

# Strategies for non-invasive management of high-grade cervical intraepithelial neoplasia

Citation for published version (APA):

Koeneman, M. M. (2019). *Strategies for non-invasive management of high-grade cervical intraepithelial neoplasia: prognostic biomarkers and immunotherapy*. [Doctoral Thesis, Maastricht University]. Maastricht University. <https://doi.org/10.26481/dis.20190116mk>

## Document status and date:

Published: 01/01/2019

## DOI:

[10.26481/dis.20190116mk](https://doi.org/10.26481/dis.20190116mk)

## Document Version:

Publisher's PDF, also known as Version of record

## Please check the document version of this publication:

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## CHAPTER 11

### Valorisation



## Why is this thesis relevant?

### Relevance of non-invasive management of high-grade CIN

High-grade Cervical Intraepithelial Neoplasia (CIN2 and CIN3) is the precursor of cervical cancer. Not all high-grade CIN lesions progress to cervical cancer: this happens in approximately 30% of lesions, while spontaneous regression occurs in 20-40% of cases. Because the natural prognosis of an individual lesion cannot be predicted, high-grade CIN lesions were – until recently – all treated by surgical excision. This obviously results in overtreatment of those lesions that would regress spontaneously. In the Netherlands, approximately 5,000 women are treated for high-grade CIN yearly, most commonly by surgical excision of the cervical transformation zone (Large Loop Excision of the Transformation Zone – LLETZ). This is an effective treatment modality, but it is associated with a twofold increase in the risk of premature birth in subsequent pregnancies, probably due to cervical insufficiency. Premature birth, both early and late, has significant impact on neonatal development and parental quality of life. The risk of premature birth after LLETZ treatment could be avoided by non-invasive management of high grade CIN.

### The role of prognostic biomarkers in non-invasive management of high-grade CIN

A first strategy towards non-invasive treatment of high-grade CIN is observational management of those lesions that will show spontaneous regression. This would reduce overtreatment of high-grade CIN lesions. Current histopathological assessment is unable to differentiate between lesions that will progress to cervical cancer and those that will regress spontaneously. Instead, prognostic biomarkers could be applied to this aim. A wide variety of prognostic biomarkers has been studied, but none have reached clinical implementation. This thesis provides an overview of all studied prognostic biomarkers in high-grade CIN, which could serve as a general overview and as a basis for further research. Based on this review and our own biomarker studies, we have formulated several recommendations for future biomarker research, which include the application of the PROBE-criteria and the development of biomarker profiles or prediction models rather than individual markers.

We developed one such biomarker profile for spontaneous regression of CIN2. Although guidelines recommend observational treatment of CIN2 in younger women, adherence to this recommendation is not optimal. This could be due to fear of disease progression by both the patient and the physician. Our prediction model can be applied in such cases, to provide patients (and physicians) with a more individual risk prediction. This improves individual counseling of women with CIN2 and may reassure women that observational treatment is a good option when the chances of disease regression are high. The model consists of simple clinical parameters, instead of expensive or complicated markers, to make it widely applicable. To improve individual counseling of women with hrHPV positive CIN2, which concerns almost all lesions since the introduction of the new cervical cancer screening program, we identified two prognostic markers in this subgroup of patients. Smoking status and parity influence the natural prognosis of hrHPV positive CIN2 and these factors can now be taken into account when counseling women with regard to treatment options in hrHPV positive CIN2.

### **The role of imiquimod treatment in non-invasive management of high-grade CIN**

A second strategy towards non-invasive treatment of high-grade CIN is the application of non-surgical treatment modalities. One non-surgical treatment modality is included in the Dutch treatment guideline for CIN: imiquimod, a cream with antiviral and antitumor properties. However, evidence regarding treatment efficacy and clinical applicability is scarce and clinical application is very limited. The studies in this thesis provide additional evidence on the desirability and clinical applicability of imiquimod as a treatment modality for high-grade CIN. First, we identified reasons for the currently limited application: this seemed to be the result of a lack of awareness among physicians, but also a perceived lack of evidence regarding treatment efficacy and a high rate of side effects. Subsequently, a patient preference study was conducted to assess the desirability of imiquimod treatment among women. This study indicated a subgroup of women with a future pregnancy wish as potential candidates for imiquimod treatment. These results show that there seems to be an area of indication for imiquimod in treatment of high-grade CIN, but additional evidence on treatment efficacy and side effects is necessary. The TOPIC3 study was designed to provide this evidence. The inclusions of this study have been completed and the results are expected in the spring of 2019. Upon confirmation of its efficacy and tolerability, the results of this study may increase the clinical application of imiquimod as an alternative to LLETZ, with the aim to reduce future premature birth as a side effect of surgical treatment.

