Cervical Cone Measurements and Residual Disease in LLETZ Conisation for Cervical Intraepithelial Neoplasia

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Abstract. Aim: To investigate the oncologically safe limits of excision in large loop excision of the transformation zone (LLETZ) conisation performed for cervical pathology. Patients and Methods: A retrospective study conducted at the Colposcopy Unit in a University Hospital setting. Three hundred and sixty-one cases of LLETZ conisation were conducted in a 2-year period. Data concerning age, cone dimensions, lesion types and excision margins were recorded. Results: The mean age of women was 36.7 years, with 181 (50.5%) low-grade squamous intraepithelial lesion cases, 166 (45.7%) high-grade squamous intraepithelial lesion, and 14 (3.8%) with stage-IA1 cervical carcinoma. Mean conisation depth and cone volume were 10.9 mm and 2.2 ml, respectively. Incomplete removal of lesions occurred in 25% of women and correlated to severity of cervical intraepithelial neoplasia and conisation depth. The higher the grade of the lesion, the greater the percentage of residual disease. Conisation depth exceeding 10 mm, in our cohort, led to significantly less residual disease. Conclusion: Results indicate that a conisation depth of <10 mm may be a risk factor predicting positive resection margins, while cone volume is an inappropriate clinical marker.

During the past 20 years, there has been a profound decrease in the incidence of invasive cervical cancer due to the treatment of pre-invasive lesions detected through screening programs (1). Cervical conisation is considered necessary for definitive diagnosis and/or treatment in a significant number of women with cervical pathology. Large loop excision of the transformation zone (LLETZ) is considered the conservative method of treatment and removes the transformation zone containing abnormal cells and preserves cervical function at the same time (2, 3). LLETZ is considered a popular conisation procedure (2) as it combines the advantages of a comprehensive histological investigation of the removed tissue with the precise assessment of excision margins, in addition to being a simple procedure of relatively short duration, low cost, good compliance and has an easy learning curve (4).

In this retrospective observational study, we aimed to correlate the geometric measurements of cone biopsies removed by LLETZ and the presence of residual disease. Three hundred and sixty-one (n=361) cases of cervical conisation with LLETZ technique were reviewed in our Department and intraepithelial lesion type, cone volume, conisation depth and excision margins were recorded.

Patients and Methods

Between January 2007 and June 2009, 361 cervical conisations were conducted with LLETZ technique for intraepithelial lesions on the basis of abnormal PAP smears and/or colposcopic findings by colposcopists working at our department. At the time of conisation, colposcopy was repeated with the use of acetic acid and Lugol’s iodine in order to define the lesion and therefore determine the extent of excision. Post-conisation, data concerning the patients’ age, lesion type and excision margins were retrospectively collected from the hospitals’ Pathology Department archive. Cervical cone dimensions were also available from the pathology examination report of the cone specimen and were used to estimate the conisation depth and cone volume. Size measurements were made before tissue fixation. Cone volume was calculated with the geometric formula for an ellipse: volume=(D1×D2×D3) π/6; where π≈3.14 and D1, D2, and D3 are the three diameters of the cone, with D3 being the conisation depth/height of the cone.

Although relevant, cytology/colposcopy referral data obtained prior to conisation and lesionional follow-up was not recorded. The primary end-point of this study was to correlate cone dimensions and the precise histopathologic diagnosis regarding residual disease. For this reason, only cervical cone data based on the patients’ pathology report was included.

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Written informed consent from women attending the Colposcopy Unit was obtained for the use of their medical data. Study approval was also received from the Institutional Ethics Board. Descriptive statistical analysis was performed with the use of SPSS version 17.0 (SPSS Inc, Chicago, IL, USA). Pearson’s correlation coefficient and independent samples t-test were used and findings were considered significant at the level of \( p<0.05 \).

**Results**

The mean age of women in our cohort (n=361) was 36.7 years (range 17-76 years) for the general cohort, and 38.1 (range 18-76 years), 34.8 (range 17-73 years) and 43.0 years (range 25-74 years) for the low-grade squamous intraepithelial lesion (LGSIL), high-grade squamous intraepithelial lesion (HGSIL) and cervical cancer subgroups, respectively. The pathology report of the cervical cone specimens revealed 181 (50.1%) cases of LGSIL, 166 (45.9%) HGSIL and 14 (3.8%) stage IA1 cervical carcinoma (Table I).

Mean conisation depth was 10.9 mm (range 1-27 mm), with 38.5% of cases >10 mm, whereas the mean cone volume was 2.2 ml (range 0.5-6.8 ml) with 6.9% of cases >4 ml (Table I). Women of reproductive age (arbitrarily selected range between 17-40 years old) (Table II) represented 64.3% of the general cohort, 59.1% of LGSIL, 71.1% of HGSIL and 50% of the cervical cancer group. In this sub-group of women of reproductive age, 38.3% received a conisation depth of >10 mm and 6.0% had a cone volume of >4 ml.

Cone excision margins were non-free in 90 out of 361 women, indicating that the possibility of residual disease for a woman undergoing cervical conisation in our department over the last two years was 25% in the total group. Pearson’s correlation coefficient revealed that residual disease correlated significantly to conisation depth (\( r=-0.113; \ p<0.05 \)) and cervical intraepithelial neoplasia (CIN) severity (\( r=0.257; \ p<0.001 \)). This means that the smaller the conisation depth and higher the CIN severity, the greater the risk of residual disease.
percentage of women with residual disease. Table I shows that our colposcopists excised larger cone volumes and performed greater conisation depths in higher grade lesions, as one would normally expect. Nevertheless, the intraepithelial lesions were not fully eradicated, leading to a higher percentage of residual disease as lesion type progressed from LGSIL to HGSIL and invasive cancer.

