Management and treatment of cervical intraepithelial neoplasia in the Netherlands after referral for colposcopy

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ABSTRACT

Introduction

The aim of this study was to describe trends in diagnosis and treatment of women referred from screening with cervical intraepithelial neoplasia (CIN) in the Netherlands, compare this to national guidelines and identify potential areas for improvement for the new primary high-risk HPV screening programme.

Material and methods

We conducted a population-based cohort study using data from Dutch pathology archive. Women aged 29-63 years who took part in the Dutch cervical screening programme between 1 January 2005 to 31 December 2014 were selected. Three referral groups were identified: direct referrals and those referred after either one (first indirect referrals) or two (second indirect referrals) repeat cytology tests, totaling 85,239 referrals for colposcopy. The most invasive management technique and most severe diagnosis of each screening episode were identified. Rates of management techniques were calculated separately by referral type, highest CIN diagnosis and age group.

Results

In all, 85.1% of CIN 3 lesions were treated with excision (either large excision or hysterectomy) and 26.4% of CIN 1 lesions were treated with large excision. Rates of overtreatment (CIN 1 or less) in see-and-treat management were higher for indirect referrals than for direct referrals and increased with age. Large excision rates increased with CIN diagnosis severity.

Conclusions

Despite guideline recommendation not to treat, CIN 1 lesions were treated in just over 25% of cases and approximately 15% of CIN 3 lesions were possibly undertreated. Given the expected increase in CIN detection in the new primary high-risk HPV screening programme, reduction in CIN 1 treatment and CIN 2 treatment in younger women is needed to avoid an increase in potential harm.

KEY MESSAGE

Both over- and undertreatment of cervical intraepithelial neoplasia occurs after referral from organized cervical screening, despite treatment guidelines being available.

INTRODUCTION

In the Netherlands, cervical intraepithelial neoplasia (CIN) detection rates have increased over the last decade, largely independent of socio-economic and demographic factors.[1] The replacement of conventional cytology by high-risk human papillomavirus (hrHPV) DNA testing as primary screening test in the Dutch Cervical Cancer Screening Program in 2017 will likely further increase CIN detection, given the higher sensitivity of hrHPV testing for CIN 2+ lesions.[2] Recent Dutch modeling estimated that the number of detected CIN lesions would increase by 196% for CIN 1 and 54% for CIN 2 over the lifetime of women entering the program in 2017 due to primary hrHPV screening.[3]

As more CIN lesions are detected, there is concern about overtreatment, which could result in increased harm associated with screening.[4] Evidence suggests that there is an association between excisional treatments for CIN and adverse obstetric outcomes including preterm birth and low birthweight.[5,6] Increasing excision volume has been associated with increased risk.[6,7] Additionally, a robust randomized controlled trial concluded that immediate side-effects of excisional treatments such as discharge and pain occur more frequently, more severely and for longer in women treated with large loop excision of the transformation zone (LLETZ) compared with both colposcopy-only and biopsy-diagnosed women.[8]

The Dutch Association of Obstetrics and Gynecology has published consensus-based guidelines for CIN treatment and management which detail the recommended treatment practices, including recommending no treatment of CIN 1 and excisional treatment of CIN 2+.[9] However, compliance with these guidelines has never been evaluated. The lack of evaluation of CIN management in the Dutch setting has been recognized by others[4] as a knowledge gap in an otherwise closely monitored program. Our study intends to objectify current clinical management of CIN to understand discrepancies between guideline recommendations and observed interventions. By doing so, we aim to identify potential areas for improvement for the new primary hrHPV screening program.

MATERIAL AND METHODS

National organized cervical screening has taken place in the Netherlands since the 1980s. Women are invited for cytology screening every five years from ages 30 to 60. Screening takes place within primary care. Women are referred to a gynecologist when colposcopy is required. Details of clinical guidelines for management of CIN are given in Table 1. Since 1998, the recommendations for management of abnormal cytology have been fairly stable, allowing for more reliable measurement of procedural parameters after colpos-

Table 1: *Summary of Dutch CIN treatment guidelines*

	2004 Guidelines[9]	2015 Guidelines[21]
Histological diagnosis at colposcopy	Targeted biopsies are required only with an atypical transformation zone.	Biopsy can be omitted if there is slight cytological dysplasia and no visible colposcopic abnormalities, in situations when the whole transformation zone can be seen. At least two random biopsies should be taken where there are severe cytological abnormalities with no colposcopic abnormalities. In the case of severe cytological and colposcopic abnormalities, either two targeted biopsies can be taken or 'see-and-treat' management can be used.
CIN 1	Generally not treated.	In principle, should not be treated. In the case of persistent low-grade cytology outside of reproductive age, treatment options may be discussed with the patient.
CIN 2	Should be treated, preferably by LLETZ*	Individual assessment is required, particularly in younger women, weighting up the risks and benefit of treatment. If treatment is decided on, LLETZ* is recommended.
CIN 3	Should be treated, preferably by LLETZ*	Should always be treated. Women with high-grade cytology (moderate dyskaryosis/dysplasia or worse) and colposcopy are eligible for see-and-treat management. LLETZ* recommended.
Glandular disease	Conization is preferred if there is suspicion of AIS	It should be discussed with the patient whether she wants an excisional treatment or hysterectomy, provided that invasive carcinoma is excluded as far as possible. Conization is preferred for AIS as it allows for better assessibility of the endocervical area and margins. If LLETZ is chosen, the pathologist must be notified for a better assessment of the margins.

* Large loop excision of the transformation zone
CIN: Cervical intraepithelial neoplasia; AIS: adenocarcinoma in situ.

copy. In 2017, hrHPV testing replaced cytology as the primary screening test within the program.[10]

Our study is a population-based cohort study. Women aged 29 to 63 years who participated in the national screening program and received referral advice between 1 January 2005 and 31 December 2014 were included. Possible referral pathways within the Dutch screening program can be found in Figure 1. Three groups of referrals were identified:

- Direct referrals: Women who received referral advice after primary cytology of high-grade squamous intraepithelial lesion (HSIL)/adenocarcinoma in situ (AIS)/atypical endometrial glandular cells (AGC)/AGC favoring neoplasia/cancer. The classification ASC-H (atypical squamous cells cannot exclude HSIL) is not utilized in the Netherlands.
- First indirect referrals: Women who received referral advice for repeat testing six months after primary cytology of atypical squamous cells of undetermined significance (ASC-US)/low-grade squamous intraepithelial lesion (LSIL) or endocervical AGC.

