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The performance of Dynamic Spectral Imaging colposcopy depends on indication for referrals

J.A. Louwers [a,*], A. Zaal [b], M. Kocken [c], J. Berkhof [d], E. Papagiannakis [e], P.J.F. Snijders [c], C.J.L.M. Meijer [c], R.H.M. Verheijen [b]

[a] Department of Obstetrics and Gynaecology, VU University Medical Center, Amsterdam, The Netherlands
[b] Division of Women and Baby, Gynaecological Oncology, University Medical Center Utrecht, Utrecht, The Netherlands
[c] Department of Pathology, VU University Medical Center, Amsterdam, The Netherlands
[d] Department of Epidemiology and Biostatistics, VU University Medical Center, Amsterdam, The Netherlands
[e] DySIS Medical Ltd, Alba Campus, Livingston, United Kingdom

HIGHLIGHTS

- DSI increases the sensitivity of colposcopy, irrespective of most referral reasons.
- If DSI and conventional colposcopy are combined, the sensitivity increases the most.
- DSI colposcopy may enable a baseline sensitivity of the colposcopic exam.

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ABSTRACT

Objective. A previous study has shown that Dynamic Spectral Imaging (DSI) colposcopy increases the sensitivity of the colposcopic examination in women referred with abnormal cytology. In this study we have re-analyzed the performance of DSI and conventional colposcopy for new referral conditions and for low-grade cytology referrals versus high-grade cytology referrals.

Method. Data from a previous validation trial was used to assess the performance of DSI in different cytology groups: Women referred with BMD (borderline and mild dyskaryosis) cytology and women referred with >BMD cytology either hrHPV positive or negative were separately analyzed. Furthermore, we tried to assess the clinical performance by appropriate filtering of patients to replicate two different referral strategies.

Results. The sensitivity of DSI and conventional colposcopy to detect CIN2+ lesions in women referred with BMD cytology is 82% and 44% respectively ($p = 0.001$) and in the >BMD group 77% and 64% respectively ($p = 0.24$). If the two techniques are combined the sensitivity is 85%. When the conditions of new screening strategies are applied DSI colposcopy has a higher sensitivity to detect CIN2+ than conventional colposcopy. Findings are similar when CIN3+ is used as a threshold.

Conclusion. We found that in most cases DSI colposcopy has a higher sensitivity than conventional colposcopy, even when referral criteria are changed. Unlike conventional colposcopy, the sensitivity of colposcopy with DSI in low-grade cytology referrals was found similar to the sensitivity in high-grade cytology referrals. This suggests that a baseline colposcopy sensitivity may be possible with the adjunctive use of the DSI map, irrespective of referral cytology.

1. Introduction

Colposcopy is a visual technique, used to examine the uterine cervix for (pre)malignant disease and direct the collection of biopsy samples. Conventional colposcopy has several limitations; firstly, the prediction of disease is related to the skill and experience of the colposcopist [1]. Inter-observer agreement is only moderate, with levels of agreement increasing as cervical lesions become more severe [1]. Furthermore, the choice of biopsy site is subjective and is hampered by the suboptimal correlation between visual changes and disease severity [2,3]. These restrictions result in a modest sensitivity of approximately 55% to distinguish high-grade from low-grade lesions [4–8].

Colposcopy with Dynamic Spectral Imaging (DSI, DySIS digital colposcope, DySIS Medical Ltd, Livingston, UK), has a higher sensitivity to

* Corresponding author at: VU University Medical Center, Department of Obstetrics and Gynaecology, Room 8 F 022, P.O. Box 7057, 1007 MB Amsterdam, The Netherlands.
E-mail address: ja.louwers@vumc.nl (J.A. Louwers).

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detect high-grade premalignant cervical disease (Cervical Intraepithelial Neoplasia grade 2/3 or worse; CIN2 +) than conventional colposcopy [9,10]. Soutter et al. demonstrated that on a population referred for colposcopy with abnormal cytology or symptoms, the DSI map had a significantly higher sensitivity than conventional colposcopy to identify patients with CIN2 + lesions [10]. In our validation trial we have shown that when DSI is used adjunctively with conventional colposcopy, the sensitivity of the examination to detect patients with CIN2 + lesions is almost 90% [9]. However, this trial included women referred for colposcopy according to the Dutch national guidelines in 2008. HrHPV-testing was not incorporated in the referral strategy which included both women with borderline or mild dyskaryosis (BMD), and women with worse than borderline and mild dyskaryosis (>BMD) cytology. BMD corresponds to ASC-US/ASC-H/LSIL and >BMD equals HSIL [11]. However, it is known that the sensitivity of the colposcopic exam is highly dependent of referral cytology. If the referral cytology is more severe, the sensitivity of the colposcopic exam to detect high-grade lesions is higher [4].

Furthermore, since 2008 screening and referral guidelines have changed, both in the Netherlands and internationally as a result of the clinical efficacy and potential cost savings expected by introducing hrHPV testing [12–16]. In the Netherlands we are changing our screening program to hrHPV-testing as the primary screening test. In this strategy (which is not fully implemented yet), cytology is only used to triage women that have been tested positive for hrHPV [17]. Current screening strategies use hrHPV-testing as a reflex test to BMD cytology (e.g. UK [18] and Sweden [16]), or ASC-US cytology (e.g. USA [19] and the Netherlands), whereas all >BMD cytology is directly referred to colposcopy.

