INCOMPLETE EXCISION OF CERVICAL PRE-CANCER AS PREDICTOR OF TREATMENT FAILURE: A SYSTEMATIC REVIEW AND META-ANALYSIS

Marc Arbyn (DrTMH)[1], Charles WE Redman (MD)[2], Freija Verdoodt (PhD)[3], Maria Kyrgiou (PhD)[4], Menelaos Tzafetas (MD)[4], Sadaf Ghaem-Maghami (MD)[4], Karl-Ulrich Petry (PhD, Prof)[5], Simon Leeson (MD)[6], Christine Bergeron (MD)[7], Pekka Nieminen (PhD, Prof)[8], Jean Gondry (PhD, Prof)[9], Olaf Reich (MD)[10], Esther L Moss (MD)[11]

[1] Unit of Cancer Epidemiology, Belgian Cancer Centre, Scientific Institute of Public Health, Brussels, Belgium
[2] University Hospitals of North Midlands, Stoke and Trent, UK
[3] Unit of Virus, Lifestyle and Genes, Danish Cancer Society Research Center, Copenhagen, Denmark
[4] Division of Reproductive Biology, Department Cancer and Surgery, Imperial College, London, United Kingdom
[5] Department of Gynaecology and Obstetrics, Klinikum Wolfsburg, Germany
[6] Department of Gynaecology and Obstetrics, Betsi Cadwaladr University Health Board, Bangor, Gwyndd, UK
[7] Laboratoire Cerba, Cergy, France
[8] Department of Gynaecology and Obstetrics, Helsinki University Hospital, Finland and University of Helsinki, Finland
[9] Service de gynécologie et obstétrique, CHU d'Amiens-Picardie, Amiens, France
[10]Department of Gynaecology and Obstetrics, Medical University of Graz, Austria
[11]Department of Cancer Studies, University of Leicester, UK

Corresponding author:
Marc Arbyn, Unit of Cancer Epidemiology, Belgian Cancer Centre, Scientific Institute of Public Health, J. Wytsmanstreet 14, B1050 Brussels, Belgium.
marc.arbyn@wiv-isp.be; tel: +32 2 6425021

Funding:
The authors thank the European Federation for Colposcopy for the funding of this systematic review.
M. Arbyn was supported also by the COHEAHR Network (grant No. 603019), coordinated by the Free University of Amsterdam (The Netherlands), funded by the 7th Framework Programme of DG Research and Innovation, European Commission (Brussels, Belgium). J. Gondry and M. Arbyn received support from the COSPCC study (University Hospital of Amiens, Amiens, France), funded by *Institut National du Cancer* (Paris, France).
M. Kyrgiou was also supported by: Genesis Research Trust (P55549 - MK); Imperial College Healthcare Charity (P59319-MT, MK); British Society of Colposcopy Cervical Pathology Jordan/Singer Award (P47773)(MK); ICIC Award, MRC (PS2897, PS2857 – MK).

Key words: cervical cancer, treatment of cervical pre-cancer, outcome prediction, resection margins, human papillomavirus, diagnostic test accuracy, meta-analysis.

Research into Context

Evidence before this study

We searched PubMed and Embase with the search terms “cervical precancer OR [synonymous terms] AND excisional treatment OR (synonymous terms for treatment procedures) AND "incomplete excision OR [synonyms for marginal status] and “outcome OR cure or failure" to assess the proportion of positive resection margins, the association with treatment failure and the accuracy of the margin status to predict treatment failure. Published meta-analyses on accuracy of post-treatment HPV testing as test of cure and on obstetrical harm associated with surgical treatment of cervical precancer were searched as well. The search was not restricted for start year and included 2016 as end year; no language restriction.

A meta-analysis published 10 years ago concluded that the average risk of treatment failure (=residual/recurrent CIN2+ after surgical treatment) was six times higher when resection margins contained neoplastic tissue. The authors recommended complete removal of the lesion. No accuracy estimates of the margin status to predict treatment cure or failure were included. Several meta-analyses consistently showed an increased risk of preterm delivery associated with prior excisional treatment of cervical pre-cancer and this risk increased with the size of the excised tissue. The level of evidence on obstetrical harm and risk of failure associated with involved section margins is moderate to low (based on observational data only, but showing a consistent direction of risk).

Other systematic reviews found that post-treatment HPV testing was an accurate method to predict residual/recurrent CIN2+: pooled sensitivity and specificity of 93% and 81%, respectively.

Added value of this study

The current systematic review, updates and extends the previous meta-analyses on the oncological outcomes of surgical treatment of precursor lesions of cervical cancer, and adds new meta-analyses not yet conducted before: accuracy of the margin status to predict treatment failure and the relative accuracy of post-treatment HPV testing compared to the margin status.

Three teams of authors, that have conducted the previous reviews, have joined forces and bring a common message to clinicians who have to treat CIN. The current meta-analysis confirms findings of previous reviews regarding increased risk of residual CIN+ when margins are positive. However, our review shows that accuracy of the margin status is poor, whereas post-treatment HPV testing is a more accurate predictor of treatment outcome.

Implications of all the available evidences

Pretest-posttest probability plots demonstrate that post-treatment HPV testing is a more sensitive predictor of treatment outcome than margin involvement. Knowledge of the margins status, in general, does not provide accurate information to define post-treatment assessment.

We acknowledge absence of studies assessing both the oncological and obstetrical issues of cervical pre-cancer therapy and invite for research that target both outcomes.

Summary

Background: Incomplete excision of cervical pre-cancer is associated with therapeutic failure and is therefore considered as a quality indicator of clinical practice. Conversely, the risk of pre-term birth is reported to correlate with size of cervical excision and therefore balancing the risk of adequate treatment with iatrogenic harm is challenging.

Methods: We extended previous systematic reviews that assessed separately the risk of treatment failure associated with the margin status of the cervical excisions and the accuracy of post-treatment high-risk (hr) HPV testing to predict residual/recurrent cervical pre-cancer. Information on positive resection margins and subsequent treatment failure was pooled using procedures for meta-analysis of binomial data. The meta-analysis comparing the accuracy of the margin status with post-treatment hrHPV testing was restricted to studies with i) an average follow-up of at least 18 months post-treatment and ii) treated disease and treatment outcome were histologically confirmed cervical intra-epithelial neoplasia of grade two or worse (CIN2+).

Findings: The average rate of positive margins was 23% (95% confidence interval [CI] 20-26%) and varied by treatment procedure (ranging from 18% for laser conisation to 26% for large loop excision) and increased by the severity of the treated lesion. The overall risk of residual/recurrent CIN2+ was 7% (CI=5-8%). Treatment failure was 5 (CI=3.2-7.2) times greater with positive compared to negative resection margins. The risk of treatment failure was highest when the endo-cervical margin was positive.
The pooled sensitivity and specificity to predict residual/recurrent CIN2+ was 56% (CI=46-66%) and 84% (CI=79–88%), respectively, for the margin status, and 91% (CI 82-96%) and 84% (CI=77-89%), respectively, for hrHPV testing. The margin status was 41% less sensitive but not more specific than hrHPV. A negative hrHPV test post-treatment was associated with a risk of CIN2+ of 0.8%, whereas this risk was 3.7% when margins were free.

Interpretation: The risk of residual/recurrent CIN2+ is significantly greater with involved margins on excisional treatment. However, hrHPV post-treatment predicts treatment failure more accurately.

INTRODUCTION

In clinical medicine, finding a balance between therapeutic effectiveness and iatrogenic harm often is challenging.
The occurrence of cervical cancer is preceded by pre-malignant lesions called cervical intraepithelial neoplasia (CIN)[1]. The risk of progression to invasive carcinoma depends on the severity and the size of the CIN lesion[2-5] with approximately one third of women with untreated CIN3 eventually developing invasive cervical cancer.[6] By screening for cervical lesions and treatment of high-grade CIN, development of cancer can be avoided.[7]

The most commonly used treatment modality for CIN is an excisional biopsy (large loop excision of the transformation zone [LLETZ] or loop electrosurgical excision procedure [LEEP]), laser conisation [LC] or cold-knife conisation [CKC]).[8] The primary advantage of excisional as compared to ablative treatments is the ability to submit the abnormality in the excised specimen for pathological examination thereby confirming the diagnosis, excluding an occult malignancy and obtaining information on the completeness of excision.[8] The failure rate of excisional treatment, defined as persistent or recurrent CIN of grade 2 or worse

(CIN2+), is reported as being between 4-18%[9], the majority of which occur within two years following the primary treatment.[10,11] However, treated women are still at increased risk for subsequent invasive cervical cancer compared to the general population during at least the following 10 years.[12,13] Identifying an accurate indicator that can identify women at greater risk of recurrent CIN and/or future malignancy following treatment for cervical pre-cancer could enable tailored management according to the woman's individual risk, thereby avoiding over-treatment and reducing patient anxiety.

