



POSITIVE CONE MARGINS – A DISADVANTAGE OF THE LARGE LOOP EXCISION OF TRANSFORMATION ZONE TECHNIQUE?

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SUMMARY – The aim was to compare the efficiency of large loop excision of the transformation zone (LLETZ) and cold-knife conization according to the incidence of positive cone margins in histopathologic analysis of the cervical cone. In the study, data obtained from 568 female patients with cone biopsy due to cervical changes during a four-year period (2012-2015) were retrospectively analyzed. Group 1 included patients who were operated on using LLETZ technique and group 2 consisted of patients with cold-knife cone biopsy. LLETZ was a method of choice in 334 (59%) patients, whereas 234 (41%) patients underwent cold-knife cone biopsy. The percentage of positive cone margins was much higher with LLETZ technique, even 39% (131 patients), as compared to 20% with cold-knife cone biopsy. In conclusion, the technique and cone configuration should be individualized, depending on the specifics of the lesion. The transformation zone is not always removed during one LLETZ procedure. High percentage of positive cone margins is not a disadvantage of LLETZ technique because of differences in indications, approach and multiple cutting. The real success of conization can be measured only by the relapse frequency over a long period of time with a high number of patients.

Key words: *Conization; Cervical intraepithelial neoplasia; Uterine cervical dysplasia; Uterine cervical cancer*

Introduction

In 2011, the incidence of cervical cancer in Croatia was 12.4/100000 (total number 321) with a mortality rate of 3.5/100000 (total number 111)¹. Cervical cancer is a significant health problem in the world and the fourth most common cause of women's death. In Croatia, cervical cancer is second in incidence among malignant diseases in women in the 40-49 age group². When detected at an early stage, cervical cancer is one of the rare neoplasms that can be completely cured. There is also effective primary prevention³. Cervical

dysplasia is a frequent condition that can be found at any age, but unfortunately, it most often appears in young women during their childbearing years in the 25-35 age group⁴.

According to Bethesda Classification⁵, squamous lesions are divided into low grade squamous intraepithelial lesions (LSIL), high grade squamous intraepithelial lesions (HSIL) and atypical squamous cells (ASC). LSIL, formerly known as cervical intraepithelial neoplasia (CIN) I, has low potential for developing cervical malignancy, whereas HSIL, formerly CIN II, CIN III and carcinoma *in situ* (CIS), have a high malignancy potential. Prevention of possible cervical malignancy is a target of gynecologists worldwide but overtreatment of premalignant lesions should be avoided.

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Currently, there are two different groups of methods for cervical dysplasia treatment, one based on local destruction and the other based on excision. Cryotherapy, laser vaporization and electrocoagulation are based on local destruction but these techniques do not provide surgical specimen for pathologic evaluation, as opposed to the methods based on excision such as loop diathermy, cold-knife conization, and laser conization^{6,7}.

Large loop excision of transformation zone (LLETZ) was presented by Prendiville in 1989, and it has become the treatment of choice for women with squamous epithelial lesions⁷. According to Cochrane review of surgical treatments of CIN in 2013, LLETZ seems to be the most reliable technique with the least morbidity⁸. LLETZ is a procedure that removes the entire cervical transformation zone using low voltage diathermy loop. LLETZ is performed using a wire loop with electric current and these loops provide cutting and coagulation. Various shapes and sizes of loops are used, depending on the size and orientation of the lesion in order to avoid excessive excision^{7,9,10}. LLETZ has many advantages. It is an outpatient procedure that can be performed in local anesthesia⁷. The cost is much lower due to shorter hospital stay¹¹. It is simple and effective, provides good performance and individualization because of diverse loops that are available^{7,11}. The incidence of complications with LLETZ is lower than with cold-knife conization¹². LLETZ has a lower rate of intraoperative and postoperative bleeding and cervical stenosis than cold-knife conization^{12,13}.

Preterm birth is often cited as an indicator of conization success. LLETZ is safer than cold-knife conization, and has smaller impact on perinatal mortality and morbidity^{12,14}. A shortcoming of LLETZ is a higher percentage of positive excision margins.

The purpose of this study was to compare the efficiency of LLETZ and cold-knife conization according to the incidence of positive cone margins in histopathologic analysis of the cervical cone at the Gynecologic Oncology Unit, Department of Gynecology and Obstetrics, Sestre milosrdnice University Hospital Center, Zagreb, Croatia.

Material and Methods

The study was designed as a retrospective analysis of data obtained from 568 female patients with cone biopsy due to cervical changes at Sestre milosrdnice

University Hospital Center, Zagreb, Croatia, during a four-year period (2012-2015). Upon admission to the hospital, all patients signed an informed consent form to use their medical data for research purposes.

