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Dynamic spectral imaging colposcopy: higher sensitivity for detection of premalignant cervical lesions

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Objective To validate the dynamic spectral imaging (DSI) colposcope's colour-coded map in discriminating high- from low-grade cervical lesions and non-neoplastic tissue.

Design Prospective, comparative, multicentre clinical trial.

Setting The colposcopy clinics of three Dutch hospitals.

Population Women of 18 years or over with an intact cervix, referred for colposcopy.

Methods During a 3-minute image acquisition phase, the DSI colposcope was used as a regular video colposcope: the colposcopist located and graded potential lesions based on conventional colposcopic criteria. Subsequently, a colour-coded map was calculated and displayed, representing localisation and severity of the cervical lesion. Biopsies were collected from all atypical sites, as identified by digital mapping and/or conventional colposcopy. Furthermore, one additional biopsy was taken.

Main outcome measures Histologically confirmed high-grade cervical disease (CIN2+).

Results In total 275 women were included in the study: 183 women were analysed in the 'according-to-protocol' (ATP) cohort and 239 women in the 'intention-to-treat' (ITT) cohort. In the ATP cohort, the sensitivity of DSI colposcopy to identify women with high-grade (CIN2+) lesions was 79% (95% CI 70–88) and the sensitivity of conventional colposcopy was 55% (95% CI 44–65) ($P = 0.0006$, asymptotic McNemar test). When the DSI colour-coded map was combined with conventional colposcopy, the sensitivity was 88% (95% CI 82–95).

Conclusions DSI colposcopy has a significantly higher sensitivity to detect cervical lesions than conventional colposcopy. If the colour-coded map is combined with conventional colposcopic examination, the sensitivity increases further.

Keywords Cervical Intraepithelial neoplasia, colposcopy, sensitivity, specificity, spectrometry.

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Introduction

Colposcopy is a visual technique used to identify cervical lesions after the application of acetic acid. It requires extensive training and experience; however, recent studies have suggested that higher level of experience in colposcopy do not increase sensitivity of conventional colposcopy.[1,2] The variation in the reported performance for colposcopy is high, with the average sensitivity of colposcopy to distinguish low- from high-grade lesions and cancer being around 55%.[1,3–6] Furthermore, the low to average sensitivity and specificity of colposcopic examination is also associated with a high degree of inter- and intra-observer variability.[7–9]

Histology is the gold standard to grade cervical lesions detected by colposcopy, therefore punch biopsies or direct loop excision ('see and treat') are required for definite diagnosis. This sampling of the cervix is often stressful and painful for the woman and does not provide an immediate test result. Besides, the accuracy of the 'gold standard' itself is hindered by the variability in histological diagnosis among pathologists and the obvious sampling errors through the inaccuracy of colposcopy and tissue sampling.[10–12] Therefore, to be able to establish a 'base-line' sensitivity for the colposcopic assessment by minimising inter- and intra-observer variability would constitute a major improvement in colposcopic practice and the cervical cancer diagnostic chain in general.

Previous studies with the dynamic spectral imaging (DSI) colposcope (DySIS™, Dynamic Spectral Imaging System; Forth Photonics, Livingston, UK) have shown promising results.[13–16] Quantifying rather than qualifying optical features after application of acetic acid may increase the objectivity of colposcopy and, therefore, improve detection of high-grade lesions. Hence, we designed our study to validate the capacity of the DSI colposcope alone or in combination with conventional colposcopy to discriminate high- from low-grade cervical lesions and non-neoplastic tissue and to improve the colposcopic performance through digital documentation and analysis of sequences of colposcopic images. In addition, we compared these images with the visual interpretation of the colposcopist and histology results.

Methods

Enrollment

This study was designed as a prospective multicentre comparative clinical trial, with the participation of the colposcopy clinics of three Dutch hospitals; the VU University Medical Centre in Amsterdam, the Reinier de Graaf Hospital in Voorburg and the Sint Antonius Hospital in Nieuwegein. All relevant ethics boards approved the protocol, and the study was registered in the Dutch trial registry (ISRCTN66112760).

Consecutively, women of 18 years or over who were referred to these clinics for colposcopy were invited to participate in the study. Inclusion criteria were abnormal cervical cytology (i.e. at least borderline nuclear abnormalities) or follow-up of a cervical intraepithelial neoplasia (CIN) grade 1 or 2 lesion. Signed informed consent was obtained from all women before any study procedures. Exclusion criteria were previous surgery on the cervix, pelvic radiotherapy, current pregnancy and pregnancy in the last 3 months.