Incomplete excision of CIN, as determined by positive excision margins, is associated with an increased probability of treatment failure.[14,15] As a result, negative resection margins from cervical excisional treatments for CIN, with a benchmark of at least 20%, is viewed as a quality indicator for good clinical practice for colposcopists.[16]

There has, however, been a growing concern over the impact of cervical excision on the integrity of the cervix and specifically its ability to function during a pregnancy, resulting in pre-term birth (PTB) and adverse neonatal outcomes. Meta-analyses have identified that the depth of excision correlates with risk of PTB and that certain techniques carry greater risk (CKC more than LLETZ).[17,18] Consequentially there has been reflection within the community of colposcopists and gynaecological oncologists as how to balance the risk of under-treatment of CIN, with its potential to progress into cervical cancer, and an adverse impact on obstetric morbidity.[19] Due to the strong etiological link between persistent infection with high-risk (hr) human papillomavirus (HPV) types and the development of cervical cancer, presence or absence of the virus has been proposed as a test of treatment failure or cure, respectively. Several systematic reviews have provided consistent evidence that hrHPV testing is an accurate method to predict residual or recurrent CIN2+ after treatment of cervical pre-cancer. The question therefore needs to be asked as to the utility of positive excision margins to predict treatment failure, given the availability of post-treatment HPV testing as a potentially accurate test of cure.
In order to determine the clinical utility of the margin status, we conducted a systematic review and meta-analysis on the rate of incomplete excision and its association with treatment failure. We also compared the accuracy of the margin status with post-treatment HPV testing as a method to predict residual/recurrent cervical pre-cancer.

METHODS

Search strategy and selection criteria

Published references were retrieved through PUBMED-Medline, EMBASE and CENTRAL. The search strategy used in PUBMED is added in the Appendix (p3). Citations of previous systematic reviews related to the study questions were identified through www.scopus.com.[9,14,20,21] Reference lists of selected reports were also investigated.
A new search spanned the period 2006-2016, to articulate with study retrieval from earlier published meta-analyses. The last search was run on 01/02/2016. There was no language restriction.
Studies were deemed eligible for the assessment of the accuracy question if women (1) underwent treatment by excision of a histologically confirmed CIN2+ lesion, with verification of presence/absence of CIN at the resection margins, (2) were tested by cytology and/or and HPV assay between three and nine months after treatment, and (3) had subsequent follow-up of at least 18 months post-treatment including histological confirmation of the occurrence of CIN2+. Data on excision of CIN1+ lesions were included as well but only when severity of treated precancer was a covariate (to enlarge the spectrum of disease)

Assessed covariates were: the severity of the treated cervical lesions (CIN1, CIN2, CIN3 or AIS); the type of intervention (LLETZ, CKC or LC); year of publication, the localisation of neoplastic involvement of the resection margin (ecto-cervical, endo-cervical or both).

Procedures

Clinical questions and objectives

Our systematic review assessed the risk of therapeutic failure associated with the histological status of the margins of the tissue excised to treat cervical pre-cancer. Secondly, we estimated the accuracy of the margin status to predict occurrence of residual/recurrent high-grade CIN and compared it with post-treatment hrHPV testing. A third objective was the evaluation of the evidence to choose the proportion of involved resection margins as a quality indicator for good clinical practice in colposcopy and treatment.

PRISMA guidelines for reporting of meta-analysis were followed.[22] The PICOS components (Population-Intervention-Comparator-Outcome-Study type) of the clinical questions are elaborated in the Appendix.

Definitions

Pre-cancer was defined as CIN2+, including also cervical glandular intra-epithelial neoplasia or adenocarcinoma in situ (AIS).[23] The resection margins of the excision specimen were not graded but categorised as being positive/involved if pre-cancer was present at the cut resection margin or negative if margins were free of neoplasia[24,25]. The location of the margins was defined as ectocervical (ecto) covered by non-keratinizing, stratified squamous epithelium; endocervical (endo) covered by mucus secreting columnar epithelium; and both margins (ecto/endo).

Study selection and data extraction

Study selection and data extraction were performed by two authors (MA, FV, SGM) and possible conflicts were discussed until consensus or submitted to a senior gynaecologist for final judgement, as explained in the Appendix, p3.

Outcomes

Primary endpoints were the proportion of positive section margins and the occurrence of treatment failure associated with the marginal status. Treatment failure was defined as occurrence of residual or recurrent CIN2+ observed in studies with at least 18 months follow-up after excisional treatment. The prediction of this outcome was the object of the accuracy assessments. The quality of included diagnostic accuracy studies was scored according to the QUADAS tool.[26] A secondary endpoint was the distribution of the proportion of excisional treatments with involved margins, which according to quality indicators should be below 20%.

Statistical analysis

Proportions (occurrence of treatment failure overall and in women with positive or negative margins), were pooled using a random effects model for meta-analysis of binomial data, which involves Freeman-Tukey arcsine transformation to stabilize and normalise inter-study variability.[19] Relative risks (risk of treatment failure in women with versus women without involved resection margins) were pooled using a random effects model for ratios of proportions.[18] The percentage of total variation across studies due to heterogeneity was assessed by the I^2 index.[20] Forest plots were drawn showing the variation of the study estimates among all studies together with the pooled measure.[21] Occurrence of publication bias was explored by Egger's regression test for funnel-plot asymmetry.[27] A bivariate normal

model was used to pool sensitivity and specificity estimates.[22,23] Deeks' regression test, based on the regression of the log diagnostic odds ratio onto 1/(effective sample size), was used to assess small study effects (publication bias) in the meta-analyses of test accuracy.[28] All methods applied to pool outcomes were based on random effects models.
The utility of the assessment of resection margins to predict treatment outcome was evaluated using pretest-posttest probability (PPP) plots[29] (Appendix, p27). Analyses were performed in Stata 14.0 (College Station, TX, USA).

Role of the funding source

The funder had no role in the study design, data collection, data interpretation, or writing of the report. MA, FV, and SGM had access to the raw data.
The corresponding author had full access to all of the data and the final responsibility to submit for publication.

RESULTS

Selected studies

Ninety six studies, published between 1975 and 2016, were eligible for inclusion in the meta-analysis (
Figure **1**, Appendix p5-10), 65 of which had been included in the previous meta-analysis by Ghaem-Maghami et al[14], assessing the risk of treatment failure associated with incomplete excision.[30-96] In addition, 15 studies[97-111] could be identified from previous meta-analyses assessing the accuracy of post-treatment HPV and or cytology testing to detect residual/ recurrent CIN2+ and contained data on the margin status.[9,112,113] Sixteen new reports[15,114-128] were added which were not yet included in previous reviews. Three reports from case-controls were included in the meta-analyses of accuracy[97,101,129] but were excluded from meta-analyses of the rate of positive margins, occurrence of treatment failure or predictive value of the margin status for treatment failure. Overall, included studies enrolled 44,446 women treated for cervical pre-cancer.
For the accuracy of the margin status for the outcome of CIN2+ or CIN3+, 25 studies could be included (see
Figure **1**). Eighteen of them provided also data for the accuracy of post-treatment HPV testing, and could be used for computation of the relative accuracy (HPV vs margin status).

Quality of diagnostic accuracy studies assessed by QUADAS

The eighteen studies which evaluated the accuracy of margin status and post-treatment HPV testing, varied in quality and design and were generally scored as moderate to good (Appendix, p11). In one study, the timing of HPV testing was partly performed later than three to nine months post-treatment.[117] The most problematic design item was blinding of the outcome towards the tests: 44% of the studies (8/18) were scored as unblinded and in 28% (5/18) blinding was not clearly documented. Partial verification and differential verification were scored as problematic in 17% (3/18) and 28% (5/18), respectively.