Squamous intraepithelial lesions were confirmed in all patients by cervical cytology, followed by colposcopy evaluation and colposcopy-directed biopsy. Surgical procedures were LLETZ and cold-knife conization. The patients were divided into two groups according to the procedure type. Group 1 included patients who were operated on using LLETZ technique and group 2 consisted of patients that underwent cold-knife cone biopsy.

Cold-knife conization was performed under general anesthesia, and LLETZ under general or local anesthesia. We performed endocervical curettage in each patient before conization, and the material was saved separately for histopathologic analysis. Cold-knife conization was performed with a scalpel, and hemostasis of the cone bed was achieved by coagulation of the excision base with the ball electrode or with a cerclage suture technique if coagulation was not sufficient. Histopathologic analysis in both groups was performed in the same laboratory under identical conditions at Sestre milosrdnice University Hospital Center and classified according to the World Health Organization guidelines.

Results

Cold-knife biopsy was performed in 234 (41%) and LLETZ procedure in 334 (59%) patients (Fig. 1).

During the study period, we found a permanent increase in the use of LLETZ *versus* cold-knife cone biopsy (Fig. 2).

Large loop excision of transformation zone was the method of choice in 334 (59%) patients, whereas cold-knife cone biopsy was used in 234 (41%) patients. The percentage of positive cone margins was much higher with LLETZ technique, even 39% (n=131) as compared to 20% with cold-knife cone biopsy.

There also was a declining trend in the occurrence of positive cone margins from 2012 when the percentage was 42% until 2015 when histopathologic analysis confirmed 35% of positive cone margins with LLETZ technique. In contrast, cold-knife cone biopsy maintained almost constant incidence of positive cone margins. The incidence of positive margins was 13% in 2012 and 12% in 2015 (Tables 1 and 2).

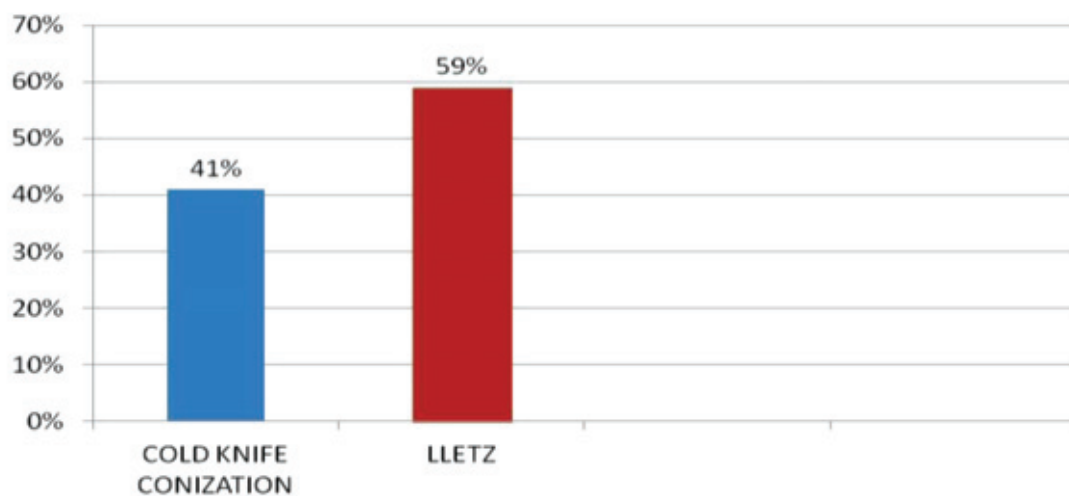


Fig. 1. Rate of cold-knife conization (41%) and large loop excision of transformation zone (59%) at Sestre milosrdnice University Hospital Center.

