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Incomplete excision of cervical precancer as a predictor of treatment failure: a systematic review and meta-analysis

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Summary

Background Incomplete excision of cervical precancer is associated with therapeutic failure and is therefore considered as a quality indicator of clinical practice. Conversely, the risk of preterm birth is reported to correlate with size of cervical excision and therefore balancing the risk of adequate treatment with iatrogenic harm is challenging. We reviewed the literature with an aim to reveal whether incomplete excision, reflected by presence of precancerous tissue at the section margins, or post-treatment HPV testing are accurate predictors of treatment failure.

Methods We did a systematic review and meta-analysis to assess the risk of therapeutic failure associated with the histological status of the margins of the tissue excised to treat cervical precancer. We estimated the accuracy of the margin status to predict occurrence of residual or recurrent high-grade cervical intraepithelial neoplasia of grade two or worse (CIN2+) and compared it with post-treatment high-risk human papillomavirus (HPV) testing. We searched for published systematic reviews and new references from PubMed-MEDLINE, Embase, and CENTRAL and did also a new search spanning the period Jan 1, 1975, until Feb 1, 2016. Studies were eligible if women underwent treatment by excision of a histologically confirmed CIN2+ lesion, with verification of presence or absence of CIN at the resection margins; were tested by cytology or HPV assay between 3 months and 9 months after treatment; and had subsequent follow-up of at least 18 months post-treatment including histological confirmation of the occurrence of CIN2+. Primary endpoints were the proportion of positive section margins and the occurrence of treatment failure associated with the marginal status, in which treatment failure was defined as occurrence of residual or recurrent CIN2+. Information about positive resection margins and subsequent treatment failure was pooled using procedures for meta-analysis of binomial data and analysed using random-effects models.

Findings 97 studies were eligible for inclusion in the meta-analysis and included 44 446 women treated for cervical precancer. The proportion of positive margins was 23·1% (95% CI 20·4–25·9) overall and varied by treatment procedure (ranging from 17·8% [12·9–23·2] for laser conisation to 25·9% [22·3–29·6] for large loop excision of the transformation zone) and increased by the severity of the treated lesion. The overall risk of residual or recurrent CIN2+ was 6·6% (95% CI 4·9–8·4) and was increased with positive compared with negative resection margins (relative risk 4·8, 95% CI 3·2–7·2). The pooled sensitivity and specificity to predict residual or recurrent CIN2+ was 55·8% (95% CI 45·8–65·5) and 84·4% (79·5–88·4), respectively, for the margin status, and 91·0% (82·3–95·5) and 83·8% (77·7–88·7), respectively, for high-risk HPV testing. A negative high-risk HPV 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 or recurrent CIN2+ is significantly greater with involved margins on excisional treatment; however, high-risk HPV post-treatment predicts treatment failure more accurately than margin status.

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Introduction

In clinical medicine, finding a balance between therapeutic effectiveness and iatrogenic harm is often challenging. The occurrence of cervical cancer is preceded by premalignant 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 a 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 cervical cancer can be avoided.[7]

The most commonly used treatment modality for CIN is an excisional biopsy: large loop excision of the transformation zone or loop electrosurgical excision procedure, laser conisation, or cold-knife conisation.[8] The primary advantage of excisional compared with 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 about 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% and 18%,[9] and the majority of these cases occur within 2 years after primary treatment.[10,11] However, all treated women are still at increased risk for subsequent invasive cervical cancer compared with the

Research in context

Evidence before this study

We searched PubMed MEDLINE, Embase, and CENTRAL, 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. We also searched 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. The search was not restricted for start year and included 2016 as end year and there were no language restrictions. A meta-analysis published 10 years ago concluded that the average risk of treatment failure (residual or recurrent cervical intraepithelial neoplasia grade 2 or worse [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 previous excisional treatment of cervical precancer 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 human papillomavirus (HPV) testing was an accurate method to predict residual or recurrent CIN2+, with a pooled sensitivity of 93% and specificity of 81%.

Added value of this study

This systematic review updates and extends previous meta-analyses about the oncological outcomes of surgical treatment of precursor lesions of cervical cancer, and adds new meta-analyses not previously done: accuracy of the margin status to predict treatment failure and the relative accuracy of post-treatment HPV testing compared with the margin status. Three teams of authors, who did the previous reviews, have now joined forces and bring a common message to clinicians who treat CIN. The current meta-analysis confirms findings of previous reviews regarding increased risk of residual CIN+ when margins are positive. However, our review also 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 evidence

Pretest–post-test probability plots show that post-treatment HPV testing is a more sensitive predictor of treatment outcome than margin involvement. Knowledge of the margin status, in general, does not provide sufficient accurate information to define post-treatment assessment. We acknowledge the absence of studies assessing both the oncological and obstetrical issues of cervical precancer therapy and that research is needed that targets both outcomes.

general population for at least the following 10 years.[12,13] Identification of an accurate indicator that can identify women at increased risk of recurrent CIN or future malignancy after treatment for cervical precancer could enable tailored management according to each woman's individual risk, thereby avoiding overtreatment 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 80%, is viewed as a quality indicator for good clinical practice for colposcopists.[16]

However, concern has been growing about the effects of cervical excision on the integrity of the cervix and specifically its ability to function during pregnancy, potentially resulting in preterm birth and adverse neonatal outcomes. Meta-analyses have identified that the depth of excision is associated with the risk of preterm birth and that some techniques carry a particularly increased risk (cold-knife conisation more than large loop excision of the transformation zone).[17,18] Consequently, the community of colposcopists and gynaecological oncologists are reflecting on how to balance the risk of undertreatment of CIN, with its potential to progress into cervical cancer, and potential adverse effects on obstetric morbidity.[19] Because of the strong causal link between persistent infection with high-risk 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 high-risk HPV testing is an accurate method to predict residual or recurrent CIN2+ after treatment of cervical precancer. 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.

To determine the clinical utility of the margin status, we did 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 or recurrent high-grade CIN (cervical precancer). Additionally, we evaluated the evidence to choose the proportion of involved resection margins as a quality indicator for good clinical practice in colposcopy and treatment.

Methods

Search strategy and selection criteria

We searched for published reviews and new references from Pubmed MEDLINE, Embase, and CENTRAL spanning the period Jan 1, 1975, to Feb 1, 2016. References already included in published reviews were extracted, whereas new references not yet included were investigated de novo. The applied search strings are in the appendix (p 3). Citations of previous systematic reviews associated with the study questions were identified through Scopus.[9,14,20,21] Reference lists of selected reports were also investigated manually.

