Management of patients with two consecutive ASC-US smears

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Summary

Introduction: To determine whether aggressive or expectative management of patients after two consecutive smears with atypical squamous cells of undetermined significance is preferable. To determine whether triage with high-risk human papillomavirus will identify all patients with cervical intraepithelial neoplasia grade 2 and 3.

Methods: 140 of 282 patients referred for colposcopy with two consecutive smears with atypical squamous cells of undetermined significance were only treated when abnormalities suggestive of high-grade cervical intraepithelial neoplasia were present at colposcopy. The other 142 patients underwent excision of all detected colposcopic abnormalities. Both groups were compared regarding the final cytological follow-up, the number of diathermy loop excisions, and the detection of cervical intraepithelial neoplasia. Retrospectively, the outcome of triage with high-risk human papillomavirus in the first group was investigated.

Results: There was no significant difference in final cytological follow-up between patients managed by expectative or by aggressive colposcopic management. Significantly less diathermy loop excisions ($p < 0.001$) are performed in case of expectative management. The sensitivity, specificity, negative- and positive predictive values of triage with high-risk human papillomavirus detection were comparable with those of colposcopy alone.

Conclusions: Patients referred with two consecutive ASC-US smears may be followed with an expectative colposcopic management and cytological follow-up. Triage with high-risk human papillomavirus will reduce the number of referrals and colposcopies, but (cytological) follow-up remains necessary in all high-risk human papillomavirus negative patients as well.

Key words: ASC-US; Management; Colposcopy; hr-HPV; Cytology.

Introduction

The management of patients with cervical smears showing minimally abnormal cells (atypical squamous cells of undetermined significance (ASC-US) remains a clinical problem [1]. Of all smears made in the context of screening programs for cervical cancer 2-10% are graded as minimally abnormal or ASC-US [1, 2]. However, more than 70% of these patients do not have (pre) malignant lesions of the uterine cervix and only a minority (6-12%) will develop cervical intraepithelial neoplasia (CIN) during follow-up [1, 3-9]. On the other hand, almost 50% of all patients eventually diagnosed with CIN2 and 3 initially had an ASC-US smear [10].

In 1992, about 12% of all smears from the screening program in the Netherlands were graded as ASC-US [11]. After revision of the screening program in 1996, by applying more precise and restrictive diagnostic criteria for ASC-US smears, less than 5% of all cervical smears are graded as ASC-US and a repeat smear after six months is advised [12]. Since 1997, the revised Dutch guidelines advise referral of patients after two consecutive ASC-US smears to a gynecologist for colposcopy. Colposcopy has a high positive predictive value (78%) in detecting CIN lesions, but its specificity is low, causing unnecessary biopsies/excisions [9, 10, 13, 14]. In order to avoid unnecessary excisions, either a more expectative management or triage prior to referral is considered. Triage with high-risk human papillomavirus (hr-HPV) detection in cervical smears, in which only hr-HPV positive patients are referred for colposcopy, has been recommended by several authors in order to reduce unnecessary treatment of patients with ASC-US smears [5, 9, 10]. In order to investigate the effects of aggressive or expectative management on patient outcome, the long-term follow-up of patients referred after two consecutive ASC-US smears treated in two different clinics was compared. Furthermore, the sensitivity, specificity, negative and positive predictive values (NPV, PPV) for the detection of patients with CIN2 or 3 by triage with hr-HPV detection was compared with colposcopy in the group with expectative management.

Materials and Methods

Patients

In retrospect, all 295 patients were included who had two consecutive ASC-US smears in the screening program, and who were referred between April 1997 and December 1999 to one of the two hospitals in Nijmegen, the Netherlands. Of the 148 patients referred to the University Medical Center in Nijmegen (UMC) and of the 147 patients referred to the Canisius Wilhelmina Hospi-

tal in Nijmegen (CWZ), respectively, eight and five patients were excluded because of cervical polyps. The remaining 140 patients of the UMC and 142 patients of the CWZ were analyzed. Referral of the patients to either the UMC or the CWZ was decided by the referring general practitioner and was not influenced by this study.

