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Are colposcopy and electrical impedance spectroscopy complementary when used to detect high-grade cervical neoplasia?

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Summary

Purpose of investigation: To evaluate if colposcopy and electrical impedance spectroscopy (EIS) are complementary and hence increase the detection of high-grade cervical intraepithelial neoplasia (HG-CIN). *Materials and Methods:* A cohort of 1,237 women with an abnormal cervical cytology result referred to a single colposcopy service to assess the value of EIS as an adjunct to colposcopy for the detection of HG-CIN. *Results:* Fifty-three (12.8%) extra cases of HG-CIN were detected by a combination of colposcopy and EIS (466 *vs.* 413). Ten cases were referred with high-grade cytology and 43 were associated with low-grade cytology. The increased detection of HG-CIN in women referred with low-grade cytology was 50% (129 *vs.* 86). The combination of colposcopy and EIS produced a highly significant improvement in the detection of HG-CIN. *Conclusions:* Comparison of the performance metrics with a previous multi-centre trial shows that use of EIS as an adjunct increases performance over that obtained from colposcopy alone. The largest improvement is in increased sensitivity and NPV when used to detect HG-CIN, particularly in women referred with low-grade cytology.

Key words: Cervical smear; Colposcopy; Cervical intraepithelial neoplasia; Electrical impedance spectroscopy; Treatment; Loop electrosurgical excision procedure.

Introduction

The performance of colposcopy is prone to considerable variation and is influenced by the prevalence of the disease in the population being examined. It may also be affected by the quality of training, reproducibility of the technique, and biopsy rates [1-4]. The sensitivity of colposcopy to detect high-grade cervical intraepithelial neoplasia (HG-CIN) may be as low as 52-55% and so several studies have proposed the use of random biopsies and endocervical curettage to increase the sensitivity of colposcopy [5-8]. Cervical biopsies however are associated with significant morbidity and financial costs to healthcare [9].

The use of high-risk human papillomavirus (hrHPV) testing either as a co-test, a triage test, or as a primary screen has been widely advocated and introduced into many cervical screening programmes [10-13]. These approaches may increase the referral of women to colposcopy but can be associated with low prevalence of disease in some referral categories [4, 14, 15]. Furthermore the performance of colposcopy may be impacted by hrHPV genotype with HPV16 associated high-grade lesions being more amenable to colposcopic detection [16, 17]. The benefit of non-visual tests in the detection of CIN has been suggested to overcome both the impact of hrHPV genotyping on colposcopic performance, but also results in an increase in referrals due to the use of hrHPV testing either as a triage tool or as a primary test [14].

Electrical impedance spectroscopy (EIS) can be used as a non-visual technique to image epithelia. EIS measures the reduction in impedance to the flow of the current as the epithelium becomes more dysregulated (normal through to CIN3 and cancer) [18]. The EIS device used by Tidy *et al.* measures EIS across a range of current frequencies and compares the acquired EIS data with finite element models corresponding to normal (squamous and glandular) cervical epithelium through to CIN3 to create a probability match for the underlying tissue type [19-23]. Real time EIS results used in conjunction with colposcopic impression, guide the colposcopist to, appropriate sites for biopsy, treatment of the patient, or confirmation of a normal colposcopic examination.

The objective of this evaluation was to see if colposcopy and EIS are complementary and hence give enhanced clinical performance when used together. The current performance of colposcopy with EIS used as an adjunct, in a cohort of 1,237 women, are compared with the performance of colposcopy and EIS alone as reported by van der Marel *et al.* and Tidy *et al*. [16, 23].