The DSI colposcope

The DSI colposcope (Figure 1) is a digital imaging instrument used to visualise the cervix during a colposcopic examination, allowing different colour-filtering and magnification options. The basic technical characteristics of the DSI colposcope (DySIS™ v2.1, Forth Photonics Ltd, Livingston, UK) used in this study are: digital video camera resolution 1024 × 768 pixels; white bright LED illumination; field of view (approximately) 25 × 35 mm; 10× to 27× magnification; polarised glare-free images; green and blue digital filter. Additionally, there is the option to measure and map the dynamics (i.e. rise-time, intensity and persistence) of the acetowhitening effect, for every point of the cervix. Modelling of the measured dynamic curves by the DSI colposcope provides a per point analysis of the acetowhitening effect.

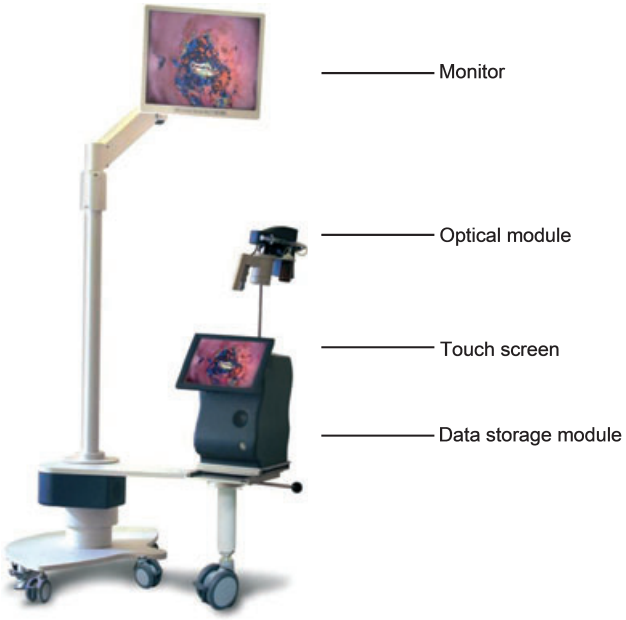

Figure 1. Dynamic spectral imaging colposcope (DySIS™, Dynamic Spectral Imaging System; Forth Photonics, Livingston, UK).

Once acetic acid has been applied, the DSI colposcope starts automatically with the measurement of the acetowhitening effect. Although the DSI acquisition period lasts approximately 3 minutes, the acetowhitening effect can last several minutes more,[13,17,18] which is the reason why no second DSI assessment can be performed immediately after the first. At the end of the examination, the DSI information is concisely presented in the form of a colour-coded map, which can be overlaid onto the colour image of the tissue (Figure 2), to assist the identification of the location and severity of cervical lesions. The DSI colposcope and the measurement principles and procedures have been described in detail previously.[14,16,18.]

Study procedures

Before participating in this study, colposcopists and supervising colposcopists had to attend an instruction meeting.

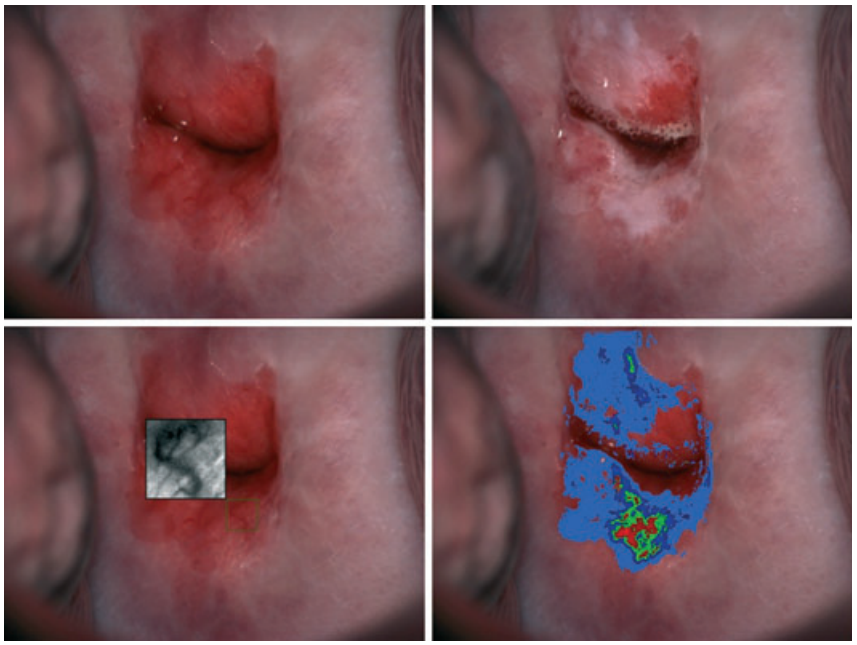

Figure 2. Examination with the dynamic spectral imaging colposcope. Top left, cervix without acetic acid; top right, cervix after the application of acetic acid; bottom left, green filter to enhance vessel viewing; bottom right, colour-coded map with red indicating the most severe acetowhite area.