For this systematic review and meta-analysis, we followed PRISMA guidelines for reporting of meta-analyses.[22] The Population-Intervention-Comparator-Outcome-Study type (PICOS) components of the clinical questions are described in the appendix (p 4).

Studies were deemed eligible for the assessment of the accuracy question if women underwent treatment by excision of a histologically confirmed CIN2+ lesion, with verification of presence or absence of CIN at the resection margins; were tested by cytology or HPV assay between 3 months and 9 months after treatment; and had subsequent follow-up of at least 18 months post treatment including histological confirmation of the occurrence of CIN2+. Data for excision of CIN1+ lesions were also included 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 adenocarcinoma in situ); the type of intervention (large loop excision of the transformation zone, laser conisation, or cold-knife conisation); year of publication; and the localisation of neoplastic involvement of the resection margin (ectocervical, endocervical, or both).

Precancer was defined as CIN2+, including also cervical glandular intraepithelial neoplasia or adenocarcinoma in situ.[23] The resection margins of the excision specimen were not graded but categorised as being positive or involved if precancer 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 if covered by non-keratinising, stratified squamous epithelium; endocervical if covered by mucus secreting columnar epithelium; or both if the margins were covered by both types of epithelia.

Data extraction and checking

Study selection and data extraction regarding margin status and association with treatment failure in studies published up until 31 Dec, 2006, was done in parallel by two co-authors (SS and S-GM) of the 2007 meta-analysis by Ghaem-Maghami and colleagues;[14] data were checked and possible conflicts were resolved by SG-M and PWS. Study selection and data extraction for more recent reports published in 2006–16 regarding the same question, as well as for the new accuracy questions (section margins and post-treatment HPV testing), were done by FV and MA. Conflicts were resolved by discussion, and if necessary were submitted to CWER for final judgment.

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+ recorded in studies with at least 18 months' follow-up after excisional treatment. The prediction of this outcome was the object of the accuracy assessments (section margins and post-treatment HPV testing). 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 defined by the European Federation for Colposcopy, should be less than 20%.[16]

See Online for appendix

Statistical analysis

We pooled proportions (occurrence of treatment failure overall and in women with positive or negative margins) using a random-effects model for meta-analysis of binomial data, which involves Freeman-Tukey arcsine transformation to stabilise and normalise inter-study variability.[19] We pooled relative risks (risk of treatment failure in women with involved resection margins *vs* in women without) using a random-effects model for ratios of proportions.[18] We assessed the percentage of total variation across studies due to heterogeneity by the I^2 index.[20] We drew forest plots showing the variation of

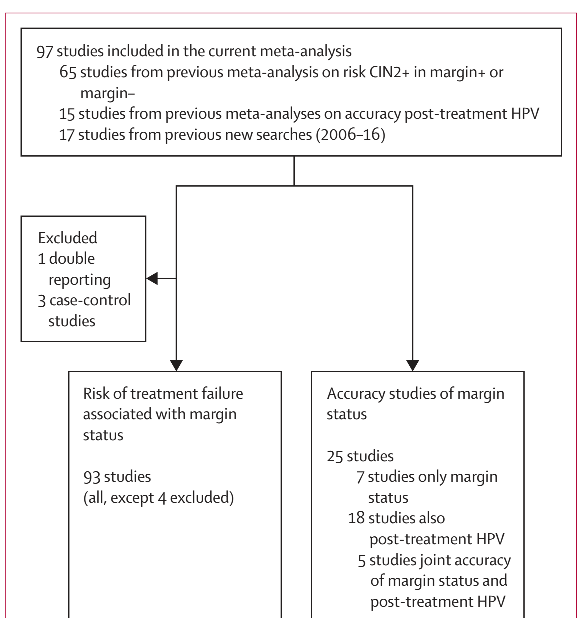

Figure 1: **Study selection**
CIN2+=cervical intraepithelial neoplasia of grade 2 or worse. HPV=human papillomavirus.