Involvement of the resection margins

The overall proportion of incomplete excisions was 23.1% (95% CI=20.4-25.9%) (Table 1). The highest rate was observed with LLETZ excision (25.9%, 95% CI=22.3-29.6%), followed by CKC (20.2%, 95% CI=14.3-26.7%), with LC having the lowest proportion (17.8%, 95% CI=12.9-23.2%) (Figure 2). The rate of positive resection margins did not change over time for CKC and LC but decreased for LLETZ, but the slope was not statistically significant (Appendix, p12).

Seventeen studies distinguished which margins (ecto-, endocervical or both) were involved. Ectocervical margins were more frequently affected when pre-cancer was treated by LLETZ, whereas endocervical margins were more frequently affected when LC or LLETZ were used. LLETZ was associated with the highest frequency of involvement of both margins (Table 1, Appendix, p13).
The proportion of positive margins increased significantly by the severity of the treated lesion (p for between-group heterogeneity = 0.019). The proportion of incomplete treatment was 22.4% (95% CI=18.7-26.4%) for CIN1+, 22.9% (95% CI=19.1-26.9%) in CIN2+ and, 29.3% (95% CI=19.8-39.9%) for CIN3+ (Appendix, p14-15).

Treatment failure

Occurrence of treatment failure

In 21 studies with at least 18 months of follow-up, we found that residual/recurrent CIN2+ occurred in 6.6% (95% CI 4.9-8.4%) of women treated for CIN2+. Failure rates were heterogeneous (range: 1.4-18.4%, I^2>80%, p<0.01) and varied by treatment procedure (2% for CKC and LC and 7% for LLETZ) (Figure 3). Treated CIN3+ lesions were not more prone to therapeutic failure than treated CIN2+ lesions (p=0.94) (Appendix, p16).

Predictive value of margin status for the risk of residual/recurrent disease

The risk of post-treatment disease (CIN2+) for women with positive margins was on average 17.1% (95% CI: 12.7-22.1) and was higher after CKC (25.6%, 95% CI: 19.6-32.2%), and lower after LC (14.1%, 95% CI: 3.0-29.5%) or LLETZ (15.6%, 95% CI: 9.2-23.3%). The risk of CIN2+ for women with clear margins was 3.7% (95% CI: 2.5-5.1%) with no significant differences by treatment procedure. The relative risk for CIN2+ for women with involved versus clear margins was of 4.8 (95% CI: 3.2-7.2; p<0.001) (Appendix, p17). No evidence for publication bias was found (p for asymmetry regression test =0.70, see Appendix, p19).
The risk of residual/recurrent CIN2+ after excisional treatment was 7.2% (95% CI=0-23.6%] when only the ecto-cervical margin was involved, but this was more than doubled when either the endo-cervical or both margins were involved (risks of 16.3%, 5.9-29.9% and 18.9%, 95% CI: 0.0-62.9%, respectively) (Appendix, p18).

Accuracy of margin involvement and HPV testing to predict treatment failure

The sensitivity and specificity of the margin status to predict residual or recurrent CIN2+, pooled from 25 studies where women were treated for histologically confirmed CIN2+ was 55.8% (95% CI=45.8-65.5%) and 84.4% (95% CI: 79.5-88.4%), respectively (Appendix, p20). The pooled accuracy did not differ significantly by treatment procedure (between-group heterogeneity: p=0.18 for sensitivity, p=0.40 for specificity). hrHPV testing, performed in 18 of the 25 studies, showed a pooled sensitivity of 91.0% (95% CI: 82.3-95.5%) and a specificity of 83.8% (95% CI: 77.7-88.7%) (Appendix, p21). The margin status was 38% less sensitive (sensitivity ratio: 0.62, 95% CI: 0.53-0.72) but as specific (specificity ratio: 1.01, 95% CI: 0.97-1.06) compared to post-treatment hrHPV testing to predict residual/recurrent CIN2+ (Figure 4, Appendix, p22). Deeks' regression test for funnel plot asymmetry did not reveal small study effects (Appendix, p23).

Five studies were retrieved where accuracy data for the combination of the margin status and post-treatment HPV testing were available. The sensitivity and specificity of the two combined tests for prediction of treatment failure were 99.1% (95% CI 94.7-100%) and 57.6% (95% CI 47.4-67.5%), respectively, which was not more sensitive but significantly less specific (ratio=0.75, 95% CI 0.67-0.84) than HPV testing alone. The accuracy of HPV

testing was not significantly different in women with positive or negative margins (Appendix, p24-26).

Clinical utility of the margin status

The PPP plots (Figure 5) show that positive resection margins are associated with an average risk of post-treatment CIN2+ not reaching 20% and, in addition, negative resection margins are associated with CIN2+ risk exceeding 2%. However, a positive post-treatment hrHPV test increases the risk of treatment failure to 28%, whereas a negative hrHPV results decreases this risk 0.8%.

The stratification of the CIN2+ risk according to the joint margin and post-treatment HPV status identifies one group with intermediate probability of treatment failure (risk of 13% if margin negative/HPV positive), whereas this risk was 53% if both criteria were positive and below or equal to 1% if hrHPV negative, whatever the margin status (Appendix, p28.

Benchmark of 20% involved margins

The target of less than 20% positive resection margins was not achieved in 56% of included studies, and this proportion varied by treatment procedure: 35% for CKC, 46% for LC, 67% for LLETZ (Appendix, p30).

DISCUSSION

Summary of findings

Our meta-analysis shows that excisional treatment of cervical pre-cancer fails in on average seven percent of cases and confirms that incomplete removal of neoplastic tissue increases this risk about five times compared to women with CIN-free resection margins. Incomplete excision occurs in approximately one quarter of cases and varies by severity of the lesion and excisional technique. Our findings are in agreement with the systematic review conducted 10 years ago[14]. In our review we also assessed the accuracy of the margin status, which has not been systematically reviewed before. In spite of the significant association with treatment failure, the margin status is not an accurate test to predict the treatment outcome. Only 56% of women with residual or recurrent CIN2+ over a period of at least 18 months had margins involved, whereas 16% of women, considered as cured, showed positive resection margins. Eighteen studies also performed hrHPV DNA testing between three to nine months post-treatment, which was substantially more sensitive (91% vs. 56%) and similarly specific (84% vs 84%) compared to the margin status.

Clinical utility

Meta-analyses of diagnostic test accuracy do not answer the question whether a test is clinically useful in a given setting. The PPP plot, displaying the pre-test probability of disease against the post-test probabilities, allows a straightforward interpretation of the clinical utility of the two evaluated tests. The pretest risk of therapeutic failure was 6.6% and this risk rose to 28% for women with a positive post-treatment HPV test, exceeding the decision threshold accepted for referral, which is usually defined at risk of CIN2+ >20% (red zone in Figure 5).[29] Moreover, the CIN2+ risk dropped to 0.8% for hrHPV-negative women (<2%, generally accepted as sufficiently low to release the patient from further follow-up, green zone in Figure 5). On the contrary, knowledge of the margin status on its own did not allow clear definition of patient management (post-test CIN2+ risk <20% if margin-positive, and >2% if margin-negative). However, stratification of the risk, according to the different combinations

of the margin and post-treatment HPV status, could enable differentiating management decisions in agreement with particular patient characteristics.
A strategy based on HPV testing would refer about one fifth of women for further diagnosis/retreatment and three to five referrals would result in finding one residual/recurrent CIN2+. Combination of the marginal and post-treatment HPV status would refer almost halve of treated women, without significant better protection against treatment failure (Appendix, p29).