Colposcopists had to perform at least 20 colposcopies with the DSI colposcope, supervising colposcopists at least five.

Before colposcopy, a cervical sample for high-risk human papillomavirus (hrHPV) and hrHPV viral load testing was collected and stored in Universal Collection Medium® (UCM) (Qiagen Corp., Gaithersburg, MD, USA). The sampling was carried out with special attention to avoid excessive bleeding that would impair the colposcopic examination. Subsequently, colposcopy was performed or supervised by expert colposcopists, according to national colposcopy guidelines,[19] using the DSI colposcope as a regular video colposcope during the 3-minute data acquisition phase. After completion of the data acquisition, the colposcopic impression was digitally recorded by the colposcopist, with annotation of the most atypical location and predicted severity of the lesion. Up to this point, the colposcopist was blinded to the DSI analysis of the images, and if desired, the colposcopist was able to continue the colposcopic inspection by (re)applying acetic acid and/or iodine.

The collected images were digitally analysed by the DSI colposcope, and the resulting quantitative colour-coded map of the acetowhitening effect was subsequently revealed and overlaid on the image of the cervix, but not before the entry of the colposcopist's final predictions. Based on comparison with pre-determined threshold values,[16] the DSI colour-coded map provided a prediction for the presence and grade of neoplasia, and indication of the most atypical site for biopsy sampling accordingly. The colour-coded map was compared with the colposcopist's own impression and punch biopsies were taken from all identified suspicious sites. These included those indicated by the colposcopist and the DSI colposcope as well as one additional control biopsy of apparently normal cervical tissue on the opposite side of the lesion(s). If both colposcopist and DSI colposcope evaluated the cervix as normal, one biopsy was taken from the transformation zone at the 12 o'clock position, to ensure that no lesions were missed and to reduce ascertainment bias. In 27 of the women no punch biopsies were collected, but a loop electrosurgical excision procedure was performed immediately ('see and treat' procedure). The colposcopic examination data were saved for further evaluation and the biopsy sampling procedure was recorded on video and later reviewed to obtain objective evidence on whether the tissue sample was collected from the annotated area. Taking punch biopsies from a rather small lesion can easily lead to a biopsy sampling error, something that may also happen during conventional colposcopic examinations. In both situations, this may lead to under detection of high-grade cervical disease. In this study we corrected for this by taking an additional biopsy from every woman and ensuring that at least one biopsy sample was collected from women who were not suspected for high-grade disease.

Finally, all women were given two questionnaires: one to evaluate demographics and risk factors and another to evaluate patient satisfaction.[20,21] Subsequent treatment and follow up of the women was performed at the discretion of the attending physician according to national guidelines.[19]

Clinical specimen handling

High-risk HPV and viral load were tested in the cervical sample using the GP5+/6+ polymerase chain reaction (PCR) enzyme immunoassay test and real-time PCR respectively according to protocols routinely running in the VU University Medical Centre laboratory and as previously described.[22,23]

All histology was independently reviewed by a pathologist specialising in gynaecological pathology (FK). In case of disagreement between original assessment and review (defined as no neoplasia/low-grade lesion [CIN0–1] versus high-grade lesion [CIN2–3, adenocarcinoma *in situ* or carcinoma]), a third expert reviewer (CM) graded the lesion (19.0% of all tissue samples), blinded to all previous results, and final diagnosis was determined by the majority decision.

Statistical analysis

Before the start of the study, a power analysis was performed based on the presumption that conventional colposcopy has a sensitivity of 70% and DSI colposcopy a sensitivity of 80%. Therefore, 200 women would be needed for this study to detect this difference (80% power, 5% alpha).