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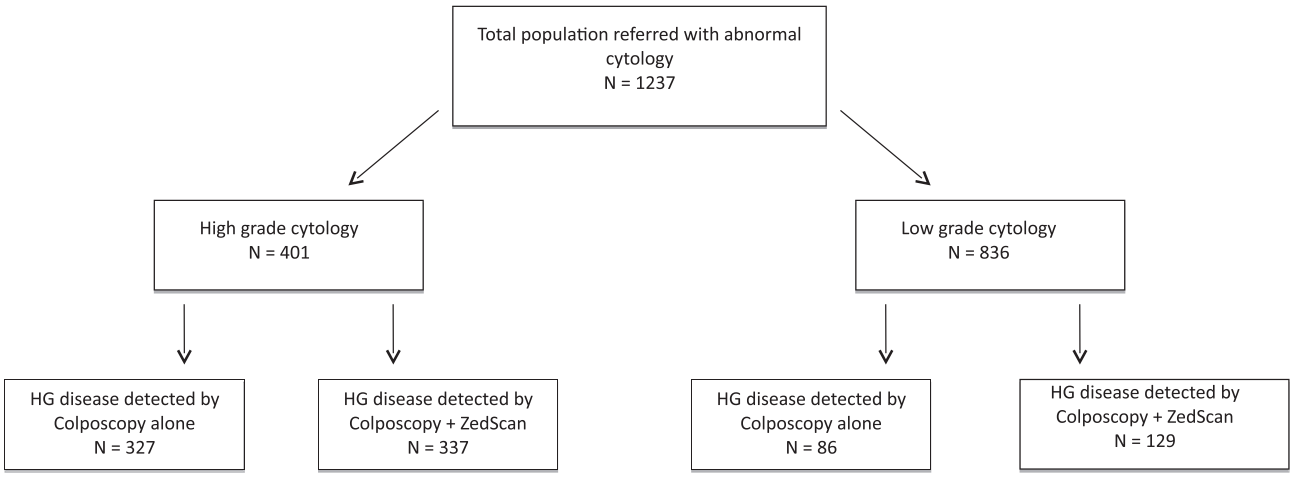

Figure 1. — Flow chart for women entering the evaluation by cytology and outcome by detection of high grade disease (CIN2+ and HG-CGIN).

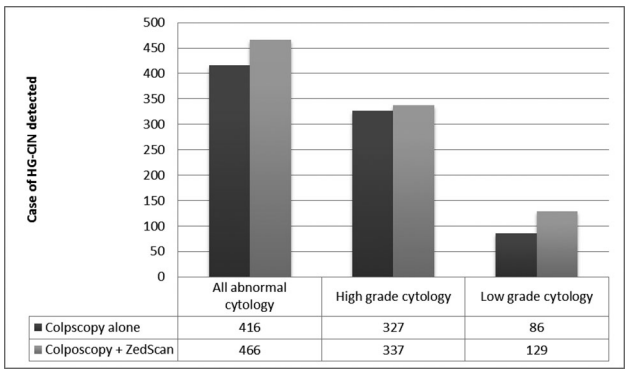

Figure 2. — Cases of HG-CIN detected by colposcopy alone and colposcopy + ZedScan I.

Materials and Methods

A cohort of women referred to the colposcopy clinic with abnormal cervical cytology from the English National Cervical Screening Programme underwent colposcopy and ZedScan *I* examination. Cytology reporting was as per the English National Cervical Screening Programme. Colposcopic examination was performed according to local protocols and national guidance. Sheffield is currently taking part in an evaluation of primary hrHPV screening on behalf of the English Cervical Screening Programme. All women referred to the colposcopy clinic with abnormal cervical cytology will also be positive for hrHPV. High-risk HPV testing was performed using the Cobas 4800 system. All colposcopists were BSCCP accredited. ZedScan *I* colposcopic examinations were carried out according to the manufacturer's protocol. Biopsies and treatments [large loop excision of the transformation zone (LLETZ)] were undertaken based on colposcopic impression and ZedScan *I* results. Treatment at first visit (See and Treat (S&T)) for women referred with high-grade cytology is a recognised management option in the English Cervical Screening Programme. Random biopsies of normal cervical transformation zone and endocervical curettage were not performed as per local and national guidance [13]. All biopsies and LLETZ specimens were analysed by specialist gynaecological pathologists.

Cytology referrals were placed into two groups, low-grade (borderline nuclear change in squamous and endocervical cells [ASCUS+AGCUS) and low-grade dyskaryosis (LSIL)], and high-grade [high-grade dyskaryosis, moderate or worse (HSIL), and glandular neoplasia (AGC)] in order to reflect the different prevalence of high-grade disease within these categories. A previous study of hrHPV triage of low-grade cytology reported similar rates of HG-CIN in borderline and low-grade dyskaryosis cytologies, 15.6% and 17.1%, respectively [24]. To estimate the performance of colposcopy with and without ZedScan *I,* the authors correlated colposcopic impression at the site of biopsy whether colposcopically directed or ZedScan *I* directed, to the biopsy outcome. To calculate the detection of disease the authors used all biopsies taken, irrespective of colposcopic impression or ZedScan *I* to calculate the presence of all disease. If HG-CIN was detected following a positive ZedScan *I* directed biopsy with a normal or low-grade colposcopic impression, the authors considered this to be an extra case detected by ZedScan *I*. Statistical analyses were used where appropriate and included descriptive statistics, Chi square, Fisher's exact test, and McNemar's test.