	Country	Treatment procedure	Reference standard	Margins	Mean follow-up (months)	Maximum follow-up (months)	Treated disease	Residual or recurrent disease	Patients, n
Ahlgren et al (1975)[30]	Sweden	CKC	Histology	Ecto or endo	ND	60	Cervical cancer	CIN1+, CIN2+	303
Bjerre et al (1976)[31]	Sweden	CKC	Histology or cytology	Ecto or endo	ND	60	ND	CIN1+, CIN2+	1340
Burghardt et al (1980)[32]	Austria	Mixed	Histology or cytology	Ecto or endo	ND	ND	Cervical cancer	CIN2+	1012
Larsson (1981)[33]	Sweden	CKC	Histology	Ecto or endo	ND	204	ND	CIN1+, CIN2+	726
Grundsell et al (1983)[34]	Sweden	LC	Histology or cytology	Ecto or endo	ND	24	CIN1+	CIN1+	294
Abdul-Karim et al (1985)[35]	USA	Mixed	Histology or cytology	Ecto or endo	ND	ND	ND	CIN1+	427
Demopoulos et al (1991)[36]	USA	CKC	Histology or cytology	Ecto or endo	44	ND	CIN3+	CIN1+, CIN2+	341
Moore et al (1992)[37]	Ireland	CKC	Histology	Ecto or endo	ND	ND	ND	CIN1+	112
Murdoch et al (1992)[38]	UK	Mixed	Histology	Ecto or endo	ND	3	CIN1+	CIN1+	565
Paterson-Brown et al (1992)[39]	UK	CKC	Histology or cytology	Ecto or endo	12	12	ND	CIN1+	273
Vergote et al (1992)[40]	Norway	LC	Histology	Ecto or endo	0	59	CIN1+	CIN1+, CIN2+	98
Hallam et al (1993)[41]	UK	LLETZ	Cytology	Ecto or endo	23	60	CIN1+	CIN1+, CIN2+	879
Lopes et al (1993)[42]	UK	LC	Cytology	Ecto or endo	38	ND	CIN1+	CIN1+	307
Shafi et al (1993)[43]	UK	LLETZ	Histology or cytology	Ecto or endo	ND	24	ND	CIN1+	153
Spitzer et al (1993)[44]	USA	LLETZ	Histology or cytology	Ecto or endo	11	26	CIN1+	CIN1+	172
Vedel et al (1993)[45]	Denmark	CKC	Histology	Ecto or endo	ND	60	CIN1+	CIN1+	385
White (1993)[46]	USA	CKC	Cytology	Ecto or endo	ND	12	CIN1+	CIN1+, CIN2+	149
Andersen et al (1994)[47]	Denmark	LC	Histology	Ecto or endo	70	ND	CIN1+	CIN1+	473
Felix et al (1994)[48]	USA	LLETZ	Histology	Ecto or endo	ND	12	CIN2+	CIN1+	57
Goff et al (1994)[49]	USA	LLETZ	Histology	Ecto or endo	ND	3	CIN1+	CIN1+	102
Guerra et al (1996)[50]	Italy	Mixed	Histology	Ecto or endo	ND	79	CIN2+	CIN1+, CIN2+	330
Santos et al (1996)[51]	Peru	Mixed	Histology or cytology	Ecto or endo	28	ND	CIN1+	CIN1+	289
Chua and Hjerpe (1997)[97]	Sweden	LC	Histology	Ecto or endo	46	ND	CIN3+	CIN2+	433
Gardeil (1997)[52]	Ireland	LLETZ	Histology	Ecto or endo	ND	24	CIN3+	CIN1+	204
Hanau and Bibbo (1997)[53]	USA	LLETZ	Cytology	Ecto or endo	11	28	CIN1+	CIN1+	87
Mohamed-Noor et al (1997)[54]	Australia	CKC	Histology	Ecto or endo, ecto, endo, ecto and endo	62	252	CIN1+	CIN1+	626
Skjeldestad et al (1997)[55]	Norway	LC	Histology or cytology	Ecto or endo	ND	120	CIN2+	CIN1+	1060
Baldauf et al (1998)[56]	France	LLETZ	Histology	Ecto or endo	39	68	CIN1+	CIN1+	267
Bandieramonte et al (1998)[57]	Italy	LC	Histology	Ecto or endo	ND	92	CIN2+	CIN1+, CIN2+	144
de Cabezon et al (1998)[58]	Spain	LLETZ	Histology	Ecto or endo	ND	2	CIN1+	CIN1+	70
Hagen et al (1998)[59]*	Norway	LC	Histology or cytology	Endo, ecto	NA	12	CIN2+	CIN1+	1053
Hulman et al (1998)[60]	UK	LLETZ	Histology	Ecto or endo	ND	42	CIN1+ CIN2+ CIN3+	CIN1+	669
Robinson et al (1998)[61]	USA	LLETZ	Histology	Ecto or endo	13	36	CIN1+	CIN1+	122
Bertelsen et al (1999)[62]	Norway	LC	Histology or cytology	Ecto or endo	113	174	CIN3+	CIN1+	561
Bornstein et al (1999)[63]	Israel	Mixed	Histology	Ecto or endo	ND	12	CIN2+	CIN1+	74
Ioffe et al (1999)[64]	USA	Mixed	Histology or cytology	Ecto or endo	ND	40	CIN1+	CIN1+	100
Livasy et al (1999)[65]	USA	LLETZ	Histology or cytology	Ecto or endo	20	ND	CIN3+	CIN1+, CIN2+	200
Murta et al (1999)[66]	Brazil	CKC	Histology	Ecto or endo	32	168	CIN3+	CIN1+, CIN2+	131
Bar-Am et al (2000)[67]	Israel	LLETZ, mixed	Cytology	Ecto or endo	59	118	CIN2+	CIN1+	137
Dobbs (2000)[68]	UK	LLETZ	Histology	Ecto or endo, ecto, endo	73	95	ND	CIN1+, CIN2+	321
Izumi et al (2000)[69]	Japan	LC	Histology	Ecto or endo	ND	60	CIN1+	CIN1+, CIN2+	72
Zaitoun et al (2000)[70]	UK	LLETZ	Cytology	Ecto or endo	54	120	CIN1+ CIN2+	CIN1+	1411
Flannelly et al (2001)[71]	UK	LLETZ	Histology	Ecto or endo, Ecto, Endo, Ecto and endo	35	85	CIN1+	CIN1+	2799
Gonzalez et al (2001)[72]	USA	LLETZ	Histology or cytology	Ecto or endo	24	59	CIN1+	CIN1+, CIN2+	161
Jain et al (2001)[97]	Taiwan	LLETZ	Histology	Ecto or endo	2	ND	CIN3+	CIN1+	79
Kucera et al (2001)[98]	Austria	LLETZ	Histology	Ecto or endo	12	ND	CIN1+	CIN1+	142

(Table 1 continues on next page)