All clinical data collected were analysed using 2×2 tables, chi-square tests, asymptotic McNemar tests[24] and 95% CI (SPSS software package version 15.0; SPSS, Chicago, IL, USA). For all statistical tests a two-tailed *P*-value ≤0.05 was considered significant. For data analysis two cohorts were formed: the according-to-protocol (ATP) cohort and the intention-to-treat (ITT) cohort. The data in the ITT cohort, even though protocol criteria (e.g. not all DSI indications for high-grade lesions were sampled or the device was used even though there was a hardware problem) were not adhere to in all women, was analysed to approximate the performance of DSI colposcopy under clinical conditions (*clinical performance*). The ATP cohort is a subset of the ITT cohort where the protocol was strictly adhered to for all women and reflects the device performance (*proof of principle*).

Results

Between 1 July 2008 and 1 September 2009, 275 consecutive women were recruited from the three hospitals. Of these 275 women, 36 (13.1%) were excluded. The main reasons for exclusion were unsaved examination data (n = 9, 25.0%) and no colour-coded map available (n = 9, 25.0%). This resulted in an ITT cohort of 239 women. A detailed flow-chart describing the study profile is presented in Figure 3. Management of 56 (20.4%) women did not strictly adhere to the protocol and could therefore only be analysed in the ITT cohort, resulting in an ATP cohort (subset of the ITT cohort) of 183 women.

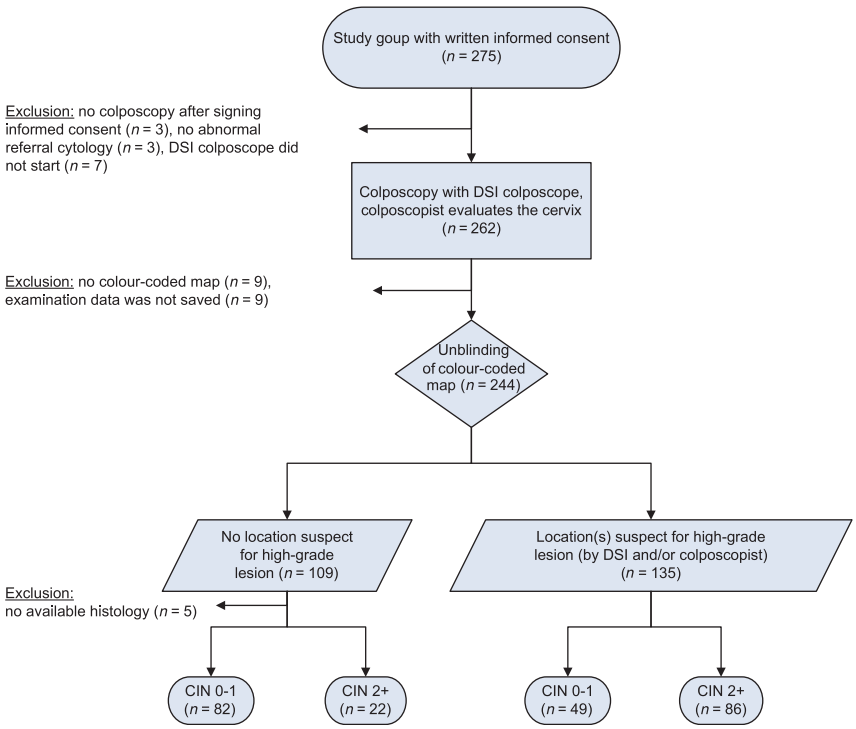

Figure 3. Study profile (intention-to-treat cohort).

Main reasons for exclusion from the ATP cohort were inability to visualise 75% or more of the transformation zone during the DSI image collection (n = 19, 33.9%) and no available histology from a high-grade location indicated by the colour-coded map (n = 14, 25.0%) (Table 1). The baseline characteristics of the study population, partly derived from the demographics and risk factors questionnaire, can be seen from Table 2. No significant differences were observed between the ATP and ITT cohorts.

In the ATP cohort a total of 332 punch biopsies, 18 endocervical curettages and 84 treatment specimens (mainly loop electrosurgical excision procedure) were obtained. In total, 153 control biopsies were taken from apparently normal tissue of which 39 (25.5%) were classified as high-grade disease. Altogether, 86 women (47.0%) had a high-grade lesion, including three women with cervical adenocarcinoma. The adenocarcinomas were correctly identified by both DSI and the colposcopist as high-grade disease.