Results

Between December 2013 and December 2015, 1,237 consecutive women were referred to colposcopy with an abnormal cytology result and underwent both adequate colposcopic and ZedScan *I* examination (Figure 1). Median age of the women referred was 29.6 years; age range was 20.3 to 66.1 years. Of those referred, 401 (32.4%) had high-grade cytology; 836 (67.6%) low-grade cytology (Figure 1).

High-grade disease was detected in 466 (37.7%) women

Table 1. — *Performance metrics for colposcopy with ZedScan I as an adjunct for the detection of HG-CIN.*

Sensitivity	97.9% (95% CI 96.6% - 99.2%)
Specificity	58.4% (95% CI 55.1% - 62.1%)
PPV	58.6% (95% CI 55.6% - 62.0%)
NPV	97.8% (95% CI 96.5% - 99.1%)

Table 2. — *2 x 2 table showing the true and false-positive (TP and FP) and the false and true-negative (FN and TN) results. McNemar's test, $p < 0.0001$.*

	Biopsy result	
	HG-CIN	≤ LG-CIN
Colposcopic Impression and/or ZedScan positive	TP 456	FP 319
Colposcopic Impression and ZedScan negative	FN 10	TN 452
Total	466	771

Table 3. — *Performance metrics taken from van der Marel et al. [16] and Tidy et al. [23] for colposcopy alone and for ZedScan I alone.*

	Colposcopy alone n=196	Colposcopy alone n=610	ZedScan I alone n=196
Sensitivity	88.5% (95% CI 79.9% - 94.4%)	87.9% (95% CI 83.2% - 96.4%)	86.2% (95% CI 77.1 – 92.7%)
Specificity	38.5% (95% CI 29.4% - 48.3%)	44.3% (95% CI 39.0% - 49.8%)	56.0% (95% CI 46.1% - 65.5%)
PPV	53.5% (95% CI 45.0% - 61.8%)	54.9% (95% CI 50.2% - 59.6%)	61% (95% CI 52.4% - 69.2%)
NPV	80.8% (95% CI 67.5% - 90.4%)	82.6% (95% CI 76.4% - 87.4%)	83.6% (95% CI 75.1% - 92.1%)

on cervical punch biopsy or LLETZ specimen; 337 women with high-grade cytology had HG-CIN; 129 women with low-grade cytology had HG-CIN. The majority (98.8%) of women referred with high-grade cytology underwent LLETZ or diagnostic biopsy; 52% of women referred with low-grade cytology underwent LLETZ or diagnostic biopsy. Of the women who had a diagnostic biopsy, only 91.0% had a single biopsy (high-grade cytology 80.9%, low-grade cytology 94.0%). Multiple diagnostic biopsies were performed in 19.1% of women referred with high-grade cytology compared with 6% of women referred with low-grade cytology. The average number of biopsies was 1.07 per women if a biopsy was taken and 0.5 for all women referred to colposcopy.

Fifty-three (12.8%) extra cases of HG-CIN were detected by ZedScan *I* (466 *vs.* 413, $p = 0.0289$). Ten of the 53 cases (19%) were referred with high-grade cytology and 43 (81%) were associated with low-grade cytology. The increased detection of HG-CIN in women referred with low-grade cytology was 50% (129 *vs.* 86 $p = 0.0021$) (Figure 2). Table 1 shows the performance metrics for colposcopy used with ZedScan *I* as an adjunct for the detection of HG-CIN; Table 2 gives the associated 2 x 2 table. Sixty-six women with a normal colposcopic impression and negative ZedScan *I* result still had a directed biopsy and 12 of the 66 (18%) had HG-CIN. (Figure 2) (Table 1)

See and treat (S&T) is a recommended management option for women referred with high-grade cytology; 273 women underwent treatment at first visit based on colposcopic impression of HG-CIN and a positive ZedScan *I* result; 260 (95.2%) had confirmed HG-CIN with 83.5% having CIN3+.