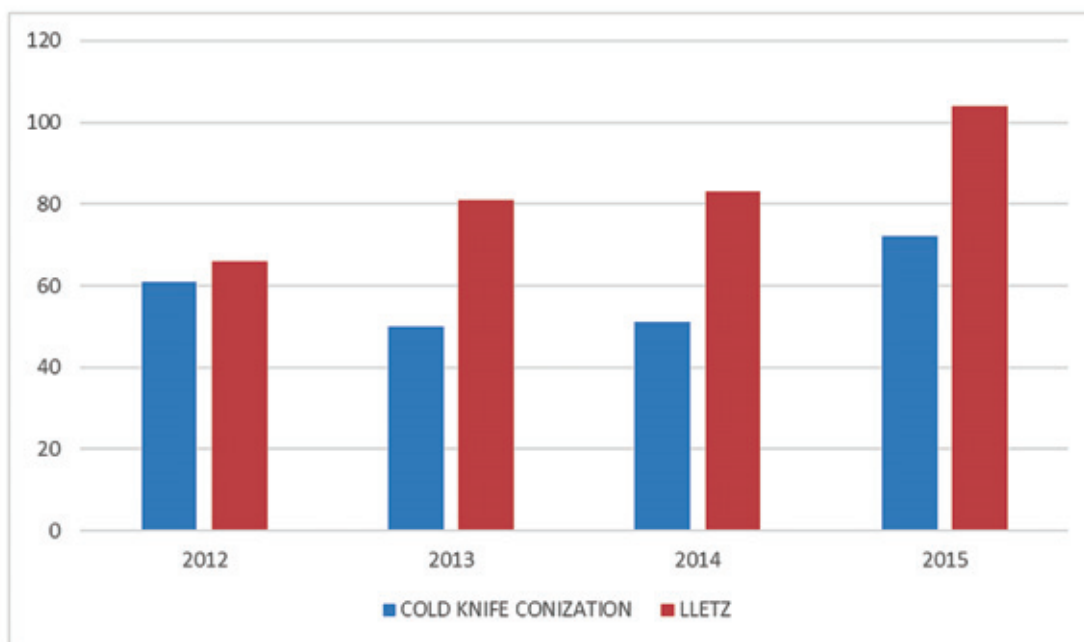


Fig. 2. Rate of cold-knife conization and large loop excision of transformation zone procedure at Sestre milosrdnice University Hospital Center during the 2012-2015 period.

Table 1. Incidence of positive cone margins with LLETZ technique during the 2012–2015 period

Year	LLETZ	Positive margins, n	Positive margins, %
2012	66	28	42
2013	81	35	43
2014	83	32	39
2015	104	36	35
Total	334	131	39

LLETZ = large loop excision of transformation zone

Table 2. Incidence of positive cone margins with cold-knife conization during the 2012–2015 period

Year	Cold-knife conization	Positive margins, n	Positive margins, %
2012	61	8	13
2013	50	5	11
2014	51	6	11
2015	72	9	12
Total	234	28	12

Discussion

The LLETZ technique has become favored among clinicians and patients because of its reported advantages (shorter hospital stay, shorter recovery, possibility of local anesthesia). It is not just a therapeutic method but also a diagnostic technique because it obtains surgical specimen for pathologic evaluation^{12,15}. Despite its cost-effectiveness, with rapid and safe performance, there still are lots of controversies and disagreements about cone margins after using LLETZ technique and its outcome.

The goal of LLETZ procedure is excision of the entire transformation zone with adequate cervical margins¹⁶. Studies have shown that after using LLETZ technique, positive cone margins are more often than after using cold-knife conization. In the meta-analysis by Jiang *et al.*¹², the prevalence of positive margins was 22% (343/1595) after LLETZ and 13% (200/1596) after cold-knife conization.

A meta-analysis by Gheam-Maghami *et al.*¹⁷ showed that high-grade post-treatment disease occurred in 18% (597/3335) of women who had incomplete excision compared with 3% (318/12493) of those with complete excision. Positive margin after conization is the most important predictor for cervical change recurrence¹⁸. This raises a question of LLETZ being appropriate method for the treatment of women with high-grade cervical preinvasive lesions. Studies show there is no evidence for significant differences in the residual disease rate between LLETZ and cold-knife conization technique¹².

There are two explanations to clarify a definitive histopathologic specimen after LLETZ. First is thermal artifact and second is fragmentation of LLETZ specimen^{19,20}. Thermal damage can make cone margins after LLETZ unclear, and the outcome depends on electrical energy and operator's speed of incision¹⁵. At

the same time, thermal destruction at the conization site can have therapeutic effect. Thermal artifact can be reduced by taking a single piece of tissue instead of tissue fragments.

However, LLETZ is a technique where the operator should find a balance between maximal treatment and minimal damage to cervical tissue. The transformation zone is not always removed in a single act by cone biopsy. The technique and cone configuration should be individualized, depending on the specifics of lesions. If the lesion is large, and/or we are limited in technical equipment, such as loop size, a single piece of tissue cannot be excised in one act and this can influence the status of excisional margins²¹.