The performance of DSI colposcopy, conventional colposcopy or a combination of the two in identifying high-grade CIN lesions was assessed on a per-patient basis (Table 3). Sensitivity, specificity, positive and negative predictive values with 95%CI were calculated and are represented in Table 4. In the ATP cohort the DSI colposcope identified correctly 68 of the 86 women with histologically confirmed high-grade disease, whereas conventional colposcopy was able to identify 47 women with high-grade disease, resulting in sensitivities of 79% (95% CI 70–88) and 55% (95% CI 44–65), respectively. This difference is statistically significant (P = 0.0006, asymptotic McNemar test). When used in combination, DSI and conventional colposcopy detected 76 of the 86 examples of high-grade disease, resulting in an overall sensitivity of 88% (95% CI 82–95). The specificity of DSI colposcopy was 77% (95% CI 69–86) and of conventional colposcopy 85% (95% CI 77–92) (P = 0.144, asymptotic McNemar test). DSI combined with conventional colposcopy had a specificity of 69% (95% CI 60–78).

In the ITT cohort, of the 108 women with histologically confirmed high-grade disease the DSI colposcope identified 70 correctly, whereas conventional colposcopy detected 56.

Table 1. Reasons for complete exclusion or exclusion from according-to-protocol cohort (these women were still included in the intention-to-treat cohort)

Reason	*n* (%)
Complete exclusion	
Examination data were not saved	9 (25.0)
No colour-coded map	9 (25.0)
DSI colposcope did not start	7 (19.4)
No available histology	5 (13.9)
No abnormal referral cytology	3 (8.3)
No (DSI) colposcopy after signing informed consent	3 (8.3)
Total	36 (100)
Exclusion from according-to-protocol cohort	
Transformation zone not (completely) visible with DSI	19 (33.9)
No biopsy from DSI colposcope high-grade location	14 (25.0)
Image quality unsatisfactory	7 (12.5)
Hardware failure	6 (10.7)
Too much blood	3 (5.4)
DSI colposcope started too late*	2 (3.6)
Miscellaneous	5 (8.9)
Total	56 (100)

*That is, the measurement of the acetowhitening effect did not start automatically after the application of acetic acid.

Table 2. Baseline characteristics

	ATP cohort (n = 183) (%)	ITT cohort (n = 239) (%)
Centre*		
Centre A	96 (52.5)	127 (53.1)
Centre B	54 (29.5)	74 (31.0)
Centre C	33 (18.0)	38 (15.9)
Age (years)		
Mean (range)	36.6 (18.7–62.6)	36.7 (18.7–62.6)
Median	35.4	35.3
Indication for colposcopy		
Abnormal cytology	166 (90.7)	219 (91.6)
Follow-up CIN1–2	17 (9.3)	20 (8.4)
Result of last smear**		
Normal	4 (2.2)	5 (2.1)
BMD cytology	118 (64.5)	153 (64.0)
>BMD cytology	61 (33.3)	81 (33.9)
hrHPV test		
Negative	54 (29.5)	73 (30.5)
Positive	123 (67.2)	158 (66.1)
Test not performed	6 (3.3)	8 (3.3)
Current smoker	69 (37.7)	87 (36.4)
Mean age at first sexual contact, years (range)	16.9 (9–30)	17.0 (9–30)
Mean number of sexual partners in last year (range)	1.3 (0–5)	1.2 (0–5)
Condom use		
Always	10 (5.5)	13 (5.4)
Sometimes	35 (19.1)	46 (19.2)
Never	122 (66.7)	154 (64.4)
Missing /not applicable	16 (8.7)	26 (10.9)
Mean number of pregnancies (range)	1.3 (0–5)	1.3 (0–9)

*Centre A, VU University Medical Centre, Amsterdam; Centre B, Reinier de Graaf Hospital, Voorburg; Centre C, Sint Antonius Hospital, Nieuwegein, the Netherlands.
**Follow-up CIN1–2, BMD, borderline or mild dyskaryosis; >BMD cytology, worse than borderline or mild dyskaryosis.

Table 3. Cross-tabulation of the results

	ATP cohort			ITT cohort		
	CIN0–1	CIN2+	Total	CIN0–1	CIN2+	Total
DSI colposcope						
Prediction N/LG	75	18	93	92	38	130
Prediction HG	22	68	90	39	70	109
Total	97	86	183	131	108	239
Colposcopist						
Prediction N/LG	82	39	121	107	52	159
Prediction HG	15	47	62	24	56	80
Total	97	86	183	131	108	239
DSI and conventional colposcopy combined						
Prediction N/LG	67	10	77	82	22	104
Prediction HG	30	76	106	49	86	135
Total	97	86	183	131	108	239

HG, high-grade; N/LG, normal/ low-grade.
Rows: Prediction according to DSI or conventional colposcopy or a combination of the two. Columns: Histology result (after revision: 'golden' standard).