	Country	Treatment procedure	Reference standard	Margins	Mean follow-up (months)	Maximum follow-up (months)	Treated disease	Residual or recurrent disease	Patients, n
(Continued from previous page)									
Lin et al (2001)[99]	Taiwan	Mixed	Histology	Ecto or endo	2	ND	CIN3+	CIN1+	75
Paraskevaidis et al (2001)[73]†	UK	LLETZ	Histology/ Cytology	Ecto or endo	68	ND	CIN1+	CIN1+	845
Stamatopoulos et al (2001)[74]	Greece	LC	Histology	Ecto or endo	ND	24	CIN3+	CIN1+	153
Acladious et al (2002)[100]	UK	Mixed	Histology	Ecto or endo	24	ND	CIN1+	CIN1+	153
Bodner et al (2002)[75]	Austria	LLETZ	Histology	Ecto or endo	24	ND	CIN2+	CIN1+	37
Milojkovic (2002)[76]	Croatia	CKC	Histology	Ecto or endo	ND	36	CIN3+	CIN1+	934
Reich et al (2001)[77]; Reich et al (2002)[78]	Austria	CKC	Histology	Ecto, endo, ecto and endo	228	360	CIN3+	CIN2+	4807
Bretelle et al (2003)[79]	France	Mixed	Histology	Endo	ND	12	ND	CIN1+, CIN2+	189
Houfflin et al (2003)[80]	France	LLETZ	Histology or cytology	Ecto or endo	18	ND	CIN2+	CIN1+	205
Johnson et al (2003)[81]	UK	LLETZ	Cytology	Ecto or endo, ecto, endo	ND	30	CIN1+	CIN1+	682
Chao et al (2004)[82]	China	Mixed	Histology or cytology	Ecto or endo	16	42	CIN2+	CIN1+, CIN2+	765
Lin et al (2004)[83]	Taiwan	Mixed	Histology	Ecto or endo	ND	ND	ND	CIN1+	211
Maluf et al (2004)[84]	Brazil	CKC	Histology	Ecto or endo	5	ND	CIN3+	CIN1+, CIN2+	58
Murta et al (2004)[85]	Brazil	CKC	Histology	Ecto or endo	30	80	ND	CIN1+	145
Nagai et al (2004)[86]	Japan	LLETZ	Histology	Ecto or endo, ecto, endo	48	91	CIN3+	CIN2+	143
Orbo et al (2004)[87]	Norway	CKC,LC, mixed	Histology	Ecto or endo, ecto, endo, ecto and endo	ND	276	CIN2+	CIN1+, CIN2+	500
Skinner et al (2004)[88]	USA	LLETZ	Histology	Ecto or endo, ecto, endo	24	ND	CIN2+	CIN1+, CIN2+	456
Hernadi et al (2005)[101]	Israel	Mixed	Histology	Ecto or endo	6	24	ND	CIN1+	61
Mazouni et al (2005)[89]	France	CKC	Histology	Ecto or endo, ecto	62	157	CIN1+	CIN1+	460
Alonso et al (2006)[90]	Spain	LLETZ	Histology	Ecto or endo, ecto, endo	20	66	CIN2+	CIN1+, CIN2+	201
Bollmann et al (2006)[91]	Germany	Mixed	Cytology	Ecto or endo	ND	24	CIN2+	CIN1+, CIN2+	147
Lu et al (2006)[92]	China	LLETZ	Histology	Ecto or endo, ecto, endo	ND	ND	CIN2+	CIN1+	449
Mints et al (2006)[93]	Sweden	LLETZ	Cytology	Ecto or endo	6	ND	CIN1+	CIN1+	148
Ueda et al (2006)[94]	Japan	LC	Cytology	Ecto or endo	68	252	CIN1+	CIN1+	1874
Verguts et al (2006)[95]	Belgium	LLETZ	Histology	Ecto or endo	24	ND	CIN2+	CIN1+, CIN2+	72
Bae et al (2007)[113]	South Korea	LLETZ	Histology	Ecto or endo	14	24	CIN2+	CIN1+	114
Fambrini et al (2008)[102]	Italy	LC	Histology	Ecto or endo	25	30	CIN2+	CIN2	52
Prato et al (2008)[114]	Italy	LLETZ	Histology	Ecto or endo	24	ND	CIN2+	CIN1+	115
Riethmuller et al (2008)[115]	France	LC	Histology	Ecto or endo	23	ND	CIN2+	CIN1+	386
Aerssens et al (2009)[103]	Belgium and Nicaragua	LLETZ	Histology	Ecto or endo	22	32	CIN2+	CIN2+	122
Brismar et al (2009)[116]	Sweden	LLETZ	Histology	Ecto or endo	39	115	CIN2+ CIN1+	CIN2+, CIN1+	85
Fuste et al (2009)[117]	Spain	LLETZ	Histology	Ecto or endo	18	24	CIN2+	CIN1+	105
Jeong et al (2009)[104]	South Korea	Mixed	Histology	Ecto or endo	24	ND	CIN2+	CIN1+	95
Park et al (2009)[118]	South Korea	Mixed	Histology	Ecto or endo	24	57	CIN1+	CIN1+	243
Gallwas et al (2010)[119]	Germany	Mixed	Histology	Ecto or endo	21	76	CIN2+	CIN2+	107
Kang et al (2010)[105]	S-Korea	LLETZ	Histology	Ecto or endo	24	ND	CIN2+	CIN2+	672
Ribaldone et al (2010)[120]	Italy	LLETZ	Histology	Ecto or endo	36	ND	CIN2+	CIN1+	78
Ang et al (2011)[121]	UK	LLETZ	Histology	Ecto, endo, ecto and endo	77	132	CIN2+	CIN2+	1558
Ghaem-Maghami et al (2011)[15]	UK	Mixed	Histology or cytology	Ecto or endo, ecto, endo, ecto and endo	55	93	CIN1+	CIN2+	2455
Leguevaque et al (2011)[122]	France	Mixed	Histology	Ecto or endo	73	ND	CIN2+	CIN1+	352

(Table 1 continues on next page)

	Country	Treatment procedure	Reference standard	Margins	Mean follow-up (months)	Maximum follow-up (months)	Treated disease	Residual or recurrent disease	Patients, n
(Continued from previous page)									
Trope et al (2011)[106]	Norway	Mixed	Histology	Ecto or endo	ND	18	CIN2+	CIN2+	344
Persson et al (2012)[123]	Sweden	Mixed	Histology or cytology	Ecto or endo	44	184	CIN1+	CIN1+, CIN2+	141
Ryu et al (2012)[107]	S-Korea	LLETZ	Histology	Ecto or endo	25	60	CIN1+	CIN2+	183
Simões and Campaner (2013)[124]	Brazil	Mixed	Histology or cytology	Ecto or endo	27	134	CIN2+	CIN1+	274
Torne et al (2013)[108]	Spain	LLETZ	Histology	Ecto or endo	24	ND	CIN2+	CIN2+	132
Kong et al (2014)[109]	South Korea	CKC	Histology	Ecto or endo	25	106	CIN2+	CIN2+	691
Zhao et al (2014)[110]	USA	Mixed	Histology or cytology	Ecto or endo	36	87	CIN2+	CIN1+, CIN2+	988
Gosvig et al (2015)[125]	Demark	LLETZ	Histology	Ecto or endo	24	24	CIN2+	CIN2+, CIN3+	588
Herfs et al (2015)[126]	Belgium	LLETZ	Histology	Ecto or endo, ecto, endo, ecto and endo	21	42	CIN2+	CIN1+, CIN2+	131
Kang and Kim (2016)[127]	South Korea	LLETZ	Histology	Ecto or endo	46	94	CIN2+	CIN2+	206
Wu et al (2016)[128]	China	LLETZ	Histology	Ecto or endo	20	60	CIN2+	CIN2+	854

CIN1+=cervical intraepithelial neoplasia grade 1 or worse. CIN2+=CIN grade 2 or worse. CIN3+=CIN grade 3 or worse. ND=not determined. Ecto=involvement of ectocervical margin only. Endo=involvement of endocervical margin only. Ecto and endo=involvement of both ectocervical and endocervical margins. Ecto or endo=involvement of ectocervical or endocervical margin, or both, without precision. CKC=cold knife conisation. LC=laser conisation. LLETZ=large loop excision of the transformation zone. Mixed=mixture of excisional treatment methods. *Hagen and colleagues[59] was excluded because data also reported in Skjeldestad and colleagues.[55] †Paraskevaidis and colleagues designed also a case-control study129 nested in the cohort study, in which high-risk HPV testing was performed in 41 cases with residual or recurrent CIN and 82 controls without residual or recurrent CIN.

Table 1: **Population and study characteristics**

	Cold-knife conisation		Laser conisation		Large loop excision of the transformation zone		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)
Ectocervical and endocervical	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.

Table 2: **Pooled proportions of incomplete excisions by treatment procedure and location of the margin involvement**

the study estimates among all studies together with the pooled measure.[21] We assessed publication bias by Egger's regression test for funnel-plot asymmetry.[27] We used a bivariate normal model to pool sensitivity and specificity estimates.[22,23] We used Deeks' regression test, based on the regression of the log diagnostic odds ratio onto 1/(effective sample size), 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–post-test probability plots[29] (appendix p 21). We did statistical analyses using Stata 14.0.