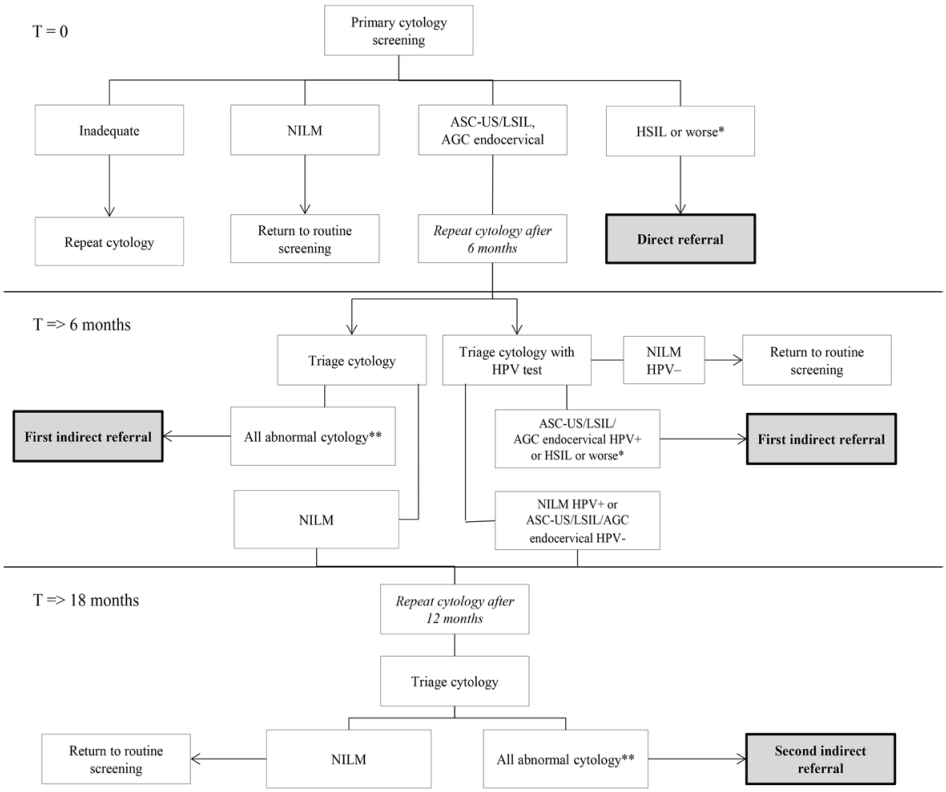


Figure 1: *Pathways to referral within the Dutch Cervical Cancer Screening Program, adapted from Bekkers et al.*[31] *and Rozemeijer*[32]

* Includes HSIL, AGC endometrial, AGC favor neoplasia, adenocarcinoma in situ and cancer irrespective of hrHPV status.

** Includes ASC-US, LSIL, AGC endometrial and HSIL or worse* cytology results.

ASC-US/LSIL: Atypical squamous cells of undetermined significance/ low-grade squamous intraepithelial lesion

AGC: Atypical glandular cells

HSIL: High-grade squamous intraepithelial lesion

- Second indirect referrals: Women who received referral advice after two triage cytology tests (at six and 18 months), with the first repeat cytology being negative, hrHPV-negative with endocervical ASC-US/LSIL/AGC or hrHPV positive with negative cytology, and second triage cytology being ASC-US or higher.

We excluded women with primary smears taken by a gynecologist, as women under the care of a gynecologist in the Netherlands are usually already receiving specialist care. Indirect referrals must have been referred within four years of primary screening to be included, in line with the definitions used in the monitoring of the national screening program. Repeat cytology testing at six months could be performed either with or with-

out hrHPV triage. As hrHPV triage was not standard practice in all pathology labs during the study period, we did not include hrHPV status information in our study.

There is no national registry of gynecological treatments in the Netherlands. Therefore, we used an extract of all cervical cytology and histology records from the nationwide network and registry of histo- and cytopathology in the Netherlands (PALGA). PALGA has a nationwide coverage of all pathology labs.[11] Women are identified by the first eight letters of their surname (maiden name is used for married women) and date of birth. Information about primary screening as well as up to five follow-up cytology and/or histology samples were selected. Follow-up of primary smears was included until the end of the database – 31st March 2016. We defined 'episode of screening' as the period starting with the primary screening test, possibly followed by follow-up tests and/or treatment and ending with the next primary cytology in the database. We only analyzed information recorded during this window (see Appendix S1). As PALGA is not a registry of treatments, we validated our results with two expert groups and with clinical data from one gynecology clinic (see Appendix S2).

Our primary outcome measure was the proportion of the most invasive diagnostic tests and therapeutic treatments by the most severe CIN diagnosis within a screening episode. Our secondary outcome measure was the proportion of overtreatment in see-and-treat management. The most severe diagnosis within the screening episode was identified from all diagnostic codes recorded after referral advice as follows: most to least severe – cancer, CIN 3, CIN 2, CIN 1, benign/reactive, cytology only, no diagnosis recorded.

Diagnostic tests and therapeutic treatments are pre-coded by PALGA. The most aggressive test/treatment of the episode after referral was ranked as follows: most to least aggressive - hysterectomy, large excision [including cone biopsy, LLETZ, other excisional treatments], polypectomy, endometrial curettage, endocervical curettage, punch biopsy [excluding cone biopsy], cytology only, other techniques. This ranking was verified by gynecologists and pathologists.

See-and-treat management involves combining colposcopy and treatment in the same outpatient visit.[12] A large excision in the next record after referral was considered indicative of see-and-treat management. We estimated possible overtreatment in see-and-treat management as the proportion of women with CIN 1 or lower histological diagnosis as the highest diagnosis of the episode who were treated with large excision at the first contact with a gynecologist divided by all women who were treated with large excision at the first contact with a gynecologist (definition from Ebisch et al[12]). Age at primary screening was grouped into 5-year age groups.