This resulted in sensitivities of 65% (95% CI 56–74) for DSI colposcopy and 52% (95% CI 42–61) for conventional colposcopy, also a statistically significant difference ($P = 0.039$, asymptotic McNemar test). When the two techniques were combined, 86 incidences of high-grade disease were correctly identified, resulting in a sensitivity of 80% (95% CI 72–87). The specificity of DSI colposcopy in this cohort was significantly lower than that of conventional colposcopy: 70% (95% CI 62–78) versus 82% (95% CI 75–88) ($P = 0.011$, asymptotic McNemar test). The combination of DSI with conventional colposcopy led to a specificity of 63% (95% CI 54–71) in this cohort.

The high-grade disease missed by DSI or conventional colposcopy was compared with the detected high-grade disease (Table 5). In the ATP cohort, 11/18 (61.1%) of the women with high-grade disease missed by DSI colposcopy were hrHPV positive, compared with 59/68 (86.8%) of the women whose disease was correctly identified ($P = 0.016$, chi-square test). Furthermore, only 1 of the 18 women (5.6%) whose high-grade disease was missed by DSI was hrHPV type 16 positive, whereas 31/68 (45.6%) women with the correctly identified disease were hrHPV 16 positive ($P = 0.003$, chi-square test), suggesting a trend that the lesions missed by DSI colposcopy are less clinically relevant. For conventional colposcopy, there were no differences between the missed and detected disease in overall hrHPV or hrHPV-16-positive status.

Finally, the patient satisfaction questionnaire was completed by 178 (97.3%) women in the ATP cohort. The main result was that DSI colposcopy was no extra burden for the majority of the participating women, compared with conventional colposcopy. No adverse events were reported during the study period.

Discussion

In the ATP cohort, DSI colposcopy has a significantly better sensitivity to detect high-grade lesions than conventional colposcopy (79% versus 55%, $P = 0.0006$), without any statistically significant differences in the specificity, confirming the *proof of principle* of DSI colposcopy. If the DSI colposcope is used in combination with conventional colposcopic examination, the sensitivity increases to almost 90%.

A substantial number of women could only be analysed in the ITT cohort, which reflects the *clinical performance*. In this cohort the sensitivity of DSI colposcopy was also significantly higher than of conventional colposcopy (65% versus 52%, $P = 0.039$). Combining DSI with conventional colposcopy resulted in a sensitivity of 80% (95% CI 72–87) in this cohort. So, even when the DSI colposcope cannot be used completely or adequately, but is used in combination with conventional colposcopy, the clinical sensitivity

Table 4. Sensitivity, specificity, positive and negative predictive values

	n	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
According-to-protocol cohort					
DSI colposcope	183	79 (70–88)	77 (69–86)	76 (67–84)	81 (73–89)
Colposcopist	183	55 (44–65)	85 (77–92)	76 (65–86)	68 (59–76)
DSI and colposcopist combined	183	88 (82–95)	69 (60–78)	72 (63–80)	87 (80–95)
Intention-to-treat cohort					
DSI colposcope	239	65 (56–74)	70 (62–78)	64 (55–73)	71 (63–79)
Colposcopist	239	52 (42–61)	82 (75–88)	70 (60–80)	67 (60–75)
DSI and colposcopist combined	239	80 (72–87)	63 (54–71)	64 (56–72)	79 (71–87)

NPV, negative predictive value; PPV, positive predictive value.