Proportion of complete excision as a quality criterion for good clinical practice
Certain scientific societies recommend gynaecologists to achieve 80% or more complete excisions as a criterion of good professional practice.[16] Our meta-analysis showed that in the majority of studies this benchmark is not reached, in particular when women were treated by LLETZ. The goal to achieve less than 20% of involved margins, may promote larger excisions, which may diminish the number of incomplete excision but which may also increase the risk of obstetrical harm.[18,19]

Influencing factors
The patient's age, the size of the lesion and the size of the excised cone and the skill of the performing clinician have all been suggested as important covariates that can affect the success of treatment, some of them having a direct link with the clearance of the excision margin. Several authors have shown more frequent margin involvement and a stronger association with recurrent disease in older women.[71,90,121,130,131] Some studies have also shown an association between risk of recurrence and cone size[15,51,132], whereas others have not[133]. Further studies have suggested that well-trained colposcopists have lower rates of positive margins[15,134,135], and in one study it was shown that this also translates into lower rates of residual/recurrent CIN2+.[15] The history of prior diagnosis and treatment of cervical lesions was another item that may determine therapeutic decisions and their outcomes. The higher proportion of positive margins after LLETZ might be explained by the higher rate of fragmented specimens and the diathermy effects that hampers the interpretation of the margin status that can be overcalled as positive in many cases.[104] The large inter-study heterogeneity in the margin positivity rate that was observed in our pooled analysis may be partly explained by the difference in tissue destruction observed from different treatment techniques. CKC is known to affect the margin interpretation the least[136], followed by LLETZ and then LC, which produces the greatest amount of thermal tissue artifact. [137] Studies were clinically heterogeneous with respect to design, timing/duration of follow-up visits and outcome assessment.
As shown previously, the accuracy of hrHPV testing did not show heterogeneity in the accuracy by test assay, when restricted to HC2 and validated PCR tests.[9] However, with more diverse HPV assays included, heterogeneity by test platform appeared. The literature consistently shows that HPV testing can be made considerably more specific by identifying the same HPV type in the excised cone or in pre-treatment specimens as in the post-treatment specimens.[106,117,127,138-140] However, certain studies report that type-specific HPV persistence is accompanied by a certain loss in sensitivity.[117,138] whereas other did not observe this.[106,141]

Weakness and strengths
Our meta-analysis included almost 100 studies with approximately 45,000 women. However, in spite of this large number of studies and subjects, confidence intervals around pooled estimates of test positivity, disease occurrence, accuracy and predictive values of the margin status were wide due to the large inter-study heterogeneity. The sensitivity of the margin status to predict treatment failure, in particular, varied over wide ranges (9-94%).[50,119] This

large heterogeneity suggests low reproducibility of the assessment of the resection margins and limits its use as a quality indicator of treatment performance. Because of the wide variability observed in published studies, no unpublished grey literature was looked for, since this could even increase bias and imprecision. We considered that only population-based screening registries with treatment and follow-up data would be useful to include as well, but we did not have access to such databases.

Our meta-analysis contributes only low quality evidence for the finding that LLETZ is less effective than CKC or LC (see Figure 3). Indeed comparisons are indirect with only two studies each contributing data for CKC and LC. More convincing evidence should be attributed to a Cochrane review of randomised trials which did not reveal significant differences in efficacy between treatment procedures.[8] An important warning for readers is to observe the spread of observations and not to focus only on the pooled estimate and its confidence interval which by averaging over many studies may look rather precise.[142,143]

In addition to updating previous reviews on margin status, our meta-analysis, bridged evidence towards a more promising test of cure by including a comparison with hrHPV testing. However, as in earlier reviews, we must acknowledge in our meta-analysis, the lumping over broad categories of treated CIN impeding clear assessment of the severity of pre-cancer (both at the level of treatment and outcome). Absence of residual/recurrent CIN2+ often was not verified histologically. We had to accept negative colposcopy and negative repeated cytology also as sufficient ascertainment for absence of CIN2+ after the treatment.

A general limitation inherent to meta-analyses of aggregated data extracted from published data is the limited number of potentially influential covariates that could be accounted for. We were unable to perform subgroup meta-analyses or to conduct meta-regression that incorporated influential factors such as age, lesion size and transformation zone types. To address this limitation, individual patient data meta-analysis should be set up, such as the COSPCC study, funded by *Institut National du Cancer*, which aims to quantify the correlation between cone depth and the subsequent risk of preterm delivery.[144]

Future research

A recently updated meta-analysis on the risk of adverse pregnancy outcomes in women who were previously treated for CIN included 71 studies[18], whereas ours, on treatment failure contained 96 studies. It is quite remarkable that none of the reports included in either of these meta-analyses addressed both outcomes (oncological and obstetrical safety) within one study.

All the authors of our meta-analysis strongly recommend to set up large linkage studies in countries with good population-based registries joining personal records from 1) centres specialised in diagnosis and treatment of cervical pre-cancer; 2) birth registries and 3) pathology registries capturing diagnosis of recurrent pre-cancer or cancer. Only evidence derived from such a large linkage study would provide the information enabling precise quantification of the balance between cure and harm.

The finding from our review showing that free margins are associated with higher cure rates, together with knowledge that older women have higher risks of recurrent CIN2+, may justify recommendations for more aggressive treatment at ages where reproductive safety is no longer an issue. Suspicion of invasive cancer, presence of glandular pre-cancer and unsatisfactory colposcopy are other indications where gynaecologists may decide to perform a large excision.

Conclusion

This meta-analysis confirms that the risk of residual/recurrent CIN2+ is significantly greater with positive excision margins however, hrHPV post-treatment predicts treatment failure

more accurately. Combined results of the margin and post-treatment HPV status maybe used to stratify risk and diversify management.
There is a need to balance the achievement of negative resection margins and the depth of cervical excision in women of childbearing age in light of the potential for increased PTB risk.

Author contributions:
Study concept and protocol: MA, CR, JG
Formulation of the clinical question and identification of PICOS components: MA, FV
Identification of studies: MA, FV, SGM
Elaboration of the data extraction forms: MA
Extraction of data: MA, FV, SGM
Statistical analyses: MA, FV
Writing of manuscript: MA, EM
Critical revision of manuscript: CR, FV, MK, MT, SGM, KUP, SL, CB, PN, JG, EM

Acknowledgements
We acknowledge Mss Victoria N. Nyaga for statistical support with the production of PPP plots and Koen De Visscher for the production of high quality eps files.

Conflicts of interest
KUP declares support from Beckton Dickinson and Roche Diagnostics.
All other authors did not declare a conflict of interest related to the study subject.

References

1. Ostor AG. Natural history of cervical intraepithelial neoplasia: a critical review. *Int J Gynecol Pathol* 1993;**12**: 186-92.

2. Melnikow J, Nuovo J, Willan AR, Chan BK, Howell LP. Natural History of cervical squamous intraepithelial lesions : a meta-analysis. *Obstet Gynecol* 1998;**92**: 727-35.

3. Holowaty P, Miller AB, Rohan T, To T. Natural History of Dysplasia of the Uterine Cervix. *J Natl Cancer Inst* 1999;**91**: 252-8.

4. Jarmulowicz MR, Jenkins D, Barton SE, et al. Cytological status and lesion size: a further dimension in cervical intraepithelial neoplasia. *BJOG* 1989;**96**: 1061-6.

5. Sherman ME, Wang SS, Tarone R, Rich L, Schiffman MA. Histopathologic extent of cervical intraepithelial neoplasia 3 lesions in the atypical squamous cells of undetermined significance low-grade squamous intraepithelial lesion trage study: implications for subject safety and lead-time bias. *Cancer Epidemiol Biomarkers Prev* 2003;**12**: 372-9.

6. McCredie MR, Sharples KJ, Paul C, et al. Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: a retrospective cohort study. *Lancet Oncol* 2008;**9**: 425-34.

7. Miller AB. Evaluation of the impact of screening for cancer of the cervix. *IARC Sci Publ* 1986; 149-60.

8. Martin-Hirsch PP, Paraskevaidis E, Bryant A, Dickinson HO, Keep SL. Surgery for cervical intraepithelial neoplasia. *Cochrane Database Syst Rev* 2010; CD001318.

9. Arbyn M, Ronco G, Anttila A, et al. Evidence regarding HPV testing in secondary prevention of cervical cancer. *Vaccine* 2012;**30 Suppl 5**: F88-F99.

10. Paraskevaidis E, Jandial L, Mann EM, Fisher PM, Kitchener HC. Pattern of treatment failure following laser for cervical intraepithelial neoplasia: implications for follow-up protocol. *Obstet Gynecol* 1991;**78**: 80-3.