Statistical analysis

Chi-squared tests were performed to compare differences between proportions. Analysis of variance was used to compare mean ages across referral types. For one-way tables, a chi-square goodness of fit test was applied. Confidence intervals for proportions were calculated using a binomial distribution. All analyses were performed using SAS Base v9.4 (SAS Institute Inc., Cary, NC, USA).

Ethical approval

We used a retrospective, anonymized dataset from PALGA, which is exempt from ethical approval by a Medical Ethical Testing Committee. We obtained anonymized clinical data (only women referred from screening) for validation as part of the evaluation of the national cervical screening program (evaluation of national screening programs is legislated in the Population Screening Act in the Netherlands). We received written approval from the Medical Director of the specialist outpatient clinic to use their clinical data for research purposes.

RESULTS

From the 5,450,148 primary cytology smears taken within the screening program from women aged 29–63 years between 2005–2014, 98.9% were taken by a non-gynecologist and eligible for inclusion (n = 5,389,342). Of these smears, 44,209 (0.8%) resulted in a direct referral to a gynecologist, 34,282 (0.6%) resulted in a first indirect referral and 6,748 (0.1%) resulted in a second indirect referral (Table 2). The majority of referrals were within reproductive age range (29-43 years: 65.5%). The number of referrals was higher in the period 2010 - 2014 than in the period 2005 - 2009 for all referral types (Table 2).

Of all women directly referred, 81.1% were diagnosed with a CIN lesion (that is CIN 1, 2 or 3) within the episode of screening (Table 2). The proportion of indirectly referred women diagnosed with a CIN lesion was lower, 64.9% for first indirect referrals and 39.9% for second indirect referrals (Table 2). When restricted to only referrals that resulted in a histological diagnosis (i.e. excluding episodes with no recorded diagnosis or no histology taken), there were still differences in the proportion of episodes diagnosed with a CIN lesion between the referral groups (direct: 88.7%; first indirect: 78.1%; second indirect: 67.0%) and the differences were statistically significant (X^2 (2, N = 72,902) = 2,161.98, $p < 0.001$) (figures not presented). Among direct referrals, there was a higher proportion of women with a CIN 3 diagnosis (53.5%) than among indirect referrals (first indirect: 17.5%; second indirect: 8.8%) (Table 2).

The highest proportion of CIN lesions were diagnosed in women aged 29-33 years; 79.8% of all referrals in this age group were diagnosed with a CIN lesion (Figure 2). The

***Table 2**: Demographic characteristics of women referred for colposcopy following participation in the Dutch cervical screening program, all referral types, 2005–2014, rounded percentages*

Variable	Direct referrals *N (%)*	First indirect referrals *N (%)*	Second indirect referrals *N (%)*	*P*
Total referrals	44 209	34 282	6 748	
Total unique woman ID*	43 827	34 081	6 725	
Age				
Mean age	39.16 (*SD*: 8.58)	39.54 (*SD*: 8.49)	41.35 (*SD*: 8.74)	< 0.001
29–33	12 452 (28.2%)	9 086 (26.5%)	1 352 (20.0%)	< 0.001
34–38	9 373 (21.2%)	6 661 (19.4%)	1 117 (16.6%)	
39–43	8 151 (18.4%)	6 351 (18.5%)	1 250 (18.5%)	
44–48	6 027 (13.6%)	5 448 (15.9%)	1 196 (17.7%)	
49–53	3 944 (8.9%)	3 567 (10.4%)	1 005 (14.9%)	
54–58	2 527 (5.7%)	2 022 (5.9%)	513 (7.6%)	
59–63	1 735 (3.9%)	1 147 (3.4%)	315 (4.7%)	
Period				
2005–2009	20 630 (46.7%)	14 400 (42.0%)	2 803 (41.5%)	< 0.001
2010–2014	23 579 (53.3%)	19 882 (58.0%)	3 945 (58.5%)	
Highest diagnosis of the episode after referral				
No recorded diagnosis	1 770 (4.0%)	1 275 (3.7%)	835 (12.4%)	< 0.001
Cytology only	2 023 (4.6%)	4 540 (13.2%)	1 894 (28.1%)	
Benign/Other†	3 019 (6.8%)	6 072 (17.7%)	1 306 (19.4%)	
CIN 1	4 039 (9.1%)	9 024 (26.3%)	1 411 (20.9%)	
CIN 2	8 152 (18.4%)	7 219 (21.1%)	688 (10.2%)	
CIN 3	23 649 (53.5%)	5 996 (17.5%)	594 (8.8%)	
Cancer‡	1 557 (3.5%)	156 (0.5%)	20 (0.3%)	

* Some IDs have more than one referral within the same referral type. The number of unique IDs represents the number of individual women referred within the referral type.
†Benign/Other includes histological results that are lower grade than CIN 1.
‡ Includes micro-invasive and invasive disease
SD: Standard deviation; CIN: Cervical intraepithelial neoplasia
See Figure 1 for description of referral types.

proportion of episodes with no recorded diagnosis or no histology increased with age (Figure 2). In women aged 44 years and older, 61.3% of the no recorded diagnosis and 55.3% of the no histology group had no further primary screening episodes after referral, and the remainder had further cytology and/or histology tests taken in the next primary episode, which were excluded from analysis (figures not presented).

The more severe the CIN diagnosis, the higher the proportion of women treated with large excision (Table 3). Women who were directly referred and diagnosed with CIN 1