Twenty-two of 1237 women (1.8%) were referred with potential cervical glandular intraepithelial neoplasia (CGIN); nine with glandular neoplasia (AGC), and 13 with borderline changes in endocervical cells (AGUS). Eight of nine women (89%) referred with glandular neoplasia had high-grade disease, three had HG-CGIN alone, two had HG-CGIN + HG-CIN, one had HG-CGIN + LG-CIN, two had HG-CIN, and the remaining patient was normal. Of the 12 women with high-grade disease, nine had a colposcopic impression of high-grade disease and a positive ZedScan *I* result, two had a normal colposcopic impression and a positive ZedScan *I* result, and one had a colposcopic impression of high-grade disease and a negative ZedScan *I* result. Of the two cases where there was a positive ZedScan *I* result and normal colposcopy all the women had HG-CGIN with out any CIN in the directed biopsy and LLETZ specimen. These women had all been referred with borderline changes in endocervical cells.

Discussion

The aim of an organised cervical screening programme is to be as efficient as possible while maintaining a high level of safety. The English programme is based on the early detection and treatment of high-grade disease to prevent cervical cancer, and the return of women with no abnormality back to routine screening. Following the introduction of the programme, both the incidence of and mortality from cervical cancer has declined by 50% [25]. The effectiveness of colposcopy in detecting disease has been shown to be dependent on the prevalence of high-grade disease in the population being examined. Colposcopy performs poorly as a screening test when the prevalence of disease is low. However there is evidence of better but variable performance when used in a referral population with sensitivity and specificity ranging between 30-99% and 32-92%, respectively [1]. Recent and better quality studies have reported sensitivity of 56-84% and a positive predictive value of 69%. [2, 3, 5, 7, 16, 25] Some authors have also advocated the use of random biopsies at the time of colposcopy to enhance detection of disease [5, 7].

EIS offers the opportunity of integrating an additional 'real time' test that works independently of the established colposcopic features used to detect CIN, aceto-whiteness, and changes in vascular pattern. The changes in epithelial cell disorganisation associated with the development of CIN are well described and include changes in nuclear: cytoplasmic ratio, increased extra-cellular space, and loss of differentiation [18]. These changes affect EIS of the tissue and so can be measured and used to detect CIN [19-23]. ZedScan *l*, a Conformité Européenne (CE) marked device, exploits the changes in EIS to produce a real time assessment of the cervical transformation zone and so provide the colposcopist with an additional non-visual test to detect and manage women who might have CIN [23].

This evaluation was designed to assess if colposcopy and EIS were complementary and increased the detection of high-grade disease. This approach is most likely to reflect routine clinical practice if EIS was used in addition to colposcopy as recommended by Leeson in 2014 [15].

This evaluation was a cohort study with no separate group where EIS was not used, therefore it was not possible to determine the performance metrics for colposcopy or EIS alone. To compare the performance of the combined test with colposcopy alone and EIS alone, data from two recently published trials were used (Table 3). Comparison of the 95% confidence intervals with those shown in Table 1 for the current study shows significantly higher sensitivity, specificity, and negative predictive value (NPV) in the current study with no confidence interval overlap ($p < 0.003$). The positive predictive value (PPV) for colposcopy alone, EIS alone, and colposcopy combined with EIS was similar, however the prevalence of high-grade disease was significantly less ($p < 0.0001$) in this evaluation as compared with other studies (Table 3).

The PPV of any test falls if the prevalence of disease being detected also falls; unless the accuracy of test improves. The accuracy of the colposcopy and ZedScan was 78.2%, whereas colposcopy alone was 63.5 to 66.1%. The combination of colposcopy and EIS increased detection of HG-CIN by 12.8% overall ($p = 0.0289$) and by 50% ($p = 0.0021$) in low-grade referrals, the improved performance of the combined test in both confirming and excluding the presence of high-grade disease was highly significant with a diagnostic odds ratio of 65 ($p > 0.0001$).