The operator should also take cone dimensions in consideration while performing LLETZ. Papoutsis *et al.*²² in their study showed that women with cone depth <10 mm, cone volume <2.1 cm³ or less than 8.6% of initial cervical volume, and cone base surface less than 1/3 of the total external surface of ectocervix had an increased risk of positive cone margins. Age of women is an important factor in LLETZ performance; while most of cervical changes occur in reproductive age, the sparing factor of LLETZ technique plays a major role because safe obstetric limits are different from oncologic ones. Studies have shown that the risk of preterm delivery increases when the cone depth is more than 10 mm; indeed, the risk of preterm delivery increases with each millimeter of excised tissue^{4,14}.

Excision of cervical tissue should be performed by an experienced clinician. The success of surgical conization depends on the quality of technical equipment, training of colposcopists and operators, and selection of candidates^{19,23}. The minimally invasive technique is the main advantage of LLETZ. It offers a potentially curative procedure without the risk of complications recorded in the cold-knife excision technique.

Conclusion

The technique and cone configuration should be individualized, depending on the specifics of lesion. The transformation zone is not always removed in a single act by LLETZ cone biopsy. The high percentage of positive cone margins is not a disadvantage of LLETZ technique because of differences in indications, approach, and multiple cutting.

References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, *et al.* Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*. 2015;136:E359-86. doi: 10.1002/ijc.29210.
2. Croatian National Cancer Registry, Croatian National Institute of Public Health, Zagreb, Croatia. Bulletin No. 44, Zagreb, 2021.
3. Petry KU. Management options for cervical intraepithelial neoplasia. *Best Pract Res Clin Obstet Gynaecol*. 2011;25:641-51. doi: 10.1016/j.bpobgyn.2011.04.007.
4. Kyrgiou M, Koliopoulos G, Martin-Hirsch P, Arbyn M, Prendiville W, *et al.* Obstetric outcomes after conservative treatment for intraepithelial or early invasive cervical lesions: systematic review and meta-analysis. *Lancet*. 2006;367:489-98. doi: 10.1016/S0140-6736(06)68181-6.
5. Wilbur DC, Nayar R. Bethesda 2014: improving on a paradigm shift. *Cytopathology*. 2015;26:339-42. doi: 10.1111/cyt.12300.
6. Jones HW. Treatment of cervical intraepithelial neoplasia. *Obstet Gynecol*. 1990;33:826-36. doi: 10.1016/0002-9378(90)90035-6.
7. Prendiville W. Large loop excision of the transformation zone. *Clin Obstet Gynecol*. 1995 Sep;38(3):622-39. doi: 10.1097/00003081-199509000-00022.
8. Martin-Hirsch PPL, Paraskevaidis E, Bryant A, Dickinson HO. Surgery for cervical intraepithelial neoplasia. *Cochrane Database Syst Rev*. 2010 Jun 16;(6):CD001318. doi: 10.1002/14651858.CD001318.pub2.
9. Murdoch JB, Grimshaw RN, Morgan PR, Monaghan JM. The impact of loop diathermy on management of early invasive cervical cancer. *Int J Gynecol Cancer*. 1992 May;2(3):129-33. doi: 10.1046/j.1525-1438.1992.02030129.x.
10. Oz M, Cetinkaya N, Korkmaz E, Doga Seckin K, Mutlu Meydanli M, Gungor T. Optimal cone size to predict positive surgical margins after cold knife conization and the risk factors for residual disease. *J Turk Ger Gynecol Assoc*. 2016;17:159-62. doi: 10.5152/jtgga.2016.16066.
11. de Cabezon RH, Sala CV, Gomis SS, Lliso AR, Bellvert CG. Evaluation of cervical dysplasia treatment by large loop excision of the transformation zone (LLETZ). Does completeness of excision determine outcome? *Eur J Obstet Gynecol Reprod Biol*. 1998 May;78(1):83-9. doi: 10.1016/s0301-2115(98)00016-5.
12. Yan-Ming Jiang, Chang-Xian Chen, Li Li. Meta-analysis of cold-knife conization *versus* loop electrosurgical excision procedure for cervical intraepithelial neoplasia. *Onco Targets Ther*. 2016;9:3907-3915. doi: 10.2147/OTT.S108832.
13. Brun JL, Youbi A, Hocke C. Complications, sequelae and outcome of cervical conizations: evaluation of three surgical techniques. *J Gynecol Obstet Biol Reprod (Paris)*. 2002;31(6):558-64. PMID: 12407327.
14. Noehr B, Jensen A, Frederiksen K, Tabor A, Kjaer SK. Depth of cervical cone removed by loop electrosurgical excision procedure and subsequent risk of spontaneous preterm delivery. *Obstet Gynecol*. 2009;114:1232-8. doi: 10.1097/AOG.0b013e3181bf1ef2.