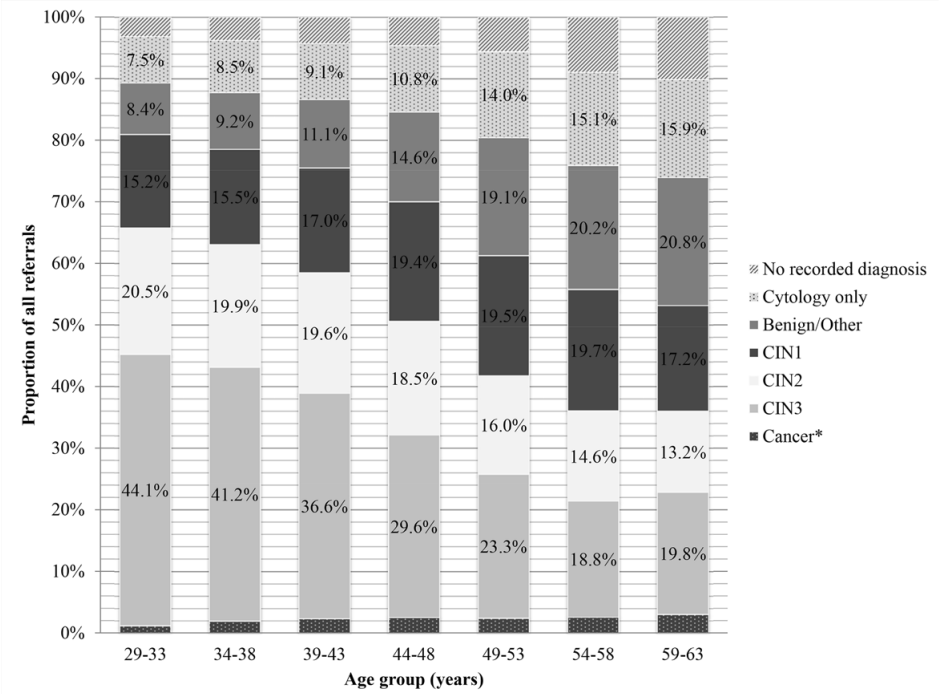


Figure 2: *Highest diagnosis of the screening episode within age groups, all women referred, rounded percentages*

* Includes micro-invasive and invasive disease

CIN: Cervical intraepithelial neoplasia

had higher rates of large excision treatment compared with women who were indirectly referred: 34.4% compared with 23.9% [first indirect] and 19.7% [second indirect]; X^2 (2, N = 14,474) = 193.1, $p < 0.001$). No age-dependency was seen in the percentage with large excision treatment of CIN 3 (figures not shown). For CIN 1 lesions, the proportion of treatment with large excision increased with age. Rates of treatment with large excision differed significantly between referral types across all age groups for CIN 1 lesions (from 13.1% to 50.4%) and for the four youngest age groups for CIN 2+ lesions (Figure 3).

See-and-treat management was observed more often in direct referrals than indirect referrals and was performed mostly in women with severe CIN lesions (Figure 4). Treatment of CIN 1 or lower in see-and-treat management increased with age across all referral types and were higher for indirect referrals in all age groups (Figure 5).

Table 3: *Most invasive management technique of the screening episode by most severe CIN diagnosis of the screening episode, rounded percentages*

	CIN I (%)	CIN 2 (%)	CIN3 (%)	*p*
		Direct referrals		
Hysterectomy	1.2	1.8	3.4	< 0.001
Large excision*	34.4	69.4	82.0	
Biopsy†	62.5	28.2	14.3	
Other techniques‡	1.9	0.6	0.3	
		First indirect referrals		
Hysterectomy	0.9	1.7	2.9	< 0.001
Large excision*	23.9	66.9	81.3	
Biopsy†	73.2	30.8	15.4	
Other techniques‡	1.9	0.6	0.4	
		Second indirect referral		
Hysterectomy	0.6	2.2	1.9	< 0.001
Large excision*	19.7	61.8	80.3	
Biopsy†	77.5	35.3	17.3	
Other techniques‡	2.2	0.7	0.5	
		All referrals		
Hysterectomy	1.0	1.8	3.3	< 0.001
Large excision*	26.4	68.0	81.8	
Biopsy†	70.7	29.7	14.6	
Other techniques‡	1.9	0.6	0.3	

* Large excision includes cone biopsy, LLETZ and other excisional therapies

† Includes all types of biopsies (exc. cone biopsy).

‡ Includes polypectomy, endometrial and endocervical curettage and histology not otherwise specified. See Figure 1 for description of referral types

DISCUSSION

Despite recommendations not to treat CIN 1 lesions, we found that 26.4% of the diagnosed CIN 1 lesions underwent an excisional procedure, ranging from 13.2% to 50.4% depending on age and referral type. Compared to the European guidelines for clinical management of abnormal cervical cytology,[13] the Dutch CIN 1 advice in the 2004 Guidelines were quite conservative. Despite this, the proportion of CIN 1 treated with large excision is slightly higher than previously reported figures from Italian colposcopy audits[14,15] with the latest reporting 16% of CIN 1 lesions were treated and that increase in the proportion of CIN 1 that was not treated was observed between audit periods. However, compared with the European Federation for Colposcopy guidelines[16] that state 85% of excisional treatments should have a definitive histology of CIN 2+, our data shows the Dutch program exceeds this benchmark at 87%. To our knowledge, no other