In England, national guidance for colposcopic practice does not recommend the use of random biopsies from the normal transformation zone or the use of endocervical curettage; the later because of poor sensitivity and specificity and associated discomfort [13]. In the evaluation biopsies were taken at the discretion of the colposcopist and as indicated by ZedScan *I*. The combination of colposcopy and ZedScan *I* is associated with a low negative likelihood ratio (0.036) indicating a large decrease in the probability of disease being present, thus providing greater reassurance when discharging women to routine screening. Taking additional biopsies or random biopsies has been shown to increase the detection of CIN; however in this evaluation the use of the combined tests did not increase the biopsy rate and so cannot be the explanation for the improved detection of HG-CIN.

Treatment at first visit (S&T) is recommended as part of colposcopy practice in the English screening program. A recent meta-analysis of over 4,600 women undergoing S&T found an over-treatment rate, defined as no CIN or low grade CIN, of 11.6% when the woman was referred with a high-grade cytology result and the colposcopic impression was of HG-CIN. This compares well with an over-treatment rate of 11-35% reported for women who first have a diagnostic biopsy and then return for excisional treatment [26]. A recent cohort study of 723 women from the Netherlands found an over-treatment rate of 6.7% for women referred with severe dyskaryosis, but this increased to 27% for women referred with moderate dyskaryosis [27]. In this evaluation 273 women referred with high-grade cytology (moderate or severe dyskaryosis) underwent S&T and 95.4% had HG-CIN in the excised tissue. This exceeds the quality standard of > 90% for the English programme [13]. In addition the combined test increased the present authors' ability to use S&T, increasing the percentage of women referred with high-grade cytology who underwent S&T from 30-33%, in the years immediately prior to the introduction of ZedScan *I*, to 68% ($p < 0.001$). The increase in use of S&T was not associated with over-treatment of CIN2 as 83.5% of the women who underwent S&T had CIN3+ and the proportion of women with CIN3+ did not change over the two years of the evaluation. Previous studies into the psychological beliefs and concerns of women who have experienced an abnormal cytology result and referral to col-

poscopy have shown that the use of S&T to manage their condition, when appropriate, is a preferred management option [28].

Colposcopy performs very poorly when trying to detect CGIN. The colposcopic features of CGIN are only present after the application of acetic acid as there is an absence of mosaic and punctate vascular pattern. Atypical blood vessels may be seen and raise the possibility of a micro-invasive cancer. The most commonly described changes are dense aceto-white columnar villi found within the columnar portion of the ectocervix and not in contact with the transformation zone, and the fusion of columnar villi [29]. Cytology has been shown to have reasonable sensitivity (66%) and PPV (81%); colposcopy is reported to have a sensitivity of only 10% but a high PPV (94%) [30]. Even when colposcopy is reported as normal between 47-87% of women had a significant lesion in the subsequent excised specimen [30]. These findings suggest that abnormal colposcopic features can be recognised but they are present in very few cases of HG-CGIN. Pure HG-CGIN is a relatively rare finding even when women are referred with an abnormal glandular cytology. The most common histological diagnosis reported in women referred with abnormal glandular cytology, once cancers are excluded, is CIN2+ followed by a combination of HG-CIN and HG-CGIN [31]. Changes in the glandular epithelium associated with HG-CGIN demonstrate similar changes in EIS to those of CIN. The use of colposcopy and ZedScan *I* in women referred with abnormal glandular cytology in this evaluation demonstrated a high level of disease detection with extra cases of CGIN being detected only by ZedScan *I* and so may be a valuable additional test in managing women at risk of glandular neoplasia.

The strengths of this study are the large number of women examined by the combination of colposcopy and ZedScan *I* within an organised screening programme following national colposcopy practice guidelines at a large colposcopy clinic. Several trained colposcopists were involved in the evaluation, which was embedded into normal routine practice and hence the results are clinically relevant [15]. The weaknesses of the study are that the evaluation was only undertaken in one colposcopy clinic and the authors did not take random biopsies to exclude or confirm disease status in all women. In fact the only way to establish the true disease status in any colposcopy study would be to undertake an excisional procedure in all cases, which of course would be unethical.

Conclusions:

The combination of colposcopy and ZedScan *I* results in a more accurate diagnostic pathway for women referred with abnormal cytology by increasing both the detection and exclusion of high- grade disease without increasing the number of biopsies taken. The combination allows the effective use of treatment at first visit without over treatment. There is also an improvement in the efficiency in managing women with abnormal cytology by increasing patient through put and reducing the need for unnecessary follow-up in colposcopy.

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