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 SG-M had access to the raw data. The corresponding author had full access to all the data and had final responsibility to submit for publication.

Results

A total of 97 studies, published between Jan 1, 1975, and Feb 1, 2016, were eligible for inclusion in the meta-analysis (figure 1), 65 of which were included in the previous meta-analysis by Ghaem-Maghami and colleagues,[14] assessing the risk of treatment failure associated with incomplete excision.[30–95] Additionally, 15 studies[96–110] were identified from previous meta-analyses[9,111,112] assessing the accuracy of post-treatment HPV and or cytology testing to detect residual or recurrent CIN2+ and contained data for the margin status. 16 new reports[15,113–128] were added that had not been included in previous reviews. Three reports from case-controls could be included in the meta-analyses of accuracy[96,100,129] 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. In total, the included studies enrolled 44 446 women treated for cervical precancer.

For the accuracy of the margin status for the outcome of CIN2+ or CIN3+, 25 studies were included (figure 1).[50,66,78,82,86–88,90,95,96,102,103,105–110,116,119,121,125–128] 18 of these 25 studies also provided data for the accuracy of post-treatment HPV testing, and could be used for computation of the relative accuracy (HPV *vs* margin status).[82,86,90,95,96,102,103,105–110,116,125–128] Characteristics of the included studies are in table 1. Studies were clinically heterogeneous with respect to design, timing, and duration of follow-up visits, and outcome assessment (appendix p 5).

The 18 studies that 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 p 5). In one study, some HPV testing was done later than 3–9 months post treatment.[116] The most

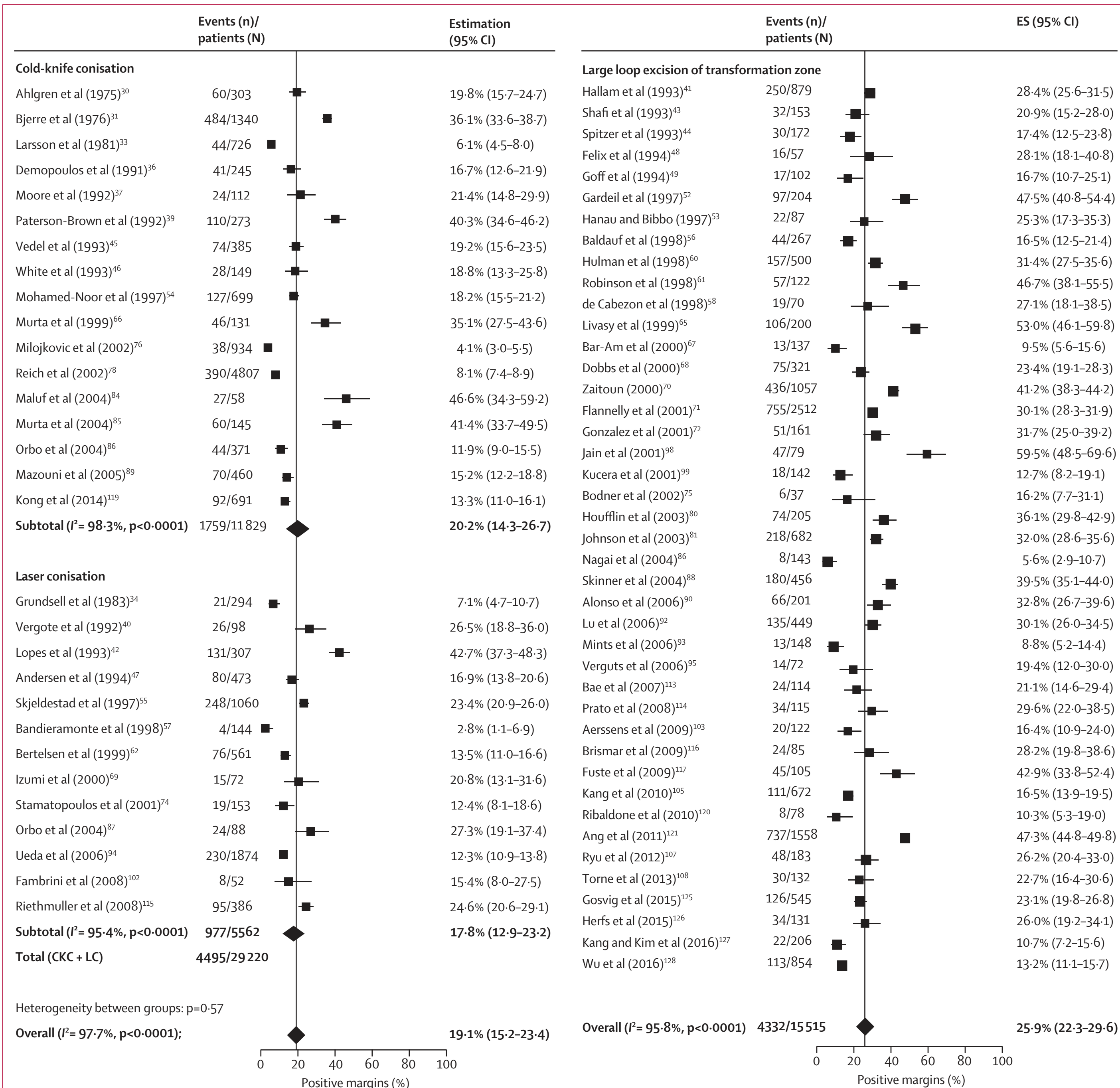

Figure 2: **Proportion of cones with positive resection margins, by treatment procedure**
Error bars represent 95% CIs. The vertical line corresponds with overall pooled effect size.

problematic design item was masking of the outcome: eight (44%) of the 18 studies were scored as unmasked and in five (28%) masking was not clearly documented. Partial verification was scored as problematic in three (17%) studies and differential verification was scored as problematic in five (28%) studies.

The overall proportion of incomplete excisions was 23·1% (95% CI 20·4–25·9; table 2) and was highly variable (range: 2.8%[57]–59·5%,[98] I^2=97·7%, p heterogeneity <0·0001). The highest proportion of incomplete excisions (positive margins) was observed with large loop excision of the transformation zone (25·9%, 95% CI 22·3–29·6), followed by cold-knife conisation (20·2%, 14·3–26·7), with laser conisation having the lowest proportion of incomplete excisions (17·8%, 12·9–23·2; table 2, figure 2). The proportion of positive resection margins did not change over time (ie, between 1975 and 2016) for cold-knife conisation or laser conisation but decreased slightly for large loop excision of the transformation zone (appendix p 6).