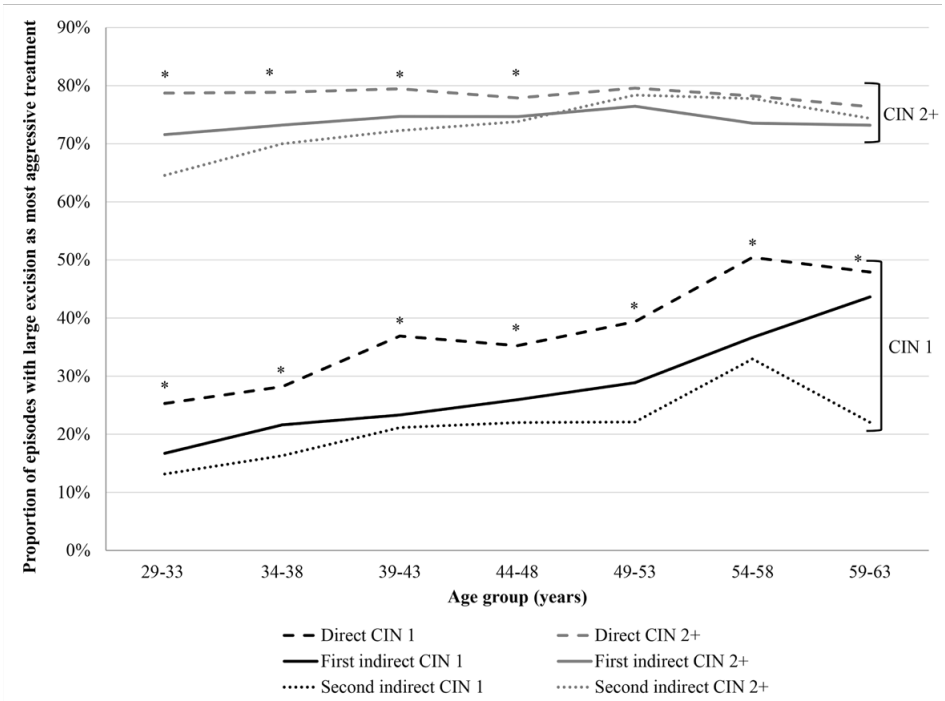
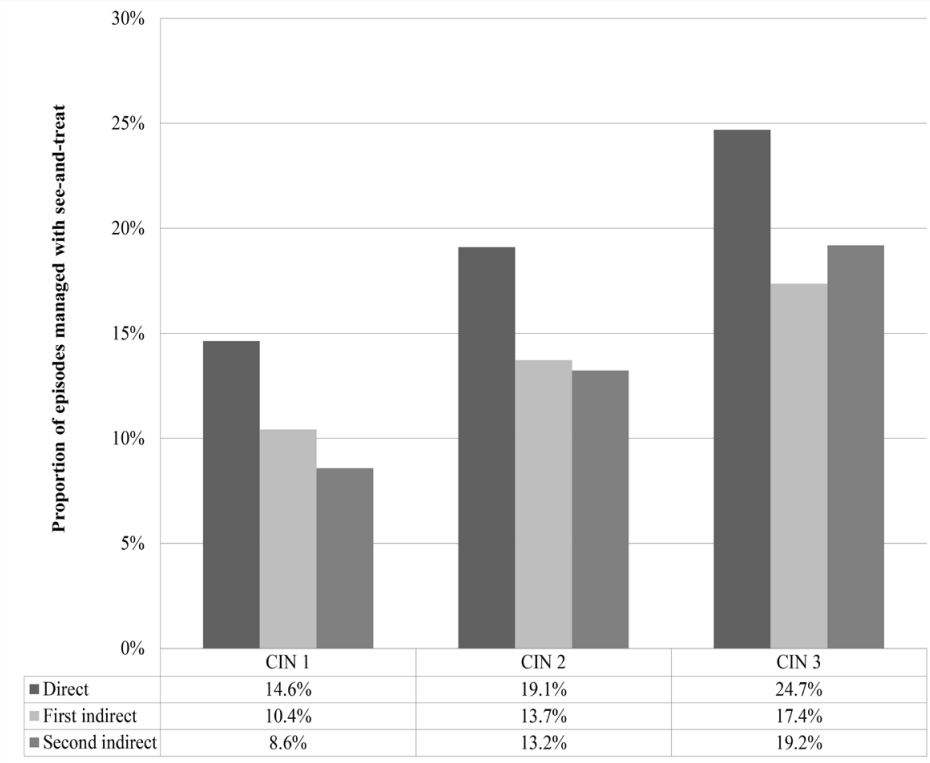


Figure 3: *Proportion of episodes with large excision as most aggressive treatment for CIN 1 and CIN 2+ (denominator: total episodes within each age group with the same highest diagnosis), by age group and referral type*
* Pearson's chi-squared test significantly different between referral types.
See Figure 1 for description of referral types
CIN: Cervical intraepithelial neoplasia

European countries have published CIN treatment rates by diagnosis in peer-reviewed journals, though Danish researchers have recommended monitoring of CIN treatment trends in light of increasing CIN treatment rates in Denmark.[17]

Monitoring of treatment rates can have a positive effect on compliance with guidelines by making practitioners cognizant of recommendations. A study from one US hospital found that active monitoring of excisional treatments led to an increase in guideline compliance and an decrease in inappropriate excisional treatments.[18] Regular monitoring should be implemented given the expected rise in CIN 1 diagnoses, due to the new, more sensitive hrHPV primary test. Modeling estimated that CIN 1 diagnoses will approximately double in the new screening program.[3] In the old cytology screening program, if CIN 1 treatment rate were 5% during the period of our study, rather than 26.4%, this would have resulted in approximately 300 fewer CIN 1 lesions treated with large excision per year. Under the new hrHPV screening program, the impact of reduced CIN 1 treatment rates could be even larger.



	CIN 1	CIN 2	CIN 3
Direct	14.6%	19.1%	24.7%
First indirect	10.4%	13.7%	17.4%
Second indirect	8.6%	13.2%	19.2%

Figure 4: *Proportion of episodes managed with see-and-treat* within each CIN diagnosis group and referral type, 2005-2014*

* See-and-treat management is defined as episodes where the first treatment after referral advice is large excision.

See Figure 1 for description of referral types

It is unrealistic to expect no CIN 1 treatment, as there will always be women with persistent or recurring low-grade abnormalities for whom treatment may be favorable or reassuring.[19] Guidelines are only one factor in clinical decision making for CIN; gynecologists consider information about colposcopy, cytology, hrHPV status, family planning, age, women's preferences and other factors when advising about treatment. Communication between pathologists and gynecologists also influences treatment decisions.[18] There may be situations where CIN 1 was preceded by HSIL cytology, hrHPV positivity and CIN 2+ colposcopic impression or biopsies. Additionally, in women with transformation zone type 3, diagnostic LLETZ after high-grade cytology is indicated in IARC guidelines.[20] In such situations, performing LLETZ may be a justifiable, appropriate treatment. Clarification of a reasonable rate of treatment for CIN 1 should be given in future guideline revisions, preferably accompanied by intuitive nomograms to assist in

