

## Recommendations for Negative Conizations of the Cervix

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### Description

Cervical Intraepithelial Neoplasias (CIN) is premalignant lesions associated with persistent High-risk Human Papilloma Virus (HPV) infections. If not treated, they can slowly progress to cervical cancer which represents the fourth most frequently diagnosed cancer in women worldwide. The gold-standard treatment for CIN is excision by cervical conization [1]. Although considered safe and largely performed, this procedure may increase the risk of bleeding, infections, and especially the risk of complications in obstetric outcomes in women in reproductive age. Avoiding unnecessary conizations is not only important for patients individually but also for public health and economic resources savings.

The absence of lesion in a cervical conization is not necessarily reassuring as many questions arise: Was the cytological and/or histological diagnosis wrong? Was the CIN not included in the excision? How to follow-up this patient? To provide some lighting to guide clinicians, a retrospective study reviewed 19 original articles that addressed this issue, with a total of 7310 cones analyzed. Negative conizations were not infrequent: The studies revealed a rate ranging from 10% to 35% of all conizations [2].

Some hypotheses that may explain why patients who were diagnosed with CIN either by cervical biopsy or by the colposcopic findings have negative cone specimens include: colposcopy over diagnosis, lesion regression and complete removal of a small lesion during biopsy, false positive biopsy, false negative result in the conization, and excisional error. Young patients with minor findings small colposcopic lesions and negative high-risk HPV test should be careful reassessed before the excision, since those are important risk factors for negative conizations [3-6].

Nevertheless, clinicians and pathologists can take some actions to improve this practice. Testing for HPV and the application of immunohistochemistry biomarkers such as p16 and ki67 aim to identify high risk HPV types and hidden dysplastic areas, mainly in difficult differential diagnosis situations. Another major important practice is limiting and recognizing diagnostic errors by performing a pathology specimen review studies show that misinterpretation rates may represent up to 25% of diagnosis, either from the cytology slides, from the cervical biopsy or from the excision specimen. Deep sectioning levels should be executed, as small dysplastic areas may

not have been sampled in the routine analysis. Recurrence rates are not necessarily lower in patients with negative conizations [3-6]. An important study concluded quite the opposite: The negative cone recurrence was greater than the positive cone recurrence with clear margins (24% vs. 15%) in short-term follow-up [6]. Regarding follow-up time there is no standard recommendation but the need for careful surveillance is common sense among all authors.

It is challenging to avoid unnecessary procedures, as well as it is unreliable to manage a negative cervical conization specimen. Since there are no current guidelines that address absence of lesion in excision specimens of the cervix our review suggests waiting an interval of 4 to 6 weeks between biopsy and excision, short-term re-evaluation for patients in young age with small colposcopic lesions, as well as for patients with normal colposcopy immediately before the conization routinely deep sectioning levels in the negative specimens; immunohistochemistry biomarkers to identify hidden dysplastic areas testing for high-risk HPV and the same 2 years follow-up used for positive cones with compromised margins [2].

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