16 studies distinguished which margins (ectocervical, endocervical, or both) were involved.[15,54,68,71,78,81,86–90,92,109,121,122,126] Ectocervical margins were affected more frequently when precancer was treated by large loop excision of the transformation zone; endocervical margins were affected more frequently when either laser conisation or large loop excision were used. Large loop excision was associated with the highest frequency of involvement of both margins (table 2, appendix p 7). The proportion of positive margins increased significantly by the severity of the treated lesion (p value for between-group heterogeneity=0·019). The proportion of incomplete treatment was 22·4% (95% CI 18·7–26·4) for CIN1+, 22·9% (19·1–26·9) for CIN2+, and 29·3% (19·8–39·9) for CIN3+ (appendix pp 8,9).

In 24 studies with at least 18 months of follow-up, we found that residual or recurrent CIN2+ occurred in 6·6% (95% CI 4·9–8·4) of women treated for CIN2+. Failure rates were heterogeneous (range 1·4–18·3%, I^2>90%, p<0.0001) and varied by treatment procedure (around 2% for cold-knife conisation and laser conisation and almost 7% for large loop excision of the transformation zone; figure 3). Treated CIN3+ lesions were not more prone to therapeutic failure than were treated CIN2+ lesions (p=0·94; appendix p 10).

The risk of residual or recurrent CIN2+ post-treatment for women with positive margins was 17·1% (95% CI 12·7–22·1) overall and was higher after cold-knife conisation (25·6%, 19·6–32·2) than after laser conisation (14·1%, 3·0–29·5) or large loop excision of the transformation zone (15·6%, 9·2–23·3; appendix p 11). 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 (appendix p 11). 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 p 11). Substantial heterogeneity in the reported risk of residual or recurrent CIN2+ was observed (I^2=92% overall; 89% for positive margins; and 92% for negative margins; figure 3, appendix p 11). No evidence for publication bias was found (p value for asymmetry regression test=0·70, appendix p 13).

The risk of residual or recurrent CIN2+ after excisional treatment was 7·2% (95% CI 0·0–23·6) when only the ectocervical margin was involved, but this was more than doubled when either the endocervical margin (16·3%, 5·9–29·9) or both margins (18·9%, 0·0–62·9) were involved (appendix p 12).

The sensitivity and specificity of the margin status to predict residual or recurrent CIN2+, pooled from 25 studies in which women were treated for histologically confirmed CIN2+ was 55·8% (95% CI

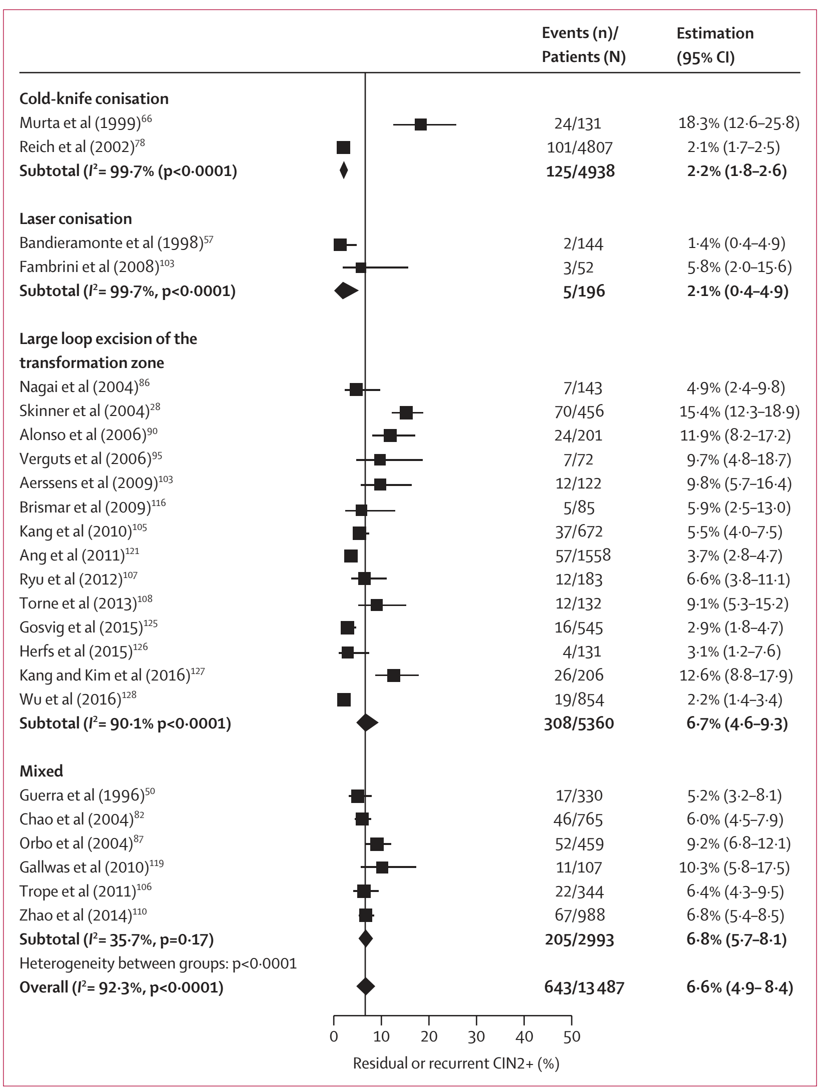

Figure 3: **Occurrence of treatment failure (residual or recurrent CIN2+) in women treated for cervical precancer (CIN2 or CIN3), observed in cohort studies with at least 18 months of follow-up**
CIN2+=cervical intraepithelial neoplasia of grade 2 or worse. Error bars represent 95% CIs. The vertical line corresponds with the overall pooled effect size.

45·8–65·5) and 84·4% (79·5–88·4), respectively (appendix p 14). Very large inter-study heterogeneity in the accuracy estimates was observed (p<0·0001). In particular, the sensitivity was highly variable, ranging from 9·1%[119] to 94·1%.[50] The pooled accuracy did not differ significantly by treatment procedure (between-group heterogeneity p=0·18 for sensitivity, p=0·40 for specificity). High-risk HPV testing, done 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% (77·7–88·7; appendix p 15). Margin status was 38% less sensitive (sensitivity ratio 0·62, 95% CI 0·53–0·72) but equally as specific (specificity ratio 1·01, 95% CI 0·97–1·06) as post-treatment high-risk HPV testing to predict residual or recurrent CIN2+ (figure 4, appendix p 16). Deeks' regression test for funnel plot asymmetry did not reveal small study effects (appendix p 17).