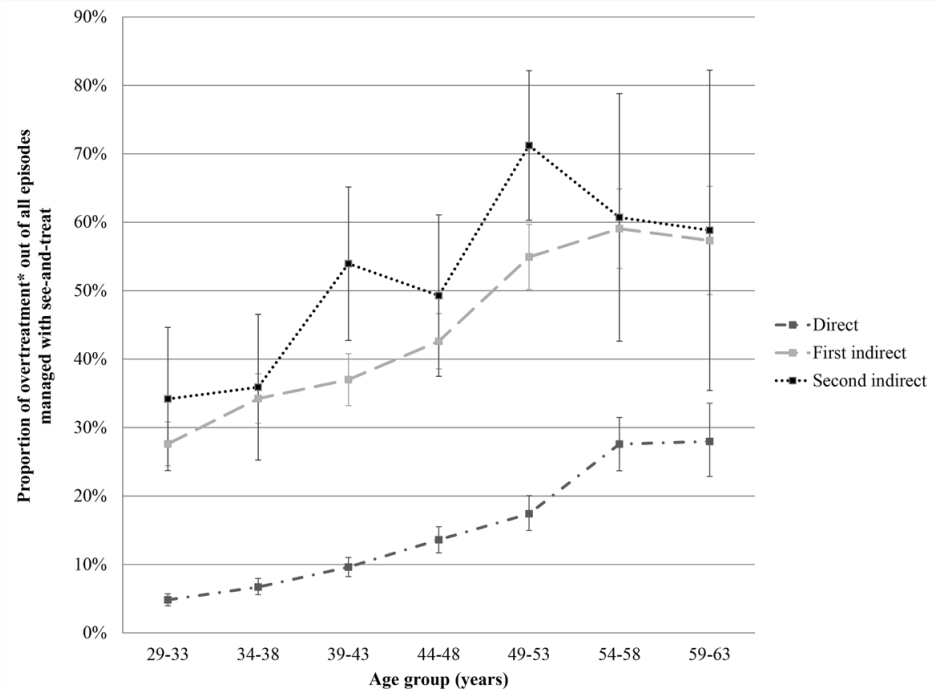


Figure 5: *Proportion of overtreatment* in see-and treat management by age group and referral type*
* Overtreatment in see-and-treat management is defined as the proportion of women with CIN 1 or lower histological diagnosis who were treated with large excision at the first contact with a gynecologist divided by all women who were treated with large excision at the first contact with a gynecologist.
See Figure 1 for description of referral types
CIN: Cervical intraepithelial neoplasia

decision making, for example, that hrHPV negative biopsies can be observed rather than treated.

The treatment guidelines were revised in 2015[21] and now advise see-and-treat for a subcategory of women. Although this approach has advantages (reduced loss to follow-up, convenience for women, lower costs),[22] overtreatment is a risk.[23] See-and-treat needs careful implementation to reduce overtreatment risks. We found that treatment of CIN 1 or lower was more frequent in indirect referrals than direct referrals, and increased with age. These findings are similar to those of other Dutch studies.[24] Given the higher number of CIN 1 and lower diagnoses in the two indirect referral groups, this finding is unsurprising. Our results are consistent with Ebisch and colleagues, who found women with low-grade cytology had higher overtreatment rates than women with high-grade cytology.[12] Restricting see-and-treat to women with concordant high-grade cytology and colposcopy could minimize overtreatment, as could the use of a grading system, such as the Swede score, which has shown to have high specificity for CIN 2+ lesions.[25]

It is not surprising that rates of treatment with large excision for CIN 2+ lesions vary little by age within referral types. Up until 2015, treatment guidelines for CIN 2 were not age-specific. However, the 2015 Guidelines[21] state that women with CIN 2 lesions should be individually assessed as to whether benefits of treatment outweigh the risks, largely related to future childbearing. Active surveillance of young women allows time for CIN 2 lesions to regress, which is likely to occur in most CIN 2 cases.[26] However, active surveillance also comes with the risk of loss to follow-up or progression to a higher-grade lesion. Going forward, we expect CIN 2 treatment will vary by age, as more young women are conservatively managed. As such, both the treatment and outcomes for women with CIN 2 lesions should be monitored to ensure that clinical practice reflects guidelines.

As expected, women diagnosed with CIN 3 had the highest rates of treatment with excisional techniques. This is consistent across referral types with no differences by age (figures not shown). On the other hand, between 14.6% and 17.8% of women diagnosed with CIN 3 were not managed with an excisional treatment (large excision or hysterectomy). This apparent undertreatment may be the result of several factors. Although uncommon in the Netherlands, these women may have been treated non-invasively using electrocoagulation, cryotherapy or imiquimod prescription and these procedures are not recorded in PALGA. Undertreatment may be overestimated due to data issues, such as records belonging to one woman not being properly linked. Finally, a clinician can decide to use an expectant management strategy if diagnostic biopsy removed most of the lesion. Regardless, guidelines state that CIN 3 should always be treated given the risks of progression; long-term follow-up of women in an unethical study in which treatment was delayed or withheld from women with high-grade lesions showed the cumulative incidence of cervical or vaginal vault cancer was 31.3% at 30 years, with a higher cumulative incidence (50.3%) amongst women with persistent high-grade lesions.[27] Timely and effective treatment of CIN 3 is therefore necessary to avoid the risk of disease progression. Communication of these results directly with gynecologists is essential, emphasizing that the benefits of treatment for these women greatly outweigh the risks.

Our study is the first to use a national database to investigate CIN treatment practices in the Netherlands. Analysis in this study was split by referral type, allowing us to investigate women with different risk profiles separately, as the severity of the initial cytology influences follow-up. Reflective of this, we found that women who are directly referred have a much higher proportion of CIN 3 diagnoses.

Our study has some limitations. We did not include information about hrHPV status in our analysis, as the practice of hrHPV testing was not universally conducted during the study period. However, knowledge of hrHPV status may have resulted in more aggressive treatment for women who were hrHPV positive. We were also unable to evaluate conization and large loop excisions separately, or analyze by depth of excision or lesion

size. This is not coded in PALGA. This information would be useful for stratification of results, as depth of excision can have implications for both the risk of adverse obstetric outcomes[5,6,28] and the risk of recurrent or progressive disease.[29] Furthermore, we do not have information about results of colposcopy. If a woman is referred to a gynecologist and examined with colposcopy, but has no accompanying test or treatment, no information is reported to PALGA.

Validation of our results with clinical data found that PALGA may slightly overestimate CIN 1 treatments (Appendix S2), although these clinical data came from a highly specialized clinic with physicians who almost exclusively treat cervical dysplasia. As such, treatment of CIN 1 with excision at this clinic is likely to occur less often than average. One Dutch study compared the impact of different CIN management strategies (more or less aggressive) in two hospital facilities in the same city and found that 68% less CIN 1 lesions were found with the less aggressive strategy.[30] As PALGA has national coverage, the treatment rates we observed were not influenced by policies or practices of any single clinic.