### **Target groups**

The results of this thesis are relevant for gynaecologists, pharmacists, high-grade CIN patients and research groups in the areas of prognostic biomarkers and imiquimod treatment of high-grade CIN. Application and development of prognostic biomarkers may improve individual patient counseling and management, reducing overtreatment of high-grade CIN. When the TOPIC-3 study confirms the clinical applicability of imiquimod as a treatment modality for high-grade CIN, it can be offered to women as an alternative to surgical treatment. Both strategies contribute to a reduction of surgical side effects, with the risk of future preterm birth as the most important.

### **Activities and innovation**

We have provided a first overview of all previously studied prognostic biomarkers in high-grade CIN and further investigated two promising markers. These results can function as a tool for future biomarker research. For these studies, we collaborated with our colleagues at the Stavanger University Hospital in Norway, where a database and biopsy material is available from a cohort of women with high-grade CIN who were left untreated for a mean of 16 weeks. We developed a first prediction model for spontaneous regression of CIN2 and identified for the first time prognostic biomarkers for hrHPV positive CIN2, which may aid physicians in a more individual patient management. For these studies, we collaborated with the department of Clinical Epidemiology and Medical Technology Assessment of the Maastricht University. To assess the clinical applicability of imiquimod treatment, we not only started a clinical study on treatment efficacy and side effects of imiquimod in high-grade CIN, but we also performed an inventory among gynecologists and a patient preference study to assess the support among these

groups for this treatment modality. This is important in the context of personalized medicine and shared decision-making. The patient preference study was performed in collaboration with the Clinical Epidemiology and Medical Technology Assessment of the Maastricht University. The TOPIC3 study is a national multicenter study, in which we collaborate with the Erasmus MC and the Catharina Ziekenhuis Eindhoven. To generate awareness of our study results, all studies were submitted to international scientific journals and many have been presented at international congresses.

### Schedule and implementation

This thesis provides evidence and tools for non-invasive management strategies in high-grade CIN, focusing on the prediction of spontaneous regression with prognostic biomarkers and immunotherapy with imiquimod. The results of this thesis could lead to the following implementations and future research opportunities.

- We recommend further research on prognostic biomarkers in high-grade CIN. This should be conducted according to the PROBE criteria for biomarker research, in order to improve interpretation, comparison and pooling of study outcomes. We believe that studies should aim for the development of biomarker panels or prediction models, in order to increase prognostic properties. Ideally, given the distinct difference in natural history of CIN2 and CIN3 lesions, prognostic markers should be studied in these groups separately.
- The prediction model and individual prognostic markers for spontaneous regression of CIN2 can be applied in clinical care, to improve individual patient counseling with regard to their chances of spontaneous regression. Furthermore, prognostic factors that can be influenced should be more actively addressed with patients. The results of our studies once again show the important effect of smoking. We therefore advocate that smoking cessation programs should be offered to smoking women with CIN2/3.
- The results of the inventory among gynecologists and the patient preference study, which show support for imiquimod as a treatment modality for high-grade CIN upon confirmation of its efficacy, serve as a justification for the performance of the TOPIC3 study and, hopefully, future clinical implementation of this treatment modality in specific patient groups.
- The TOPIC3 study will clarify the clinical applicability of imiquimod cream as a treatment modality for high-grade CIN. It will provide additional evidence on short- and long-term treatment efficacy, side effects and quality of life of imiquimod treatment. Upon the establishment of adequate treatment efficacy and clinical applicability, the results could support physicians and patients in a choice for imiquimod as treatment for high-grade CIN.
- A second aim of the TOPIC3 study is the identification of predictive markers for adequate treatment outcome. This could enable selection of women in whom an adequate response to imiquimod treatment is expected. To this aim, the biological mechanisms behind imiquimod-associated clearance of high-grade CIN should be further elucidated. An intended study by the authors on cervical TLR expression and the immune response to imiquimod in high-grade CIN could contribute to this issue.
- Other indications for imiquimod treatment of high-grade CIN may be large lesions requiring

extensive excision or recurrent CIN lesion, with the aim to prevent repeated cervical surgery including hysterectomy. The efficacy of imiquimod in recurrent CIN lesions is currently being studied in the TOPIC-2 trial, performed by our research colleagues from the Erasmus MC.

- Remaining knowledge gaps with regard to imiquimod treatment of high-grade CIN are cost-effectiveness and patient and physician satisfaction with imiquimod treatment. These issues could be addressed in future studies. Finally, long-term studies should reveal whether imiquimod indeed reduces long-term side effects of surgical treatment, with emphasis on premature birth after both treatment modalities.