Figure 1 shows that the percentage of incompletely removed lesions correlated with the length of the 361 cones (total group). In the subgroups of <10 mm versus >10 mm conisation depth, the number (and percentage) of incompletely removed lesions were 64/222 (28.0%) and 28/139 (20.0%), and this difference was statistically significant (p=0.013). In other words, for cones measuring 10.0 mm or less in length there was a significantly higher proportion of non-radically removed lesions than for those having a length greater than 10.0 mm. Findings for cone volume were not significant, suggesting that the percentage of incompletely removed lesions did not correlate with the volume of the 361 cones.

Finally, the mean +2 standard deviations for conisation depth was calculated for each lesion type in patients with residual disease (Tables I and II). This conisation depth represents the upper value, containing 95% of all cervical cones with residual disease. This means that if a HGSIL patient were to have a 95% probability of having no residual disease, then conisation depth would have to reach 18 mm (Tables I and II).

Discussion

This study has shown that the higher the grade of lesion, the greater the percentage of women with conisation depth >10 mm and cone volume >4ml. Despite the greater amount of cervical tissue removed, as intraepithelial lesions progressed from LGSIL to HGSIL and early invasive cancer, the percentage of incomplete removal also increased. Irrespective
of conisation depth and cone volume, the possibility of incomplete lesion removal and thus residual disease was 25% for a woman in the general cohort, ranging from 12.7% in the LGSIL group to 34.3% and 71.5% in the HGSIL and invasive cancer group respectively.

Concerning the oncological limits for safe procedure, it can be seen in Figure 1 that conisation depth has a significant association with the complete/incomplete removal of lesions. In particular, for cones measuring <10 mm in length there was a significantly higher rate of incompletely removed lesions. If the colposcopist were to perform cervical conisation and wanted to significantly reduce the rate of residual disease, then they would have to choose the depth limit of 10 mm. If the colposcopist were to provide a HGSIL patient less than 40 years of age with a 95% chance of no residual disease, then they would have to opt for a deeper cone with depth of 18 mm.

Cone volume was unfortunately not significantly associated with complete/incomplete removal of lesions. This could be due to the method of cone volume calculation applied. Measurements of conisation depth were accurate and unequivocal in all cases with the use of a ruler prior to fixation, whereas volumes were mathematically calculated with the use of the geometric formula for an ellipse. It has been shown in phantom studies (5) that the accuracy of volume measurements with the use of this formula lies within 5-20% of the actual volume. Perhaps the lack of accuracy accounts for the non-significant findings concerning the association between free/non-free excision margins with cone volume. A far more accurate method of cone volume assessment would have been the fluid displacement technique based on Archimedes’ principle (6). In the study of Rubio et al. (6) in 1978, volumetric determinations were performed for 247 cone specimens with the use of water displacement technique and the authors demonstrated that a cone volume of <2.5 ml had a significantly higher proportion of residual disease than those cones with greater volume. This is the only report found in literature suggesting that in terms of cone volume, the limit for oncologically safe procedure may probably be 2.5 ml.

This is a retrospective observational study that aims to provide an analysis of cone measurements and to investigate the oncologically safe limits in cervical conisation. There are certain limitations to be considered about our study. First of all, the retrospective nature of our case-series data unfortunately does not warrant a very high level of evidence. Secondly, the surprisingly large proportion of cases with positive or non-free cone margins suggests that LLETZ conisation technique was not optimal, despite being performed by presumably experienced and well-trained colposcopists in our department. Moreover, although cone margins in pathology reports may be positive, the patient may in fact have no residual disease. This can be attributed to the thermal effect of the loop during conisation at the margins of the remaining cervix and also to the use of diathermy for hemostasis, which both eradicate any remaining dysplastic cells. This means that less than 25% of women in our study have residual disease. The precise number is unknown and it is difficult to determine accurately, even with close follow-up with colposcopy/cytology.

Our study has shown that conisation depth <10 mm increases significantly the rate of residual disease and may therefore be a risk factor predicting positive resection margins. Moreover, if cone depth exceeds 18-20 mm, this may lead to no residual disease with 95% probability. However, this would be an unacceptable routine practice as such deep cones (18-20 mm) would obstetrically compromise future pregnancies in women of reproductive age. There are literature reports that large cones expose the patient to a higher risk of future adverse obstetric outcomes, especially when conisation depth is >10 mm (7-9) and cone volume is >4 ml (10). Additionally, previous reports have correlated the amount of cervical tissue removed and the occurrence of adverse obstetric outcomes (11-13). Specifically, if cone depth is >10 mm, there is a significantly increased risk of preterm delivery (pooled relative risk=2.6, 95% CI: 1.3-5.3) (4, 14). Other research has highlighted the association between cone volume and adverse obstetric outcome (9, 10). In these studies, when the excised cone volume was >4 ml, the risk of preterm delivery was 31.7% versus 3.2% (10). Another report found that increased cone depth was associated with a significant increase in the risk of preterm delivery, with an estimated 6% increase in risk per each additional millimeter of tissue excised (15).

In conclusion, conisation depth of <10 mm may be a risk factor predicting positive resection margins, while cone volume is an inappropriate clinical marker. These key points should be taken into consideration by the colposcopist prior to performing LLETZ conisation. In the end, therapy should be undertaken by experienced colposcopists who can achieve the best balance between maximum eradication rates of intraepithelial lesions and minimum disruption of cervical anatomy and function.

Conflict of Interest Statement

The Authors declare that there are no conflicts of interest.

References