PALGA does not have a unique identification code to track women's screening history; women are identified by the first eight letters of their surname and date of birth. It is possible that tests of multiple women are attributed to a single identification code. In such cases, it is possible that follow-up was censored early for some women, leading to a misclassification of the highest diagnosis or most invasive treatment of the episode.

CONCLUSION

Our study shows that both under- and overtreatment takes place, despite guidelines being available. Regular monitoring of national trends and reviews of treatment rates should be implemented at each clinic that treats women for CIN, to make both gynecologists and pathologists aware of the guidelines and their own performance in relation to them. This may lead to greater compliance with the guidelines, reducing potential harms to women referred from screening.

ABBREVIATIONS

CIN – Cervical intraepithelial neoplasia
hrHPV – high-risk human papillomavirus
LLETZ – Large loop excision of the transformation zone
PALGA – Nationwide network of cyto- and histopathology in the Netherlands
ASC-US – atypical squamous cells of undetermined significance
LSIL – low-grade squamous intraepithelial lesion
HSIL – high-grade squamous intraepithelial lesion
AIS – adenocarcinoma in situ
AGC – atypical glandular cells

Conflict of interest statement

CA, EJ and IdK work on the Evaluation of Dutch National Cervical Cancer Screening Program project funded by the Dutch National Institute for Public Health and the Environment. RB has received speakers' fees from Roche Diagnostics and grants for contract research from SP-MSD.

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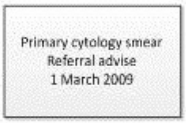
APPENDIX S1: DATA USED IN THIS STUDY

Data from the nationwide network and registry of histo- and cytopathology in the Netherlands (PALGA) was used to identify referrals from the Dutch National Cervical Cancer Screening Programme. This appendix explains which data was used in our results. Figure S1 outlines five fictitious example cases to demonstrate case- and data selection for this analysis. Explanation of these cases can be found in Supplementary Table 1.

Table S1: *Explanation of possible cases within PALGA*

Case	Referral type	Highest Diagnosis	Most invasive treatment	Notes
A	Direct	CIN 3	Large excision	The algorithm used in this analysis selects treatment and diagnosis variables from all secondary treatments regardless of chronological order, so the highest diagnosis and most invasive treatment in this screening episode are from different secondary tests.
B	Indirect	CIN 1	Biopsy	The secondary tests that are included in the analysis from this episode are two, three and four. The first secondary test results in referral advice, indicating the start of care by a gynaecologist.
C	Indirect	No histology	Cytology	This episode is counted in the total number of indirect referrals, but there is no CIN diagnosis, so this episode is not included in the main analysis in this study.
D	Direct	None	None	This woman may not have attended her referral appointment, or the colposcopy did not result in a histological or cytological examination. As such, there is no information for diagnosis or treatment for this screening episode.
E	None	None	None	This record is excluded as an indirect referral because the record that contains the referral advice after the primary cytology smear is in the next primary cytology episode. There are 421 records that are excluded from indirect referrals due to referral advice in the next primary screening round.

	Primary cytology smear indicating a direct referral or a revision within 6 months.
	Secondary test after a primary cytology that is not included in analysis of highest diagnosis or most invasive treatment. These tests are follow-up tests after a primary smear with advice of revision within 6 months.
	Secondary tests that are included on analysis are outlined as bold. The highest diagnosis and most invasive treatment of the episode are shown in bold and italic.
	Next primary cytology smear that is not counted in this analysis.

Legend for *Figure S1*

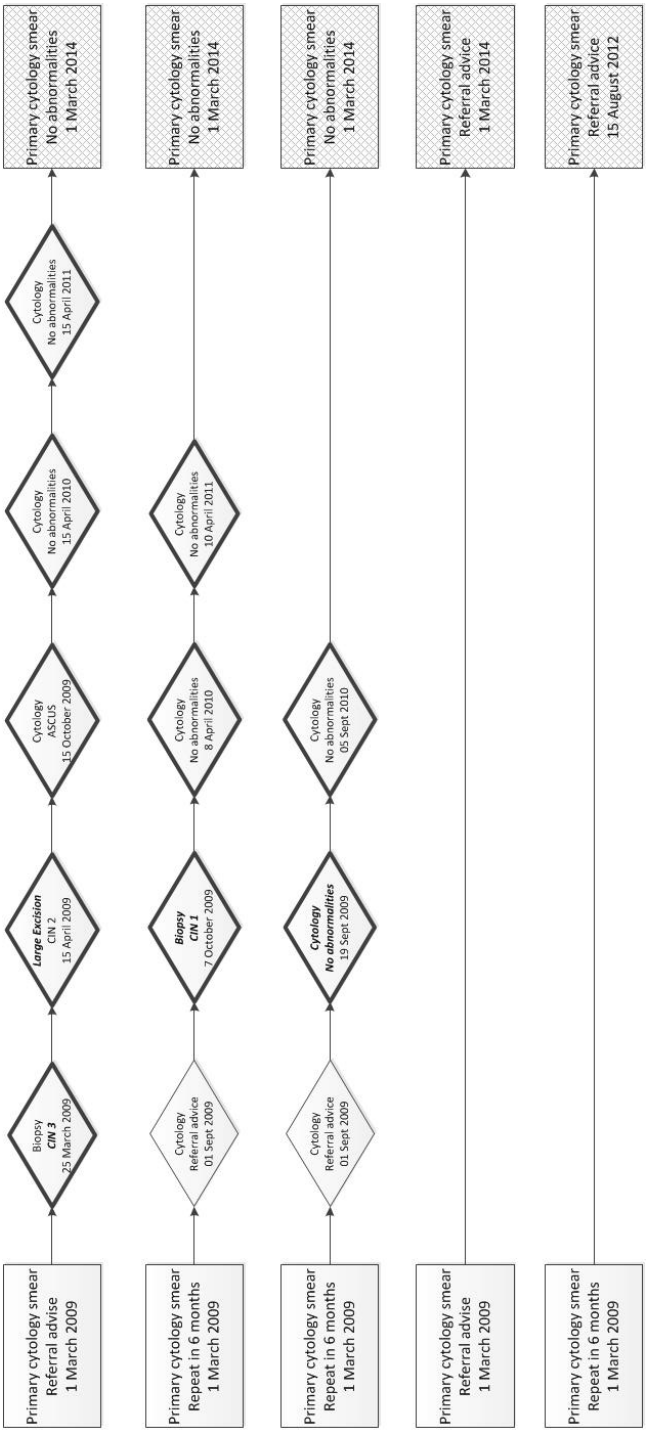


Figure S1: *Example cases - description of data used*

APPENDIX S2: VALIDATION OF RESULTS

Validation with experts

We consulted two expert groups and used clinical data from one specialist clinic to validate our results. Data experts at PALGA were consulted about quality of coding. The data in PALGA is based on information in pathologist reports. Reviews of histology records have previously been conducted by experts at PALGA to ensure that records are appropriately classified and have been found to be largely concordant with pathology reports.