11. Chew GK, Jandial L, Paraskevaidis E, Kitchener HC. Pattern of CIN recurrence following laser ablation treatment: long-term follow-up. *Int J Gynecol Cancer* 1999;**9**: 487-90.

12. Soutter WP, Sasieni P, Panoskaltsis T. Long-term risk of invasive cervical cancer after treatment of squamous cervical intraepithelial neoplasia. *Int J Cancer* 2006;**118**: 2048-55.

13. Kalliala I, Anttila A, Pukkala E, Nieminen P. Risk of cervical and other cancers after treatment of cervical intraepithelial neoplasia: retrospective cohort study. *BMJ* 2005;**331**: 1183-5.

14. Ghaem-Maghami S, Sagi S, Majeed G, Soutter WP. Incomplete excision of cervical intraepithelial neoplasia and risk of treatment failure: a meta-analysis. *Lancet Oncol* 2007;**8**: 985-93.

15. Ghaem-Maghami S, De-Silva D, Tipples M, et al. Determinants of success in treating cervical intraepithelial neoplasia. *BJOG* 2011;**118**: 679-84.

16. Moss EL, Arbyn M, Dollery E, et al. European Federation of Colposcopy Quality Standards Delphi Consultation. *Eur J Obstet Gynecol Reprod Biol* 2013;**170**: 255-8.

17. Arbyn M, Kyrgiou M, Simoens C, et al. Peri-natal mortality and other severe adverse pregnancy outcomes associated with treatment of cervical intraepithelial neoplasia: a meta-analysis. *BMJ* 2008;**337**: a1284.

18. Kyrgiou M, Athanasiou A, Paraskevaidi M, et al. Adverse obstetric outcomes after local treatment for cervical preinvasive and early invasive disease according to cone depth: systematic review and meta-analysis. *BMJ* 2016;**354**: i3633.

19. Sasieni P, Castanon A, Landy R, et al. Risk of preterm birth following surgical treatment for cervical disease: executive summary of a recent symposium. *BJOG* 2016;**129**: 1426-9.

20. Arbyn M, Sasieni P, Meijer CJLM, et al. Chapter 9: Clinical applications of HPV testing: a summary of meta-analyses. *Vaccine* 2006;**24 (SUPPL. 3)**: S78-S89.

21. Kocken M, Uijterwaal MH, de Vries AL, et al. High-risk human papillomavirus testing versus cytology in predicting post-treatment disease in women treated for high-grade cervical disease: A systematic review and meta-analysis. *Gynecol Oncol* 2012;**125**: 500-7.

22. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009;**151**: 264-9, W64.

23. Richart RM. Cervical intraepithelial neoplasia. *Pathol Annu* 1973;**8**: 301-23.

24. NHSCSP. Histopathology Reporting in Cervical Screening. Working party of the Royal College of Pahtologists and the NHS Cervical Screening Programme. Shefield: NHS Cancer Screening Programmes; 1999. Report No.:

25. Bulten J, Horvat R, Jordan J, et al. European guidelines for quality assurance in cervical histopathology. *Acta Oncol* 2011;**50**: 611-20.

26. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011;**155**: 529-36.

27. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**: 629-35.

28. Deeks JJ, Macaskill P, Irwig L. The performance of tests of publication bias and other sample size effects in systematic reviews of diagnostic test accuracy was assessed. *J Clin Epidemiol* 2005;**58**: 882-93.

29. Arbyn M, Xu L, Verdoodt F, et al. Genotyping for human papillomavirus types 16 and 18 in women with minor cervical lesions: a systematic review and meta-analysis. *Ann Intern Med* 2017;**166**: 118-27.

30. Ahlgren M, Ingemarsson I, Lindberg LG, Nordqvist RB. Conization as treatment of carcinoma in situ of the uterine cervix. *Obstet Gynecol* 1975;**46**: 135-9.

31. Bjerre B, Eliasson G, Linell F, Soderberg H, Sjoberg NO. Conization as only treatment of carcinoma in situ of the uterine cervix. *Am J Obstet Gynecol* 1976;**125**: 143-52.

32. Burghardt E, Holzer E. Treatment of carcinoma in situ: evaluation of 1609 cases. *Obstet Gynecol* 1980;**55**: 539-45.

33. Larsson G. Conization for cervical dysplasia and carcinoma in situ: long term follow-up of 1013 women. *Ann Chir Gynaecol* 1981;**70**: 79-85.

34. Grundsell H, Alm P, Larsson G. Cure rates after laser conization for early cervical neoplasia. *Ann Chir Gynaecol* 1983;**72**: 218-22.

35. Abdul-Karim FW, Nunez C. Cervical intraepithelial neoplasia after conization: a study of 522 consecutive cervical cones. *Obstet Gynecol* 1985;**65**: 77-81.

36. Demopoulos RI, Horowitz LF, Vamvakas EC. Endocervical gland involvement by cervical intraepithelial neoplasia grade III. Predictive value for residual and/or recurrent disease. *Cancer* 1991;**68**: 1932-6.

37. Moore EJ, Fitzpatrick CC, Coughlan BM, McKenna PJ. Cone biopsy: a review of 112 cases. *Ir Med J* 1992;**85**: 28-30.

38. Murdoch JB, Morgan PR, Lopes A, Monaghan JM. Histological incomplete excision of CIN after large loop excision of the transformation zone (LLETZ) merits careful follow up, not retreatment. *BJOG* 1992;**99**: 990-3.

39. Paterson-Brown S, Chappatte OA, Clark SK, et al. The significance of cone biopsy resection margins. *Gynecol Oncol* 1992;**46**: 182-5.

40. Vergote IB, Makar AP, Kjorstad KE. Laser excision of the transformation zone as treatment of cervical intraepithelial neoplasia with satisfactory colposcopy. *Gynecol Oncol* 1992;**44**: 235-9.

41. Hallam NF, West J, Harper C, et al. Large loop excision of the transformation zone (LLETZ) as an alternative to both local ablative and cone biopsy treatment: a series of 1000 patients. *J Gynecol Surg* 1993;**9**: 77-82.

42. Lopes A, Morgan P, Murdoch J, Piura B, Monaghan JM. The case for conservative management of "incomplete excision" of CIN after laser conization. *Gynecol Oncol* 1993;**49**: 247-9.

43. Shafi MI, Dunn JA, Buxton EJ, et al. Abnormal cervical cytology following large loop excision of the transformation zone: a case controlled study. *Br J Obstet Gynaecol* 1993;**100**: 145-8.

44. Spitzer M, Chernys AE, eltzer VL. The use of large-loop excision of the transformation zone in an inner-city population. *Obstet Gynecol* 1993;**82**: 731-5.

45. Vedel P, Jakobsen H, Kryger-Baggesen N, Rank FE. Five-year follow up of patients with cervical intra-epithelial neoplasia in the cone margins after conization. *Eur J Obstet Gynecol Reprod Biol* 1993;**50**: 71-6.

46. White CD. Management of residual squamous intraepithelial lesions of the cervix after conization. *W V Med J* 1993;**89**: 382-5.

47. Andersen ES, Pedersen B, Nielsen K. Laser conization: the results of treatment of cervical intraepithelial neoplasia. *Gynecol Oncol* 1994;**54**: 201-4.

48. Felix JC, Muderspach LI, Duggan BD, Roman LD. The significance of positive margins in loop electrosurgical cone biopsies. *Obstet Gynecol* 1994;**84**: 996-1000.

49. Goff BA, Rice LW, Fleischhacker DS, Abu-Jawdeh GM, Muntz HG. Large loop excision of the transformation zone in patients with exocervical squamous intraepithelial lesions. *Eur J Gynaecol Oncol* 1994;**15**: 257-62.

50. Guerra B, Guida G, Falco P, et al. Microcolposcopic topographic endocervical assessment before excisional treatment of cervical intraepithelial neoplasia. *Obstet Gynecol* 1996;**88**: 77-81.

51. Santos C, Galdos R, Alvarez M, et al. One-Session Management of Cervical Intraepithelial Neoplasia: A Solution for Developing Countries. A Prospective, Randomized Trial of LEEP versus Laser Excisional Conization. *Gynecol Oncol* 1996;**61**: 11-5.