Colposcopy

All 282 patients underwent colposcopy within one month of the intake consultation in either one of the hospitals. If a patient was referred to the UMC only lesions suspect for high-grade CIN at colposcopy were treated with diathermy loop excision on the basis of a see and treat policy [15]. If a patient was referred to the CWZ the standard policy, a diathermy loop excision, was performed unless no abnormalities were detected during adequate colposcopy. All patients of both groups and follow-up smears six and 12 months after the initial colposcopy, and in case of persistent abnormalities, every six or 12 months thereafter. Repeat colposcopy was performed at the UMC when ASC-US smears persisted for more than 12 months, or sooner when follow-up smears indicated CIN. All lesions suspect for CIN were removed with diathermy loop excision during repeat colposcopy at the UMC. Repeat colposcopy in the CWZ was combined with a diathermy loop excision when follow-up smears indicated CIN. The mean duration of long-term cytological follow-up was 41 months (24-54 months) in the UMC and 39 months (24-52 months) in the CWZ.

The management strategies of the two hospitals were compared regarding the number of persistent abnormal cervical smears, the number of diathermy loop excisions, and the occurrence of the different grades of CIN. All patients with two consecutive normal smears, or with one normal follow-up smear and a normal adequate colposcopy, were considered to have regressed to normal and/or to have been treated sufficiently. The diagnosis of CIN was made on histopathological examination of the excised material by an experienced gyneco-pathologist.

Hr-HPV detection

A liquid-based cervical smear was taken from all 140 patients at the UMC during the intake consultation with a cervix brush® (Rovers, Oss, the Netherlands). The cell suspension was processed into an AgarCyto cell block alowing for multiple analyses as previously described [16]. For HPV detection a highly sensitive short fragment polymerase chain reaction (SPF_{10} PCR) assay was performed on a section of the AgarCyto cell block. In case of a positive SPF_{10} PCR, reverse hybridization by a line probe assay (LiPA) was performed for simultaneous genotyping of 25 HPV genotypes, including hr-HPV genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68. This HPV detection assay was validated before and found to be ultrasensitive [17-22].

Triage with hr-HPV detection was retrospectively performed on all 140 patients and the sensitivity, specificity, NPV and PPV for the detection of CIN2 or 3 by respectively, hr-HPV testing and colposcopy was determined. Statistical analysis was performed using chi-square tests, independent samples (Student's t) tests, and calculation of 59% confidence intervals (95% CI). All test results with a probability (p) of < 0.05 were considered significant.

Results

Colposcopy

A diathermy loop excision was performed during the initial colposcopy in two patients (1%) at the UMC and in 119 patients (84%) at the CWZ. Histopathological examination revealed one CIN3 lesion and one CIN2 lesion in the UMC patients, and 15 CIN1 lesions, nine CIN2 lesions, five CIN3 lesions, and 90 patients without CIN in the CWZ patients.

Two UMC patients underwent a repeat colposcopy with diathermy loop excision within 12 months of follow-up, because of a follow-up smear and repeat colposcopy indicating CIN. In another nine UMC patients a diathermy loop excision was performed after more than 12 months of follow-up; in seven patients with a smear indicating CIN, and in two patients with persistent ASC-US smears and a lesion suspect for CIN at colposcopy. Histopathological examination of these secondary excisions showed CIN1 in two patients, CIN2 in five patients, and no CIN in four patients.

A repeat colposcopy with repeat diathermy loop excision was performed within 12 months of follow-up in five patients of the 119 CWZ patients who had a loop excision before, in four patients with a smear indicating CIN, and in one patient with persistent ASC-US smears at the patient's request. Histopathological examination showed residual CIN1 in three patients and no CIN in two patients. The difference in the total number of diathermy loop excisions of respectively 13 in the UMC and 124 in the CWZ was highly significant ($\chi^2 > 100$, $p < 0.001$).

CWZ patients had significantly more often ($\chi^2 = 5.80$, $p < 0.02$) a normal first follow-up smear than UMC patients (respectively 92 and 70 patients). There were no significant differences in follow-up between UMC and CWZ patients after a mean follow-up duration of respectively 41 and 39 months (Table 1).

Table 1. — *Final follow-up after initial and secondary diathermy loop excisions of UMC and CWZ patients (with 95% CI).*

Follow-up	UMC n =	UMC %	UMC 95% CI	CWZ n =	CWZ %	CWZ 95% CI
No follow-up*	0	(0)	0-1%	2	(1)	0-6%
Two normal follow-up smears*	93	(66)	58-74%	95	(68)	60-76%
Norm. colposcopy & 1 norm. FU smar*	31	(22)	15-29%	33	(23)	16-30%
Persistent ASC-US smears*	16	(11)	6-16%	12	(8)	4-12%
Total number of patients	140	(100)		142	(100)	

* = no significant difference between UMC and CWZ.