Five studies[82,95,106,107,125] were retrieved in which 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% (47·4–67·5), respectively, which was not more sensitive (ratio 1·04, 95% CI 0·97–1·11) but significantly less specific (ratio 0·75, 95% CI 0·67–0·84) than HPV testing alone (appendix pp 18,19). The accuracy of HPV testing did not differ significantly between women with positive versus negative margins (appendix p 20).

The pretest–post-test probability plots (figure 5) show that positive resection margins are associated with an average risk of post-treatment CIN2+ not reaching 20% and that negative resection margins are associated with post-treatment CIN2+ risk exceeding 2%. However, a positive post-treatment high-risk HPV test increases the risk of treatment failure to 28·4%, whereas a negative high-risk HPV result reduces this risk to 0·8% (figure 5).

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 and HPV positive), whereas this risk was 53% if both criteria were positive and below or equal to 1% if high-risk HPV negative, whatever the margin status (appendix p 22).

The target of less than 20% positive resection margins was not achieved in 53 (57%) of 93 included studies, and this proportion varied by treatment procedure: 6 (35%) of 17 for cold-knife conisation, 6 (46%) of 13 for laser conisation, and 28 (67%) of 42 for large loop excision (appendix p 24).

Discussion

Our meta-analysis shows that excisional treatment of cervical precancer fails in on average 7% of cases and confirms that incomplete removal of neoplastic tissue increases this risk by about five times compared with that in women with CIN-free resection margins. Incomplete excision occurs in approximately a quarter of cases and varies by severity of the lesion and excisional technique. These findings are in agreement with the previous systematic review addressing this question 10 years ago.[14] In our systematic review we also assessed the accuracy of the margin status, which has not previously been systematically reviewed. Despite its significant association with treatment failure, margin status is not an accurate test to predict 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 who were considered cured showed positive resection margins. 18 studies also did high-risk HPV DNA testing post-treatment, which was substantially more sensitive and similarly specific compared with the margin status.

Meta-analyses of diagnostic test accuracy do not answer the question as to whether a test is clinically useful in a given setting. The pretest–post-test probability plot, displaying the pretest 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 28·4% for women with a positive post-treatment HPV test, exceeding the decision threshold accepted for referral, which is usually defined as a risk of CIN2+ higher than 20% (shown by the red zone in figure 5).[29] Furthermore, the CIN2+ risk dropped to 0·8% for high-risk HPV-negative women, which is lower than the 2% cutoff generally accepted as sufficiently low to release the patient from further follow-up (shown by the green zone in figure 5). Knowledge of the margin status on its own did not

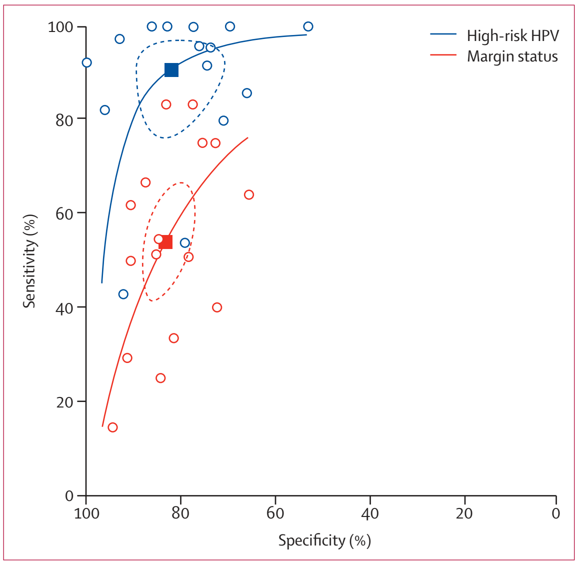

Figure 4: **Summary receiver operation characteristic plot of the sensitivity as a function of the specificity for residual or recurrent CIN2+ of margin status and high-risk DNA testing in women treated for CIN2+**
CIN2+=cervical intraepithelial neoplasia of grade 2 or worse. HPV=human papillomavirus.

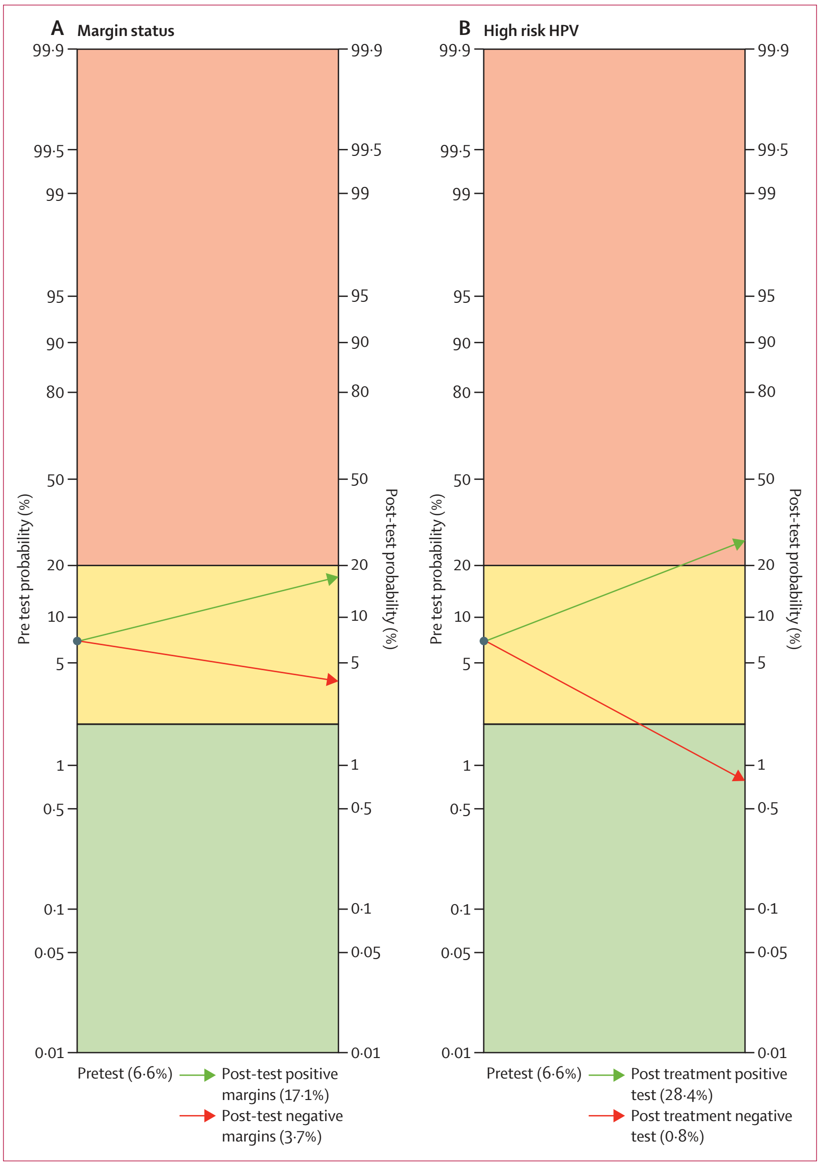

Figure 5: **Pretest and post-test probabilities of residual or recurrent CIN2+ after treatment of CIN2+, assessed by the histological evaluation of the resection margins (A) or by high-risk HPV testing (B) at 3–9 months post-treatment**