52. Gardeil F, Barry-Walsh C, Prendiville W, Clinch J, Turner MJ. Persistent intraepithelial neoplasia after excision for cervical intraepithelial neoplasia grade III. *Obstet Gynecol* 1997;**89**: 419-22.

53. Hanau CA, Bibbo M. The case for cytologic follow-up after LEEP. *Acta Cytol* 1997;**41**: 731-6.

54. Mohamed-Noor K, Quinn MA, Tan J. Outcomes after cervical cold knife conization with complete and incomplete excision of abnormal epithelium: a review of 699 cases. *Gynecol Oncol* 1997;**67**: 34-8.

55. Skjeldestad FE, Hagen B, Lie AK, Isaksen C. Residual and recurrent disease after laser conization for cervical intraepithelial neoplasia. *Obstet Gynecol* 1997;**90**: 428-33.

56. Baldauf JJ, Dreyfus M, Ritter J, et al. Cytology and colposcopy after loop electrosurgical excision: implications for follow-up. *Obstet Gynecol* 1998;**92**: 124-30.

57. Bandieramonte G, Lomonico S, Quattrone P, et al. Laser conization assisted by crypt visualization for cervical intraepithelial neoplasia. *Obstet Gynecol* 1998;**91**: 263-9.

58. de Cabezon RH, Sala CV, Gomis SS, Lliso AR, Bellvert CG. Evaluation of cervical dysplasia treatment by large loop excision of the transformation zone (LLETZ). Does completeness of excision determine outcome? *Eur J Obstet Gynecol Reprod Biol* 1998;**78**: 83-9.

59. Hagen B, Skjeldestad FE, Bratt H, Tingulstad S, Lie AK. CO2 laser conization for cervical intraepithelial neoplasia grade II-III: complications and efficacy. *Acta Obstet Gynecol Scand* 1998;**77**: 558-63.

60. Hulman G, Pickles CJ, Gie CA, et al. Frequency of cervical intraepithelial neoplasia following large loop excision of the transformation zone. *J Clin Pathol* 1998;**51**: 375-7.

61. Robinson WR, Lund ED, Adams J. The predictive value of LEEP specimen margin status for residual/recurrent cervicalintraepithelial neoplasia. *Int J Gynecol Cancer* 1998;**8**: 109-12.

62. Bertelsen B, Tande T, Sandvei R, Hartveit F. Laser conization of cervical intraepithelial neoplasia grade 3: free resection margins indicative of lesion-free survival. *Acta Obstet Gynecol Scand* 1999;**78**: 54-9.

63. Bornstein J, Yaakov Z, Pascal B, et al. Decision-making in the colposcopy clinic--a critical analysis. *Eur J Obstet Gynecol Reprod Biol* 1999;**85**: 219-24.

64. Ioffe OB, Brooks SE, De Rezende RB, Silverberg SG. Artifact in cervical LLETZ specimens: correlation with follow-up. *Int J Gynecol Pathol* 1999;**18**: 115-21.

65. Livasy CA, Maygarden SJ, Rajaratnam CT, Novotny DB. Predictors of recurrent dysplasia after a cervical loop electrocautery excision procedure for CIN-3: a study of margin, endocervical gland, and quadrant involvement. *Mod Pathol* 1999;**12**: 233-8.

66. Murta EFC, Resende AV, Souza MAH, Adad SJ, Salum R. Importance of surgical margins in conization for cervical intraepithelial neoplasia grade III. *Arch Gynecol Obstet* 1999;**263**: 42-4.

67. Bar-Am A, Daniel Y, Ron IG, et al. Combined colposcopy, loop conization, and laser vaporization reduces recurrent abnormal cytology and residual disease in cervical dysplasia. *Gynecol Oncol* 2000;**78**: 47-51.

68. Dobbs SP, Asmussen T, Nunns D, et al. Does histological incomplete excision of cervical intraepithelial neoplasia following large loop excision of transformation zone increase recurrence rates? A six year cytological follow up. *BJOG* 2000;**107**: 1298-301.

69. Izumi T, Kyushima N, Genda T, et al. Margin clearance and HPV infection do not influence the cure rates of early neoplasia of the uterine cervix by laser conization. *Eur J Gynaecol Oncol* 2000;**21**: 251-4.

70. Zaitoun AM, McKee G, Coppen MJ, Thomas SM, Wilson PO. Completeness of excision and follow up cytology in patients treated with loop excision biopsy. *J Clin Pathol* 2000;**53**: 191-6.

71. Flannelly G, Bolger B, Fawzi H, De Lopes AB, Monaghan JM. Follow up after LLETZ: could schedules be modified according to risk of recurrence? *BJOG* 2001;**108**: 1025-30.

72. Gonzalez DIJr, Zahn CM, Retzloff MG, et al. Recurrence of dysplasia after loop electrosurgical excision procedures with long-term follow-up. *Am J Obstet Gynecol* 2001;**184**: 315-21.

73. Paraskevaidis E, Koliopoulos G, Malamou-Mitsi V, et al. Large loop excision of the transformation zone for treating cervical intraepithelial neoplasia: a 12-year experience. *Anticancer Res* 2001;**21**: 3097-9.

74. Stamatopoulos P, Kasapis M, Koliopoulos G, Paraskevaidis E. Outcomes of carbon dioxide laser conization for the treatment of cervical intraepithelial neoplasia grade III. *Clin Exp Obstet Gynecol* 2001;**28**: 243-5.

75. Bodner K, Bodner-Adler B, Wierrani F, et al. Is therapeutic conization sufficient to eliminate a high-risk HPV infection of the uterine cervix? A clinicopathological analysis. *Anticancer Res* 2002;**22**: 3733-6.

76. Milojkovic M. Residual and recurrent lesions after conization for cervical intraepithelial neoplasia grade 3. *Int J Gynecol Obstet* 2002;**76**: 49-53.

77. Reich O, Pickel H, Lahousen M, Tamussino K, Winter R. Cervical intraepithelial neoplasia III: long-term outcome after cold-knife conization with clear margins. *Obstet Gynecol* 2001;**97**: 428-30.

78. Reich O, Lahousen M, Pickel H, Tamussino K, Winter R. Cervical intraepithelial neoplasia III: long-term follow-up after cold-knife conization with involved margins. *Obstet Gynecol* 2002;**99**: 193-6.

79. Bretelle F, Agostini A, Rojat-Habib MC, et al. The role of frozen section examination of conisations in the management of women with cervical intraepithelial neoplasia. *BJOG* 2003;**110**: 364-70.

80. Houfflin Debarge V, Collinet P, Vinatier D, et al. Value of human papillomavirus testing after conization by loop electrosurgical excision for high-grade squamous intraepithelial lesions. *Gynecol Oncol* 2003;**90**: 587-92.

81. Johnson N, Khalili M, Hirschowitz L, Ralli F, Porter R. Predicting residual disease after excision of cervical dysplasia. *BJOG* 2003;**110**: 952-5.

82. Chao A, Lin CT, Hsueh S, et al. Usefulness of human papillomavirus testing in the follow-up of patients with high-grade cervical intraepithelial neoplasia after conization. *Am J Obstet Gynecol* 2004;**190**: 1046-51.

83. Lin H, Chang HY, Huang CC, ChangChien CC. Prediction of disease persistence after conization for microinvasive cervical carcinoma and cervical intraepithelial neoplasia grade 3. *Int J Gynecol Cancer* 2004;**14**: 311-6.

84. Maluf PJ, Adad SJ, Murta EF. Outcome after conization for cervical intraepithelial neoplasia grade III: relation with surgical margins, extension to the crypts and mitoses. *Tumori* 2004;**90**: 473-7.

85. Murta EF, Conti R, Rodovalho J, et al. Outcome after treatment of high-grade squamous intraepithelial lesions: relation between colposcopically directed biopsy, conization and cervical loop excision. *Eur J Gynaecol Oncol* 2004;**25**: 587-90.

86. Nagai N, Mukai K, Oshita T, Shiroyama Y, Ohama K. Human papillomavirus DNA status after loop excision for cervical intraepithelial neoplasia grade. *Int J Mol Med* 2004;**13**: 589-93.

87. Orbo A, Arnesen T, Arnes M, Straume B. Resection margins in conization as prognostic marker for relapse in high-grade dysplasia of the uterine cervix in northern Norway: a retrospective long-term follow-up material. *Gynecol Oncol* 2004;**93**: 479-83.