Table 2. — *The sensitivity, specificity, PPV, and NPV for the detection of CIN2 or 3 in patients of the UMC by hr-HPV detection and colposcopy (95% CI) (n = 140).*

	Sensitivity	Specificity	NPV	PPV
Colposcopic lesions suspect for CIN 2/3 (n = 2)	29% (12-46%)	100%	96% (94-98%)	100%
Hr-HPV positive at referral (n = 48)	57% (22-92%)	67% (59-75%)	96% (92-100%)	8% (0-16%)
Colposcopic lesions suspect for CIN (n = 35)	57% (20-94%)	77% (70-84%)	96% (92-100%)	11% (1-21%)

Table 3. — *The relation between hr-HPV triage, the number of loop excisions and the final cytological follow-up.*

Cytological follow-up	hr-HPV Positive n = %	95% CI	hr-HPV Negative n = %	95% CI
Two normal cervical smears*	31 (65)	52-78%	62 (67)	57-77%
Normal colposcopy with 1 normal cervical smear*	12 (25)	13-37%	19 (21)	11-27%
Persistent ASC-US smears*	5 (10)	2-18%	11 (12)	5-19%
Total	48 (100)		92 (100)	

* = no significant difference between hr-HPV positive and negative patients.

Hr-HPV triage (UMC)

Hr-HPV genotypes were detected in the smears of 48 of the 140 UMC patients (34%). One CIN3 lesion and three CIN2 lesions were detected among the hr-HPV positive patients, and two CIN1 and three CIN2 lesions were detected among the hr-HPV negative patients. The sensitivity, specificity, NPV, and PPV for the detection of CIN2 or 3 by hr-HPV testing and colposcopy are presented in Table 2. None of these tests reached 100% sensitivity, and all tests had a NPV above 95%, but the overlapping confidence intervals indicate that the differences in performance are not significant.

There were no significant differences in final follow-up between hr-HPV positive and hr-HPV negative patients, while the percentage of patients undergoing a diathermy loop excision (respectively, 9% and 10%) was equal in both groups. However also here the 95% CI was large (Table 3).

With the use of hr-HPV detection as triage, 48 patients would have been referred for colposcopy, but two patients with CIN1 and three patients with CIN2 would not have been referred.

Discussion

Colposcopy

The optimal management of patients with ASC-US smears is still a matter of debate. The presented data confirm that patients with ASC-US smears are at relatively low risk for CIN2 or 3 lesions [1, 5-7, 9, 23-25]. With aggressive management (CWZ) CIN was diagnosed at the time of referral in 20% of all patients, including 10% with CIN2 and 3, while with expectative management (UMC) CIN was diagnosed in only 6% of the patients, including 5% with CIN2 or 3. This seems to confirm that many lesions, especially low-grade CIN lesions, do regress with an expectative management strategy and that they do not require treatment [3-5, 7].

Significantly more patients of the CWZ had a normal first follow-up cervical smear after the initial colposcopy. It seems that a diathermy loop excision in patients with ASC-US smears, independent of the presence or absence of CIN, leads to a faster normalization of cervical smears than without diathermy loop excision. Eventually, there was no significant difference in long-term cytological follow-up between the hospitals. The large majority of patients referred with two consecutive ASC-US smears had normal follow-up smears after respectively, 41 and 39 months.

The initial faster normalization of the follow-up smears with an aggressive management did not show any long-term advantage.

Many patients of the CWZ in whom a CIN lesion was suspected at colposcopy did not have CIN on histopathological examination. From the literature it is known that especially CIN1 and 2 lesions are difficult to identify correctly with colposcopy, while CIN3 lesions are often correctly identified [4].