The arrows in the PPP plot connect the pretest risk with post-test risk for patients with a positive (red) or negative (green) test result, respectively. Benchmarks are defined at risk levels of 2% and 20%. When post-test risk is >20% (red zone), referral to colposcopy is warranted, whereas when post-test risk is <2% (green zone), release to the routine screening schedule is considered acceptable. When risk of CIN2+ is between 2% and 20% (yellow zone), further surveillance is recommended.[29] CIN2+=cervical intraepithelial neoplasia of grade 2 or worse. HPV=human papillomavirus.

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 differentiation of management decisions in accordance with particular patient characteristics.

A strategy based on HPV testing would refer about a fifth of women for further diagnosis or retreatment and three to five referrals would result in the discovery of one residual or recurrent CIN2+. Combination of the marginal and post-treatment HPV status would refer almost half of treated women, without significantly improved protection against treatment failure (appendix p 23).

Some scientific societies recommend that gynaecologists should achieve 80% or more complete excisions as a criterion of good professional practice.[16] Our meta-analysis showed that in most studies this benchmark is not reached, especially when women were treated by large loop excision of the transformation zone. The goal to achieve less than 20% of involved margins might promote larger excisions, which might reduce the number of incomplete excisions but could also increase the risk of obstetrical harm.[18,19]

The patient's age, the size of the lesion and the size of the excised cone, and the skill of the clinician doing the excision procedure 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 smaller 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 one study also showed that this translates into reduced rates of residual or recurrent CIN2+.[15] The history of previous diagnosis and treatment of cervical lesions was another variable that could affect therapeutic decisions and their outcomes.[131] The higher proportion of positive margins after large loop excision of the transformation zone compared with the other treatment approaches might be explained by the high number of fragmented specimens and the diathermy effects that hamper the interpretation of the margin status that can be overcalled as positive in many cases.[103] The large inter-study heterogeneity in margin positivity that was observed in our pooled analysis might be partly explained by the variation in tissue destruction observed after different treatment techniques. Cold-knife conisation is known to affect the margin interpretation the least,[136] followed by large loop excision, and then laser conisation, which produces the greatest amount of thermal tissue artifact.[137] Studies were not only statistically but also clinically heterogeneous.

As has been shown previously,[9] the accuracy of high-risk HPV testing did not show heterogeneity in the accuracy by test assay, when restricted to HC2 and validated PCR tests. The published literature consistently shows that HPV testing can be made substantially more specific by identifying the same HPV type in the excised cone or in pretreatment specimens as in the post-treatment specimens.[105,116,127,138–140] Some studies report that type-specific HPV persistence is accompanied by a degree of loss in sensitivity,[116,138] whereas others have not shown this association.[105,141]

Our meta-analysis included almost 100 studies and around 45 000 women. However, despite this large number of studies and participants, confidence intervals were wide around pooled estimates of test positivity, disease occurrence, accuracy, and predictive values of the margin status due to the large inter-study heterogeneity. The sensitivity of the margin status to predict treatment failure, in particular, varied widely (from 9% to 94%).[50,118] 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, we did not search for or include any unpublished grey literature in the meta-analysis, since this could actually increase bias and imprecision. We considered that population-based screening registries with treatment and follow-up data would also be useful to include, but we did not have access to such databases.

Our meta-analysis contributes only low-quality evidence for the finding that large loop excision is less effective than cold-knife conisation or laser conisation. Indeed, the comparisons are indirect with only two studies each contributing data for cold-knife conisation and laser conisation. More convincing evidence should be attributed to a Cochrane review of randomised trials, which did not show significant differences in efficacy between treatment procedures.[8] In interpreting the data, readers are advised 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 might look more precise than it actually is.[142,143] In addition to updating previous reviews on margin status, our meta-analysis bridges evidence towards a more promising test of cure by including a comparison of margin status assessment with high-risk HPV testing. However, as in earlier reviews, we should acknowledge in our meta-analysis, the grouping of broad categories of treated CIN could impede clear assessment of the severity of precancer (both at the level of treatment and outcome). Absence of residual or 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 do subgroup meta-analyses or meta-regression that incorporated influential factors such as age, lesion size, and transformation zone types. To address this limitation, individual patient data meta-analyses should be established and completed; one such example is the COSPCC study, funded by the Institut National du Cancer, which aims to quantify the correlation between cone depth and the subsequent risk of preterm delivery.[144]

An updated meta-analysis on the risk of adverse pregnancy outcomes in women who were previously treated for CIN included 71 studies;[18] whereas our meta-analysis, on treatment failure, contained 97 studies. Strikingly, 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 that large linkage studies should be set up in countries with good population-based registries joining personal records from centres specialised in diagnosis and treatment of cervical precancer; birth registries; and pathology registries capturing diagnosis of recurrent precancer 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+, might justify recommendations for more aggressive treatment at ages at which reproductive safety is no longer an issue. Suspicion of invasive cancer, presence of glandular precancer, and unsatisfactory colposcopy are other indications for which gynaecologists might decide to do a large excision.

In conclusion, this meta-analysis confirms that the risk of residual or recurrent CIN2+ is significantly increased with positive excision margins compared with negative excision margins; however, high-risk HPV post-treatment predicts treatment failure more accurately than margin status. Combined results of the margin and post-treatment HPV status could be used to stratify risk and diversify management. Achievement of negative resection margins need to be balanced with the depth of cervical excision in women of childbearing age in light of the potential for increased preterm birth risk.

Contributors

MA, CWER, and JG conceived the study and protocol. MA and FV formulated the clinical question and identified PICOS components. MA, FV, and SG-M identified studies. MA created the data extraction forms MA, FV, and SG-M extracted the data. MA and FV did the statistical analyses. MA and ELM wrote the report. CWER, FV, MK, MT, SG-M, K-UP, SL, CB, PN, JG, OR, and ELM critically reviewed the report.

Declaration of interests

K-UP declares support from Beckton Dickinson and Roche Diagnostics. All other authors declare no competing interests.

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