The purpose of this study was twofold: Firstly we re-analyzed the performance of DSI and conventional colposcopy to determine the difference between low-grade cytology (BMD) referrals and high-grade cytology (>BMD) referrals. Secondly we also re-analyzed the performance of DSI and conventional colposcopy for two new referral strategies; hrHPV-testing as primary screening test and reflex hrHPV-testing in BMD cytology.

2. Methods

This study was designed as a sub-study of the DSI validation trial, a prospective multicenter comparative clinical trial that took place in three Dutch colposcopy clinics in 2008 and 2009 [9,20]. All consecutive women aged 18 years or over and referred for colposcopy were asked to participate in the trial. Indications for colposcopy were abnormal cervical cytology (i.e. at least borderline nuclear abnormalities, BMD) or follow-up of an untreated CIN1 or CIN2 lesion.

The DSI digital colposcope allows the visualization of the cervix under magnification and also the mapping of the acetowhitening based on measuring its intensity and duration. In our trial, it was first used as a regular digital video colposcope and the colposcopist located and graded potential lesions based on conventional colposcopic criteria [21]. Acetic acid (3%) was applied via an integrated applicator that triggered the acquisition of a series of images by the integrated computer. The intensity and duration of acetowhitening was measured from analyzing these images. Then, the DSI color-coded map was calculated and displayed, representing localization and severity of the suspected cervical lesion according to the assessment of cervical acetowhitening by the DSI algorithm. Biopsies were collected from all abnormal sites, identified by the colposcopist and/or the DSI color-coded map. Furthermore, from all women, one 'control' biopsy was taken from the transformation zone and from an area on the cervix considered negative for CIN by the colposcopist to ensure no lesion was missed and to reduce ascertainment bias. Before the colposcopic exam, a cervical sample was taken from all women for hrHPV-testing and typing. The institutional review boards of the three participating clinics had approved the protocol and the study was registered in the Dutch trial registry (ISRCTN66112760). Signed informed consent was obtained from all subjects before undergoing any study procedures.

In the DSI validation trial [9], two groups of women were formed during the data analysis: the according-to-protocol (ATP) and the intention-to-treat (ITT) cohort. The ITT cohort includes all recruited women, i.e. also those for whom not all protocol criteria were met (e.g. not all locations indicated as high-grade lesions by the DSI color-coded map were sampled or the DSI colposcope was used even when there was a hardware or software problem). The ATP cohort is a subset of the ITT cohort, and includes all women for whom the study protocol was strictly followed. The ATP cohort reflects the device performance (*proof of principle*), while the ITT cohort reflects the performance of DSI under clinical conditions (*clinical performance*) in the setting of the trial.

From the original database, data was abstracted to measure the performance of DSI and conventional colposcopy in low-grade cytology (BMD) referrals and high-grade cytology (>BMD) referrals. Women with >BMD cytology and hrHPV positive have a high risk for high-grade cervical disease. Less clear is the risk for women with >BMD cytology, but hrHPV negative. Therefore we also analyzed the performance of DSI colposcopy in women with >BMD cytology, but negative for hrHPV separately.

Furthermore, we assessed the clinical performance by appropriate filtering of patients to replicate two different referral strategies. These two strategies were chosen because they represent the currently most used screening strategies or advised screening strategies. [22]

- Firstly the strategy with hrHPV-testing as primary screening test and cytology as triage. For this strategy women were selected if they had a positive hrHPV test and BMD or >BMD cytology (reflects current screening guidelines where only women with a positive hrHPV test and a subsequent abnormal cytology result are referred to colposcopy).
- Secondly the strategy with hrHPV-testing as triage test. Women were selected if they had BMD cytology and a hrHPV positive test or >BMD cytology, irrespective of the hrHPV test result (reflects current screening guidelines where women with BMD cytology and negative hrHPV test are not referred to colposcopy).

All clinical data were analyzed using SPSS (software package version 20.0, Chicago, IL, USA). For all statistical tests a two-tailed p-value of ≤0.05 was considered significant. To calculate the sensitivity, specificity, negative and positive predictive values 2 × 2 tables and exact McNemar tests were used.

3. Results

In total, 183 women were included in the ATP cohort and 239 women in the ITT cohort [9]. In the ATP cohort 17 women (9.3%) were excluded from the cytology referral group analysis since they were referred for colposcopy because of follow-up of a CIN1 or CIN2 lesion. In the ITT cohort 20 women (8.4%) were excluded because of this reason. For all the 166 included women in the ATP cohort and 219 included women in the ITT cohort referral cytology results, histology and colposcopic data were available. For all but 4 women hrHPV-test results were available. Patient characteristics can be seen from Table 1. In the ATP cohort, 107 women (64.5%) were referred because of BMD cytology and 59 women (35.5%) because of >BMD cytology. In the ITT 140 women (63.9%) and 79 women (36.1%) women were referred because of BMD and >BMD cytology respectively. On average, we collected 2.0 punch biopsies per patient. In total 18 patients (10.8%) in the ATP cohort and 23 patients (10.5%) in the ITT cohort had treatment without prior punch biopsy.