88. Skinner EN, Gehrig PA, Van LL. High-grade squamous intraepithelial lesions: abbreviating posttreatment surveillance. *Obstet Gynecol* 2004;**103**: 488-92.

89. Mazouni C, Porcu G, Haddad O, et al. Conservative treatment of cervical intraepithelial neoplasia using a cold-knife section technique. *Eur J Obstet Gynecol Reprod Biol* 2005;**121**: 86-93.

90. Alonso I, Torne A, Puig-Tintore LM, et al. Pre- and post-conization high-risk HPV testing predicts residual/recurrent disease in patients treated for CIN 2-3. *Gynecol Oncol* 2006;**103**: 631-6.

91. Bollmann M, Varnai AD, Griefingholt H, et al. Predicting treatment outcome in cervical diseases using liquid-based cytology, dynamic HPV genotyping and DNA cytometry. *Anticancer Res* 2006;**26**: 1439-46.

92. Lu CH, Liu FS, Kuo CJ, Chang CC, Ho ES. Prediction of persistence or recurrence after conization for cervical intraepithelial neoplasia III. *Obstet Gynecol* 2006;**107**: 830-5.

93. Mints M, Gaberi V, Andersson S. Miniconization procedure with C-LETZ conization electrode for treatment of cervical intraepithelial neoplasia: a Swedish study. *Acta Obstet Gynecol Scand* 2006;**85**: 218-23.

94. Ueda M, Ueki K, Kanemura M, et al. Diagnostic and therapeutic laser conization for cervical intraepithelial neoplasia. *Gynecol Oncol* 2006;**101**: 143-6.

95. Ueda M, Ueki K, Kanemura M, et al. Diagnostic and therapeutic laser conization for cervical intraepithelial neoplasia. *Gynecol Oncol* 2005.

96. Verguts J, Bronselaer B, Donders G, et al. Prediction of recurrence after treatment for high-grade cervical intraepithelial neoplasia: the role of human papillomavirus testing and age at conisation. *BJOG* 2006;**113**: 1303-7.

97. Chua KL, Hjerpe A. Human papillomavirus analysis as a prognostic marker following conization of the cervix uteri. *Gynecol Oncol* 1997;**66**: 108-13.

98. Jain S, Tseng CJ, Horng SG, Soong YK, Pao CC. Negative predictive value of human papillomavirus test following conization of the cervix uteri. *Gynecol Oncol* 2001;**82**: 177-80.

99. Kucera E, Sliutz G, Czerwenka K, et al. Is high-risk human papillomavirus infection associated with cervical intraepithelial neoplasia eliminated after conization by large-loop excision of the transformation zone? *Eur J Obstet Gynecol Reprod Biol* 2001;**100**: 72-6.

100. Lin CT, Tseng CJ, Lai CH, et al. Value of human papillomavirus deoxyribonucleic acid testing after conization in the prediction of residual disease in the subsequent hysterectomy specimen. *Am J Obstet Gynecol* 2001;**184**: 940-5.

101. Acladious NN, Sutton C, Mandal D, et al. Persistant human papillomavirus infection and smoking increase risk of failure of treatment of cervical intraepithelial neoplasia (CIN). *Int J Cancer* 2002;**98**: 435-9.

102. Hernadi Z, Szoke K, Sapy T, et al. Role of human papillomavirus (HPV) testing in the follow-up of patients after treatment for cervical precancerous lesions. *Eur J Obstet Gynecol Reprod Biol* 2005;**118**: 229-34.

103. Fambrini M, Penna C, Pieralli A, et al. CO2 laser cylindrical excision or standard re-conization for persistent-recurrent high-grade cervical intraepithelial neoplasia (HG-CIN) in women of fertile age. *Anticancer Res* 2008;**28**: 3871-5.

104. Aerssens A, Claeys P, Beerens E, et al. Prediction of recurrent disease by cytology and HPV testing after treatment of cervical intraepithelial neoplasia. *Cytopathology* 2009;**20**: 27-35.

105. Jeong NH, Lee NW, Kim HJ, Kim T, Lee KW. High-risk human papillomavirus testing for monitoring patients treated for high-grade cervical intraepithelial neoplasia. *J Obstet Gynaecol Res* 2009;**35**: 706-11.

106. Kang WD, Jeong OM, Kim SM, et al. Significance of human papillomavirus genotyping with high-grade cervical intraepithelial neoplasia treated by a loop electrosurgical excision procedure. *Am J Obstet Gynecol* 2010;**203**: 72-6.

107. Trope A, Jonassen CM, Sjoborg KD, et al. Role of high-risk human papillomavirus (HPV) mRNA testing in the prediction of residual disease after conisation for high-grade cervical intraepithelial neoplasia. *Gynecol Oncol* 2011;**123**: 157-62.

108. Ryu A, Nam K, Kwak J, Kim J, Jeon S. Early human papillomavirus testing predicts residual/ recurrent disease after LEEP. *J Gynecol Oncol* 2012;**23**: 217-25.

109. Torne A, Fuste P, Rodriguez-Carunchio L, et al. Intraoperative post-conisation human papillomavirus testing for early detection of treatment failure in patients with cervical intraepithelial neoplasia: a pilot study. *BJOG* 2013;**120**: 392-9.

110. Kong TW, Son JH, Chang SJ, et al. Value of endocervical margin and high-risk human papillomavirus status after conization for high-grade cervical intraepithelial neoplasia, adenocarcinoma in situ, and microinvasive carcinoma of the uterine cervix. *Gynecol Oncol* 2014;**135**: 468-73.

111. Zhao C, Hong W, Li Z, et al. Human Papillomavirus testing and cytologic/histopathologic test of cure□follow-up results after excisional treatment for high grade cervical intraepithelial neoplasia. *J Am Soc Cytopathol* 2014;**3**: 15-20.

112. Arbyn M, Paraskevaidis E, Martin-Hirsch P, Prendiville W, Dillner J. Clinical utility of HPV DNA detection: triage of minor cervical lesions, follow-up of women treated for high-grade CIN. An update of pooled evidence. *Gynecol Oncol* 2005;**99 (Suppl 3)**: 7-11.

113. Arbyn M. Surveillance after treatment of cervical precancer. EUROGIN-2015 Conference "HPV Infection and Related Cancers: Translating Research Innovations into Improved Practice". Sevilla (Spain) 2015.

114. Bae JH, Kim CJ, Park TC, Namkoong SE, Park JS. Persistence of human papillomavirus as a predictor for treatment failure after loop electrosurgical excision procedure. *Int J Gynecol Cancer* 2007.

115. Prato B, Ghelardi A, Gadducci A, et al. Correlation of recurrence rates and times with posttreatment human papillomavirus status in patients treated with loop electrosurgical excision procedure conization for cervical squamous intraepithelial lesions. *Int J Gynecol Cancer* 2008;**18**: 90-4.

116. Riethmuller D, Gabelle C, Ramanah R, et al. [Importance of human papillomavirus (HPV) screening in the follow-up after CIN2-3 treatment]. *J Gynecol Obstet Biol Reprod (Paris)* 2008;**37**: 329-37.

117. Brismar S, Johansson B, Borjesson M, Arbyn M, Andersson S. Follow-up after treatment of cervical intraepithelial neoplasia by HPV-genotyping. *Am J Obstet Gynecol* 2009;**201**: 17.e1-17.e8.

118. Park JY, Kim DY, Kim JH, et al. Human papillomavirus test after conization in predicting residual disease in subsequent hysterectomy specimens. *Obstet Gynecol* 2009;**114**: 87-92.

119. Gallwas J, Ditsch N, Hillemanns P, et al. The significance of HPV in the follow-up period after treatment for CIN. *Eur J Gynaecol Oncol* 2010;**31**: 27-30.

120. Ribaldone R, Boldorini R, Capuano A, et al. Role of HPV testing in the follow-up of women treated for cervical dysplasia. *Arch Gynecol Obstet* 2010;**282**: 193-7.

121. Ang C, Mukhopadhyay A, Burnley C, et al. Histological recurrence and depth of loop treatment of the cervix in women of reproductive age: incomplete excision versus adverse pregnancy outcome. *BJOG* 2011;**118**: 685-92.

