy of cytology alone in detecting HG lesions. However, this was a population with abnormal cytology of any grade and it was impossible to verify any disease missed. A retrospective study from Australia looked at the role of colposcopy at 12 months after treatment; the authors concluded that colposcopy post-treatment lacks sensitivity and adds no value to cytology and HR-HPV testing alone.^[18]

It is unclear whether colposcopy can adequately assess these cases as the healing process can result in buds of epithelial cells to lie within the stroma underneath the overlying regenerated epithelium.^[19] In addition, colposcopy cannot offer information on the deeper aspects of the cervical canal, which is of concern especially in cases of previous incomplete excision at the endocervical margin. Accepting that colposcopy with DSI is likely to have the same limitations, there are currently no studies evaluating this new technology for this population.

These data, although still requiring further evaluation, do suggest a potential role for DSI colposcopy in improving the sensitivity for detecting HG CIN in this HR group of women. This may be at the cost of reduced specificity; however, it is essential that the NPV remains high minimizing the risk of missing cases of HG CIN. In addition, accepting that standard colposcopy is subjective with wide variations in inter and intraobserver agreement,^[4,5] colposcopy with DSI establishes a degree of objectivity and a baseline standard to the assessment.

Finally, the authors appreciate the inevitable speculation that the increased sensitivity in CIN detection is an outcome that could also be related to increased biopsying and not exclusively to the use of DSI mapping. This is extremely difficult to assess; mostly because of the variation in practice, with biopsy rates ranging from 26% to 96% in England,^[20] but also, as there is no well-reported data for this specific population. In this regard, the most important outcome would be to look at actual number of biopsies as opposed to percentage of patients biopsied and number of DSI versus colposcopically directed biopsies taken, which will be part of the design in the DyS-CO2 study.

5. Conclusions

Our data show that the number of women with CIN among those that fail their TOC after treatment for CIN with negative cytology may be higher than previously suggested. Accepting the limitations, we found that the sensitivity and NPV of colposcopy in identifying those with CIN2+ among them increased with the incorporation of the DSI map, leading to improved patient management decisions. Further investigation in the form of the DyS-CO2 study is required to fully evaluate the role of colposcopy with DSI for negative-cytology/failed TOC patients.

References

- [1] Tidy J. NHSCSP Publication number 20: NHS Cervical Screening Programme. Colposcopy and Programme Management, 3rd Edition, 2016; Public Health England; Available from: https://www.bsccp.org.uk/assets/file/uploads/resources/NHS_Cervical_Screening_Programme_-_Publication_Number_20_-_Third_Edition.pdf. Accessed June 13, 2017.

- [2] Legood R, Smith M, Lew JB, et al. Cost effectiveness of human papillomavirus test of cure after treatment for cervical intraepithelial neoplasia in England: economic analysis from NHS Sentinel Sites Study. *BMJ* 2012;345:e7086.
- [3] Kitchener HC, Walker PG, Nelson L, et al. HPV testing as an adjunct to cytology in the follow up of women treated for cervical intraepithelial neoplasia. *BJOG* 2008;115:1001-7.
- [4] Massad LS, Jeronimo J, Katki HA, et al. The accuracy of colposcopic grading for detection of high-grade cervical intraepithelial neoplasia. *J Low Genit Tract Dis* 2009;13:137-44.
- [5] Hopman EH, Voorhorst FJ, Kenemans P, et al. Observer agreement on interpreting colposcopic images of CIN. *Gynecol Oncol* 1995;58:206-9.
- [6] Soutter WP, Diakomanolis E, Lyons D, et al. Dynamic spectral imaging: improving colposcopy. *Clin Cancer Res* 2009;15:1814-20.
- [7] Louwers J, Zaal A, Kocken M, et al. Dynamic spectral imaging colposcopy: higher sensitivity for detection of premalignant cervical lesions. *BJOG* 2011;118:309-18.
- [8] Coronado PJ, Fasero M. Colposcopy combined with dynamic spectral imaging. A prospective clinical study. *Eur J Obstet Gynecol Reprod Biol* 2016;196:11-6.
- [9] Zaal A, Louwers JA, Berkhof J, et al. Agreement between colposcopic impression and histological diagnosis among human papillomavirus type 16-positive women: a clinical trial using dynamic spectral imaging colposcopy. *BJOG* 2012;119:537-44.
- [10] Trajman A, Luiz RR. McNemar χ^2 test revisited: comparing sensitivity and specificity of diagnostic examinations. *Scand J Clin Lab Invest* 2008;68:77-80.
- [11] Moss S, Kelly R, Legood R et al. Evaluation of Sentinel Sites for HPV triage and Test Of Cure. 2011; Available from: <http://webarchive.nationalarchives.gov.uk/20150506150512/http://www.cancerscreening.nhs.uk/cervical/sentinelfinalreport.pdf>. Accessed June 6, 2017.
- [12] Soutter WP, Sasieni P, Panoskaltis T. Long-term risk of invasive cervical cancer after treatment of squamous cervical intraepithelial neoplasia. *Int J Cancer* 2006;118:2048-55.
- [13] Kyrgiou M, Tsoumpou I, Vrekoussis T, et al. The up-to-date evidence on colposcopy practice and treatment of cervical intraepithelial neoplasia: The cochrane colposcopy & cervical cytopathology collaborative group (C5 group) approach. *Cancer Treat Rev* 2006;32:516-23.
- [14] Kreimer AR, Schiffman M, Herrero R, et al. Long-term risk of recurrent cervical human papillomavirus infection and precancer and cancer following excisional treatment. *Int J Cancer* 2012;131:211-8.
- [15] Huh WK, Sideri M, Stoler M, et al. Relevance of random biopsy at the transformation zone when colposcopy is negative. *Obstet Gynecol* 2014;124:670-8.
- [16] Wentzensen N, Walker JL, Gold MA, et al. Multiple biopsies and detection of cervical cancer precursors at colposcopy. *J Clin Oncol* 2015;33:83-9.
- [17] Soutter WP, Butler JS, Tipples M. The role of colposcopy in the follow up of women treated for cervical intraepithelial neoplasia. *BJOG* 2006;113:511-4.
- [18] Thompson V, Marin R. Is colposcopy necessary at twelve months after large loop excision of the transformation zone? A clinical audit. *Aust N Z J Obstet Gynaecol* 2013;53:571-3.
- [19] Paraskevaidis E, Bilirakis E, Koliopoulos G, et al. Cervical regeneration after diathermy excision of cervical intraepithelial neoplasia as assessed by transvaginal sonography. *Eur J Obstet Gynecol Reprod Biol* 2002;102:88-91.
- [20] Kelly RS, Patnick J, Kitchener HC, et al. HPV testing as a triage for borderline or mild dyskaryosis on cervical cytology: results from the Sentinel Sites study. *Br J Cancer* 2011;105:983-8.