Table 5. Characteristics of missed versus detected high-grade disease

	Missed by DSI, *n* (%)	Detected by DSI, *n* (%)	Missed by colposcopist, *n* (%)	Detected by colposcopist, *n* (%)
According-to-protocol cohort				
Total	18 (100)	68 (100)	39 (100)	47 (100)
Mean age, years (range)	38.8 (22.7–55.7)	36.3 (18.7–57.9)	38.4 (20.9–57.9)	35.5 (18.7–52.2)
*Centre**				
A	7 (38.9)	35 (51.5)	21 (53.8)	21 (44.7)
B	8 (44.4)	20 (29.4)	9 (23.1)	19 (40.4)
C	3 (16.7)	13 (19.1)	9 (23.1)	7 (14.9)
Indication for colposcopy				
Abnormal smear	17 (94.4)	66 (97.1)	38 (97.4)	45 (95.7)
Follow-up CIN1–2	1 (5.6)	2 (2.9)	1 (2.6)	2 (4.3)
*Result of last smear***				
Normal	0 (0)	0 (0)	0 (0)	0 (0)
BMD cytology	8 (44.4)	34 (50.0)	23 (59.0)	19 (40.4)
>BMD cytology	10 (55.6)	34 (50.0)	16 (41.0)	28 (59.6)
hrHPV positive	11 (61.1)	59 (86.8)	30 (76.9)	40 (85.1)
hrHPV 16 positive	1 (5.6)	31 (45.6)	15 (38.5)	17 (36.2)
Current smokers	7 (38.9)	21 (30.9)	16 (41.0)	12 (25.5)
Mean age at sexual debut (range)	16.8 (13–22)	16.8 (9–30)	16.2 (14–21)	17.3 (9–30)
Mean number of pregnancies (range)	0.88 (0–3)	1.4 (0–5)	1.2 (0–3)	1.4 (0–5)
Intention-to-treat cohort				
Total	38 (100)	70 (100)	52 (100)	56 (100)
Mean age, years(range)	37.4 (22.1–55.7)	36.3 (18.7–57.9)	38.1 (20.9–57.9)	35.4 (18.7–52.2)
*Centre**				
A	17 (44.7)	37 (52.9)	28 (53.8)	26 (46.4)
B	15 (39.5)	20 (28.6)	13 (25.0)	22 (39.3)
C	6 (15.8)	13 (18.6)	11 (21.2)	8 (14.3)
Indication colposcopy				
Abnormal smear	35 (92.1)	67 (95.7)	48 (92.3)	54 (96.4)
Follow-up CIN1-2	3 (7.9)	3 (4.3)	4 (7.7)	2 (3.6)
*Result of last smear***				
Normal	1 (2.6)	0 (0)	1 (1.9)	0 (0)
BMD cytology	16 (42.1)	36 (51.4)	29 (55.8)	23 (41.1)
>BMD cytology	21 (55.3)	34 (48.6)	22 (42.3)	33 (59.9)
hrHPV positive	27 (71.1)	61 (87.1)	40 (76.9)	48 (85.7)
hrHPV 16 positive	9 (23.7)	33 (47.1)	20 (38.5)	22 (39.3)
Current smokers	13 (34.2)	22 (31.4)	19 (36.5)	16 (28.6)
Mean age at sexual debut (range)	17.0 (13–22)	16.8 (9–30)	16.4 (14–21)	17.3 (9–30)
Mean number of pregnancies (range)	1.1 (0–5)	1.4 (0–5)	1.3 (0–5)	1.3 (0–5)

*Centre A, VU University Medical Centre, Amsterdam; Centre B, Reinier de Graaf Hospital, Voorburg; Centre C, Sint Antonius Hospital, Nieuwegein, the Netherlands.
**Follow-up CIN1–2, BMD, borderline or mild dyskaryosis; >BMD cytology, worse than borderline or mild dyskaryosis.

can be increased significantly (from 52% to at least 80%) in comparison with conventional colposcopy alone, highlighting the clinical value of the DSI colposcope. Naturally, this increase in sensitivity means a loss of specificity (from 82% to 63%, $P = 0.011$). Also, the prevalence of high-grade disease was quite high in our population (47%). In a population with a lower prevalence of cervical disease, it is likely that the sensitivity will be lower, arguing for a good selection of colposcopy clinic referrals.

Even though for the initial power analysis we assumed a sensitivity of 70% by conventional colposcopy to detect high-grade cervical lesions, our study yielded a sensitivity of only 55%, which is in accordance with other studies on colposcopic efficacy and was probably the result of the measures taken to reduce ascertainment bias.[1,3–6] The addition of DSI to conventional colposcopy therefore results in an almost 50% increase in sensitivity; from 55% to 79% by DSI colposcopy alone if all preconditions for a optimal

examination are met, and to 80% in combination with conventional colposcopy regardless of the circumstances or individual user adequacy. Hence, the higher sensitivity of DSI colposcopy alone or in combination with conventional colposcopy improves the detection of high-grade cervical lesions significantly and guides cervical sampling. This is emphasised further by the fact that the high-grade lesions that were missed by DSI were more often hrHPV-16-negative (and therefore less clinically relevant) than the high-grade lesions that DSI colposcopy identified successfully. The reason for this is that it seems that hrHPV 16 infections result in more intense acetowhite lesions,[25] which are more easily detected by DSI colposcopy. With the implementation of HPV vaccination programmes in many developed countries, the prevalence of hrHPV 16 is expected to decrease. However, it is unclear if there are other hrHPV types with similar acetowhitening features, because the prevalence of non-type 16 hrHPV types is quite low. We think that there will probably still be a role for DSI colposcopy in vaccinated populations.