15. Prendiville W, Cullimore NS. Large loop excision of the transformation zone (LLETZ): a new method of management for women with cervical intraepithelial neoplasia. *Br J Obstet Gynaecol.* 1989;96:1054-60. doi: 10.1111/j.1471-0528.1989.tb03380.x.
16. Wright TC Jr, Massad LS, Dunton CJ, Spitzer M, Wilkinson EJ, *et al.* 2006 American Society for Colposcopy and Cervical Pathology – sponsored Consensus Conference. 2006 consensus guidelines for the management of women with abnormal cervical cancer screening tests. *Am J Obstet Gynecol.* 2007;197:346-55. doi: 10.1016/j.ajog.2007.07.047.
17. Gheam-Maghani S, Sagi S, Majeed G, Soutter WP. Incomplete excision of cervical intraepithelial neoplasia and risk of treatment failure: a meta-analysis. *Lancet Oncol.* 2007;8(11):985-93. doi: 10.1016/S1470-2045(07)70283-8.
18. Serrati M, Siesto G, Carollo S, Formenti G, Riva C, Cromi A, *et al.* Risk factors for cervical intraepithelial neoplasia recurrence after conization: a 10-year study. *Eur J Obstet Gynecol Reprod Biol.* 2012;165:86-90. doi: 10.1016/j.ejogrb.2012.06.026.
19. Bharanthan R, Sagoo B, Subramaniam A, Larsen-Disney P, Fish A. LLETZ specimen fragmentation: impact on diagnosis, outcome, and implications for training. *J Obstet Gynaecol India.* 2013 Oct;63(5):332-6. doi: 10.1007/s13224-012-0332-8.
20. Jakus S, Edmonds P, Dunton C, King SA. Margin status and excision of cervical intraepithelial neoplasia: a review. *Obstet Gynecol Surv.* 2000;55(8):520-7. doi: 10.1097/00006254-200008000-00025.
21. Naumann RW, Bell MC, Alvarez RD, *et al.* LLETZ is an acceptable alternative to diagnostic cold-knife conization. *Gynecol Oncol.* 1994;55:224-8. doi: 10.1006/gyno.1994.1281.
22. Papoutsis D, Rodolakis A, Mesogitis S, Sotiropoulou M, Antsaklis A. Appropriate cone dimensions to achieve negative excision margins after large loop excision of transformation zone in the uterine cervix for cervical intraepithelial neoplasia. *Gynecol Obstet Invest.* 2013;75:163-8. doi: 10.1159/000345864.
23. Garcia Ramos AM, Garcia Ramos ES, Barroso dos Reis HL, Bueno de Rezende R. Quality evaluation of cone biopsy specimens obtained by large loop excision of the transformation zone. *J Clin Med Res.* 2015;7(4):220-4. doi:10.14740/jocmr1951w.

Sažetak

POZITIVNI RUBOVI KONUSA – NEDOSTATAK METODE LLETZ

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Cilj studije bio je usporediti učinkovitost metode LLETZ i konizacije hladnim nožem u odnosu na učestalost pojave pozitivnih rubova u histopatološkoj analizi cervikalnog konusa. Provedena je retrospektivna analiza podataka dobivenih od 568 bolesnica koje su bile podvrgnute biopsiji konusa zbog promjena na cerviksu u razdoblju od 2012. do 2015. godine. U prvoj skupini su bile bolesnice kod kojih je učinjen LLETZ, a u drugoj konizacija nožem. LLETZ je bila metoda izbora u 59% naših slučajeva, tj. u 334 bolesnice, dok je konizacija hladnim nožem primijenjena u 41% slučajeva, tj. kod 234 bolesnice. Postotak pozitivnih rubova bio je znatno viši kod metode LLETZ, čak 39% (131 bolesnica) u usporedbi s 20% kod konizacije hladnim nožem. Tehnika izvođenja i konfiguracija konusa trebala bi biti individualizirana ovisno o specifičnostima same lezije. Za vrijeme izvođenja metode LLETZ transformacijska zona se ne odstrani uvijek u jednom zahvatu. Visok postotak pozitivnih rubova nije nedostatak metode LLETZ kao tehnike upravo zbog razlike u indikacijama, pristupu i višestrukom rezanju. Pravi uspjeh konizacije može se mjeriti samo prema učestalosti recidiva tijekom dužeg razdoblja i s većim brojem bolesnica.

Ključne riječi: *Konizacija; Cervikalna intraepitelna neoplazija; Displazija vrata maternice; Karcinom vrata maternice*