The difference in the number of diathermy loop excisions between the hospitals is highly significant. Even if all patients with persistent cervical smear abnormalities would undergo diathermy loop excision, the number of loop excisions in CWZ would be almost 5-fold compared with the UMC. In this respect, the expectative management strategy of the UMC seems to be preferable. However, both the patient and the attending gynecologist may prefer a fast normalization of cervical smears and thus follow an aggressive management strategy. Since this was a retrospective study, we have to be cautious in interpreting the results. A difference in population seems unlikely because all patients live in the same city, the mean age of both groups is comparable, and all patients were first time referrals from the screening program with two consecutive ASC-US smears. A difference in other factors like sexual behavior, cigarette smoking, social status, and hr-HPV positivity is therefore very unlikely but cannot be ruled out. These factors have all been associated with an increased risk of developing an abnormal cervical smear/CIN lesion. However, it remains unsure whether these factors still influence the detection of CIN once an abnormal smear has been found. For this reason we consider it less likely that these factors are responsible for the large differences between the groups.

Hr-HPV triage (UMC)

The percentage of hr-HPV positive patients in this study seems lower than in other studies [9, 23, 25]. However, those studies investigated patients with ASC-US smears as well as patients with smears indicating CIN (with a higher hr-HPV prevalence), or they investigated exclusively patients with a single ASC-US smear. The prevalence of hr-HPV in patients with two consecutive ASC-US smears may be lower than in this last group, because the HPV infection may have been cleared at the time of the second cervical smear, while the abnormality did not (yet) resolve. A lack of sensitivity of the used HPV detection method is unlikely because of the published high sensitivity of the assay [17-22]. In fact, the SPE_{10} PCR assay was shown to be more sensitive in detecting hr-HPV than HPV detection methods using MY09/11 primer sets or the Hybrid Capture II test, especially in cases with multiple hr-HPV infections [20-22].

Hr-HPV detection identified the one patient with CIN3 and three of the six patients with CIN2. Several explanations are possible for not detecting hr-HPV in three patients with CIN2. Firstly it is possible that the CIN2 lesion developed in the absence of hr-HPV, a possibility that has recently been suggested [26]. Secondly it remains possible that, despite the high sensitivity of the test, the HPV test was false-negative, and thirdly it is possible that the hr-HPV infection and CIN lesion developed after the intake cervical smear was taken but before the loop excision was done. The short time interval (0-18 months) between the intake cervical smear and the final loop excision, however, makes this unlikely.

The sensitivity for detecting CIN2 or 3 lesions by hr-HPV testing or colposcopy never reached 100%. The performance of hr-HPV testing in this study was less than in other studies, summarized by Wright *et al.*, despite the high sensitivity of the used assay [1]. These other studies included patients with only a single ASC-US smear followed directly by colposcopy with histopathological confirmation of the presence or absence of CIN2 or 3. These facts may be responsible for the difference in sensitivity between those studies and this study. The low number of patients with CIN2 or 3 in this study resulting in a large 95% CI, may also partly explain that difference.

The performance of hr-HPV testing itself was equal to colposcopy in this study. Several authors have cautioned before for the overestimation of the value of hr-HPV testing [12, 27, 28]. On the other hand, it is possible that the value of hr-HPV detection has been underestimated in this study. Hr-HPV positive patients in whom no CIN was detected in this study, may develop CIN lesions at a later stage, while hr-HPV negative patients in whom CIN was detected, may have clinically irrelevant CIN lesions, because especially hr-HPV negative CIN lesions may regress with longer follow-up [29].

The high (additional) costs of hr-HPV detection may limit its use in patients with two consecutive ASC-US smears in the Netherlands. Hr-HPV testing in patients with ASC-US smears was shown to be cost-effective in the United States because of the high costs of colposcopy/histopathology in that country [1, 30, 31], but this may not be true for the Netherlands.

Conclusion

The present management of patients with two consecutive ASC-US smears in the Netherlands results in a high number of unnecessary referrals and loop excisions. An expectant management strategy that identifies all patients with high-grade CIN at colposcopy, but that postpones interventions in the other patients for at least 12 months, leads to significantly fewer loop excisions and allows for spontaneous regression of most (low-grade) lesions. Triage with hr-HPV detection before referral will reduce the number of referrals/colposcopy by about 60%, but (cytological) follow-up of all hr-HPV negative patients remains necessary to detect all patients with CIN lesions. The cost-effectiveness of hr-HPV triage in patients with two consecutive ASC-US smears needs to be assessed in the Netherlands and should be compared with triage by follow-up conventional/liquid based cytology, and/or with direct referral for colposcopy [1, 31].

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