Limitations

A possible restraint of the study was that the DSI colposcope was used for the conventional colposcopic examination as well. Those colposcopists who were not accustomed to using video colposcopes needed some time to become familiar with this method of colposcopy (i.e. observing the cervix on a screen rather than directly through eye-pieces). However, we think that the training before the study was sufficient to have this unfamiliarity resolved. Furthermore, the performance of the colposcopists in this study is similar to that typically reported for colposcopy,[1,3–6] indicating that the performance of conventional colposcopy using the DSI colposcope is not hindered by the device itself.

The main drawback of the DSI colposcope is the inherent difficulty in exploiting its full potential in certain situations; for example, during the examination it is recommended that the speculum is attached to the device, which stabilises the field of view and corrects immediately for small movements of the cervix. Although a necessity for a correct DSI examination, this sometimes hindered the complete view of the transformation zone, especially in women with a retroverted uterus; one of the main reasons for exclusion from ATP analysis. However, in clinical practice, after the data acquisition, the speculum can be released from the device and the colposcopist can review those areas which could not be analysed during the DSI examination, as would be done with any other colposcope. Therefore it is not a problem during a routine colposcopic examination outside the study protocol.

Furthermore, no second DSI examination can be performed directly after the first because of the acetowhitening effect which can last up to 45 minutes and can interfere with a DSI measurement.[13,17,18] This is not always practical in the day-to-day clinic routine. Sometimes it would have been convenient to repeat the examination, for instance when during the first examination only part of the transformation zone could be visualised. Furthermore, there are a number of circumstantial conditions that need to be met before a correct examination with the DSI colposcope can be performed. As DSI measures the backscattered light of the cervix, no other light (like the overhead lamps that are often used while inserting the speculum) should shine directly onto the cervix during the examination. Besides, no mucus or blood should be present on the cervix, because this interferes with the measurement and limits the visualisation of the lesion (as it does also in conventional practice). This may pose a particular challenge when a cervical scrape is taken before the colposcopy. Sometimes it can also be difficult to interpret whether the colour-coded map indicates a high-grade lesion. The colour-coded map that is displayed over the image of the cervix uses red, yellow and white pixels to indicate predicted high-grade lesions, and the red pixels of small lesions can be difficult to visualise on the reddish background of the cervix.

Another limitation of the study is that no follow-up data were available, so the true prevalence of cervical disease might have been underestimated. We have tried to correct for this ascertainment bias by always sampling one additional biopsy.

Conclusion

In both the ATP and ITT analyses DSI colposcopy has a higher sensitivity in the detection of high-grade cervical lesions than conventional colposcopy. The main drawbacks are its limited usefulness in some situations: e.g. when only part of the cervix can be visualised at one time or when there is an excess of blood or mucus on the cervix. Therefore it has been shown to be most effective in combination with a trained colposcopist, attaining a sensitivity of up to 88% in the ATP cohort and 80% in the ITT cohort. In this setting, the limitations of the DSI colposcope can be overcome: when DSI colposcopy fails or conditions are suboptimal, the colposcopist uses the DSI colposcope as a regular video colposcope. This signifies that in suboptimal conditions the DSI colposcope can be a valuable asset to the colposcopic examination.

Disclosure of interest

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that (1) none of the authors have received support from Forth Photonics Ltd, Livingston, UK for the submitted work;

(2) CB is a stockholder and EP an employee of Forth Photonics Ltd. UK at the time of this study; (3) their spouses, partners, or children have no financial relationships that may be relevant to the submitted work; and (4) none of the authors have non-financial interests that may be relevant to the submitted work. JL and MK received support from Forth Photonics Ltd, Livingston, UK to travel to study meetings in Athens. Furthermore, JL received a travel grant from Forth Photonics Ltd, Livingston, UK to visit a conference on colposcopy.

Contribution to authorship

RV was the project leader and designed the study with JL, MK, BH, CB, EP, PS and CM. JL, AZ and MK drafted the manuscript. JL, AZ, MK, BH, GG and JS were responsible for the colposcopies and collection of the data. PS supervised the hrHPV testing. FK and CM were responsible for revising the histology samples. All authors critically reviewed the manuscript.

Details of ethics approval

The ethics boards of the three participating clinics approved the protocol (number 2007/098). Signed informed consent was obtained from all women before any study procedures. The study was registered in the Dutch trial registry (ISRCTN66112760).

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