122. Leguevaque P, Motton S, Decharme A, et al. Predictors of recurrence in high-grade cervical lesions and a plan of management. *Eur J Surg Oncol* 2011;**40**: 174-7.

123. Persson M, Brismar WS, Ljungblad L, et al. High-risk human papillomavirus E6/E7 mRNA and L1 DNA as markers of residual/recurrent cervical intraepithelial neoplasia. *Oncol Rep* 2012;**28**: 346-52.

124. Simoes RB, Campaner AB. Post-cervical conization outcomes in patients with high-grade intraepithelial lesions. *APMIS* 2013; 1-9.

125. Gosvig CF, Huusom LD, Deltour I, et al. Role of human papillomavirus testing and cytology in follow-up after conization. *Acta Obstet Gynecol Scand* 2015.

126. Herfs M, Somja J, Howitt B, et al. Unique recurrence patterns of cervical intraepithelial neoplasia after excision of the squamocolumnar junction. *Int J Cancer* 2015;**136**: 1043-52.

127. Kang WD, Kim SM. Human papillomavirus genotyping as a reliable prognostic marker of recurrence after loop electrosurgical excision procedure for high-grade cervical intraepithelial neoplasia (CIN2-3) especially in postmenopausal women. *Menopause* 2016;**23**: 81-6.

128. Wu J, Jia Y, Luo M, Duan Z. Analysis of Residual/Recurrent Disease and Its Risk Factors after Loop Electrosurgical Excision Procedure for High-Grade Cervical Intraepithelial Neoplasia. *Gynecol Obstet Invest* 2016;**81**: 296-301.

129. Paraskevaidis E, Koliopoulos G, Alamanos Y, et al. Human papillomavirus testing and the outcome of treatment for cervical intraepithelial neoplasia. *Obstet Gynecol* 2001;**98**: 833-6.

130. Paraskevaidis E, Kalantaridou SN, Paschopoulos M, et al. Factors affecting outcome after incomplete excision of cervical intraepithelial neoplasia. *Eur J Gynaecol Oncol* 2003;**24**: 541-3.

131. Gosvig CF, Huusom LD, Andersen KK, et al. Long-term follow-up of the risk for cervical intraepithelial neoplasia grade 2 or worse in HPV-negative women after conization. *Int J Cancer* 2015;**137**: 2927-33.

132. Phadnis SV, Atilade A, Young MP, Evans H, Walker PG. The volume perspective: a comparison of two excisional treatments for cervical intraepithelial neoplasia (laser versus LLETZ). *BJOG* 2010;**117**: 615-9.

133. Costa S, De Nuzzo M, Infante FE, et al. Disease persistence in patients with cervical intraepithelial neoplasia undergoing electrosurgical conization. *Gynecol Oncol* 2002;**85**: 119-24.

134. Ulrich D, Tamussino K, Petru E, Haas J, Reich O. Conization of the Uterine Cervix: Does the Level of Gynecologist's Training Predict Margin Status? *Int J Gynecol Pathol* 2012;**31**: 382-6.

135. Panna S, Luanratanakorn S. Positive margin prevalence and risk factors with cervical specimens obtained from loop electrosurgical excision procedures and cold knife conization. *Asian Pac J Cancer Prev* 2009;**10**: 637-40.

136. Miroshnichenko GG, Parva M, Holtz DO, Klemens JA, Dunton CJ. Interpretability of excisional biopsies of the cervix: cone biopsy and loop excision. *J Low Genit Tract Dis* 2009;**13**: 10-2.

137. Paraskevaidis E, Kitchener HC, Malamou-Mitsi V, Agnanti N, Lolis D. Thermal tissue damage following laser and large loop conization of the cervix. *Obstet Gynecol* 1994;**84**: 752-4.

138. Kreimer AR, Guido RS, Solomon D, et al. Human papillomavirus testing following loop electrosurgical excision procedure identifies women at risk for posttreatment cervical intraepithelial neoplasia grade 2 or 3 disease. *Cancer Epidemiol Biomarkers Prev* 2006;**15**: 908-14.

139. Heymans J, Benoy IH, Poppe W, Depuydt CE. Type-specific HPV geno-typing improves detection of recurrent high-grade cervical neoplasia after conisation. *Int J Cancer* 2011;**129**: 903-9.

140. Venturoli S, Ambretti S, Cricca M, et al. Correlation of high-risk human papillomavirus genotypes persistence and risk of residual or recurrent cervical disease after surgical treatment. *J Med Virol* 2008;**80**: 1434-40.

141. Heymans J, Benoy IH, Poppe W, Depuydt CE. Type-specific HPV geno-typing improves detection of recurrent high-grade cervical neoplasia after conisation. *Int J Cancer* 2011;**129**: 903-9.

142. Greenland S. Can meta-analysis be salvaged? *Am J Epidemiol* 1994;**140**: 783-7.

143. Bailar JC. The promise and problems of meta-analysis. *N Engl J Med* 1997;**337**: 559-61.

144. Arbyn M, Simoens C, Goffin F, Noehr B, Bruinsma F. Treatment of cervical cancer precursors: influence of age, completeness of excision and cone depth on therapeutic failure, and on adverse obstetric outcomes. *BJOG* 2011;**118**: 1274-5.

145. Arbyn M. Surveillance after treatment of cervical precancer: EUROGIN-2015 Conference "HPV Infection and Related Cancers: Translating Research Innovations into Improved Practice. Sevilla (Spain) 2015.

Table 1. Pooled proportions of incomplete excisions by treatment procedure and location of the margin involvement.

Margin involvement	CKC		LCE		LLETZ		Mixed		Total	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Unspecified	17	20.2 (14.3-26.7)	13	17.8 (12.9-23.2)	42	25.9 (22.3-29.6)	22	23.7 (18.9-28.9)	94	23.1 (20.4-25.9)
Ectocervical only	5	6.1 (3.1-10.0)	1	6.8 (3.2-14.1)	9	13.0 (7.8-19.2)	2	12.7 (11.5-14.0)	17	10.4 (7.1-14.2)
Endocervical only	5	8.4 (4.0-14.2)	1	19.3 (12.4-28.8)	9	13.4 (10.8-16.3)	3	7.6 (6.6-8.7)	18	11.0 (8.2-14.2)
Ecto- & endo-cervical	3	0.9 (0.4-1.6)	1	1.1 (0.2-6.2)	3	6.1 (4.1-8.4)	1	4.5 (3.7-5.4)	7	2.9 (1.1-5.5)

N, number of studies; CI, confidence interval; CKC, cold-knife conisation; LC, laser conisation; LLETZ, large loop excision of the transformation zone.

Figures

Figure 1. Flow chart explaining the selection of studies included in the meta-analysis on the resection margins and associated risk of treatment failure (recurrent/residual CIN2+) and in the meta-analyses on diagnostic test accuracy.

Figure 2. Proportion of cones with positive resection margins, by treatment procedure: cold knife conisation (CKC) and laser conisation (LC), at left, and large loop excision of the transformation zone (LLETZ), at right.

Figure 3. Occurrence of treatment failure (residual or recurrent CIN2+) among women treated for cervical pre-cancer (CIN2 or CIN3), observed in cohort studies with at least 18 months of follow-up.

CKC, cold-knife conisation; LC, laser conisation; LLETZ, large loop excision of the transformation zone.

Figure 4. Summary ROC plot of the sensitivity as a function of the specificity for residual or recurrent CIN2+ of the marginal status (red) and high-risk human papillomavirus (hrHPV) DNA testing (blue), among women treated for CIN2+.

ROC: receiver operation characteristic; CIN2+: cervical intra-epithelial neoplasia of grade II or worse.

Figure 5. Pretest and posttest probabilities of residual or recurrent CIN2+ after treatment of CIN2+, assessed by the histological assessment of the resection margins (left) or by hrHPV testing at 3-9 months post-treatment (right).

Benchmarks are defined at risk levels of 2% and 20%. When post-test risk >20% (red zone), referral to colposcopy is warranted, when post-test risk <2% (green zone), release to the routine screening schedule is considered acceptable. When risk of CIN2+ is between 2 and 20%, further surveillance is suggested[29] (see Suppl. Material, chapter 20).