Following this, three practicing Dutch gynaecologists (RB, BtH, JB) were asked whether the PALGA results were broadly reflective of the clinical practice in the Netherlands, in order to assess the face validity of our results. This assessment was based on their extensive knowledge of clinical practice in the Netherlands. They agreed that the results were broadly reflective of clinical practice.

Validation with clinical data

We compared a subset of our dataset with 2012 data from a specialist gynaecology outpatient clinic. This clinic has specialist physicians that primarily work with cervical dysplasia. To do this comparison, we created a subset of our PALGA data that matched the same year (2012) and same screening region that the clinic is located in.

The proportion of treatments (figure not shown) and diagnoses (Figure S2) were comparable in both datasets (with the exception of hysterectomies, which are not performed at the specialist outpatient clinic), as well as the rates of the use of large excision and biopsy in episodes with a CIN 2 or 3 diagnosis (figures not shown). Rates of treatment of CIN 1 lesions were lower at specialist clinic than in PALGA (Figure S3), however these differences may be explained by differences in policies and practices in various clinics in screening region covered by the PALGA dataset.

Conclusion of validation

Results of our validation found that PALGA reflects the distribution of diagnoses and treatments as found in a clinical dataset. Quality of coding was found to be good and face validity was checked by practicing gynaecologists. Based on the comparison with clinical data, the treatment rates for CIN 1 may be slightly overestimated, however the clinical data came from a highly specialised clinic. As such, CIN 1 treatment practices at this clinic are likely to be lower than average.

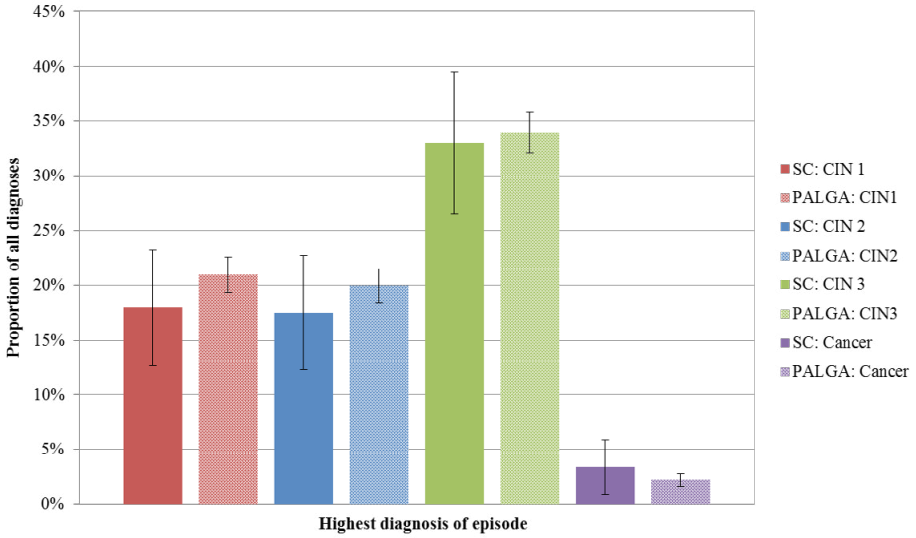


Figure S2: *Proportion of highest diagnosis of the episode by diagnosis and dataset, only CIN and cancer diagnoses shown, 95% confidence intervals*
SC: Specialist gynaecology outpatient clinic
CIN: Cervical intraepithelial neoplasia

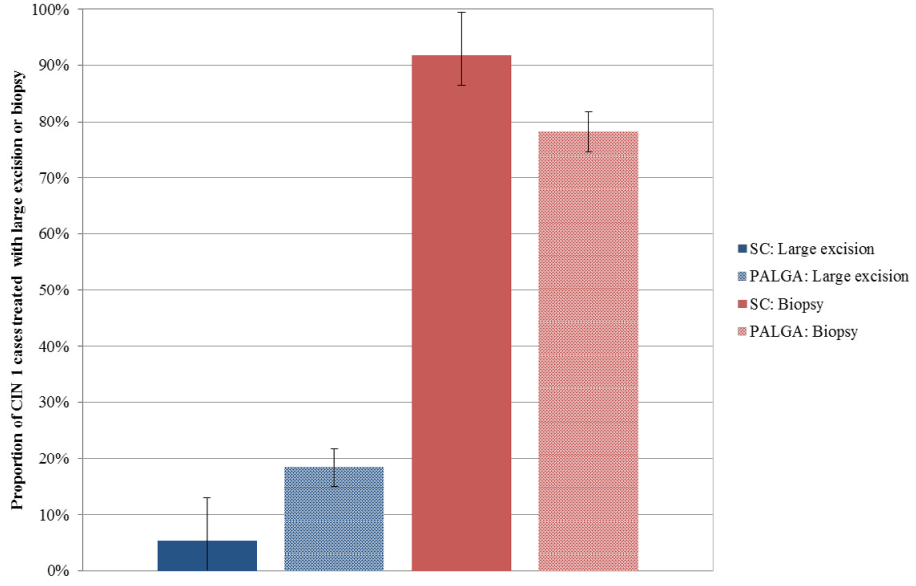


Figure S3: *Proportion of CIN 1 cases with large excision or biopsy as the most invasive technique used by data source, 95% confidence intervals*
SC: Specialist gynecology outpatient clinic
CIN: Cervical intraepithelial neoplasia