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Excision of the transformation zone: a comparison between large loop excision of the transformation zone, needle excision of the transformation zone, and laser conization

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Abstract

Objective: To compare three methods of excision of the transformation zone (ETZ).

Design: A retrospective cross-sectional study, comparing three techniques of ETZ: LASER CO_2, large loop excision of the transformation zone (LLETZ), and needle excision of the transformation zone (NETZ) in a cervical pathology unit between January 2016 and July 2017.

Material and methods: Data files were consulted and complemented with the institutional medical record SClinico®. The characteristics of the women and the specimen cone were obtained. The complications of the procedures and follow-up at 6 and 12 months were assessed. Statistical analyses were achieved using SPSS® 25 software.

Results: During the target period, 201 of women were subjected to LASER CO_2, 85 to LLETZ, and 15 to NETZ. The excisional specimens obtained did not show statistical differences in resection margin status and thermal artifacts. On average, only LASER ETZ obtained deeper excisional specimens compared to the other two techniques. During the procedures, NETZ showed a more significant bleeding risk compared to LASER ETZ (RR 0.29, 95%CI 0.09-0.93) and LLETZ (RR 0.17, 95%CI 0.05-0.65). NETZ also presented a 20% higher incidence of postoperative complications. Although the difference was not statistically significant, the women who underwent NETZ showed greater risk of maintaining cytological abnormalities and/or high risk-HPV at the 6th- and 12th-month follow-ups.

Conclusion: There is no clear evidence of the best ETZ technique, but it seems that the LASER and LLETZ methods are both safe and effective options in ETZ.

Keywords: cervical intraepithelial neoplasia, uterine cervical dysplasia, conization, papillomavirus infections

1. Introduction

Cervical cancer is the fourth most common cancer in women worldwide, with a 6.6% incidence of all cancers in 2018, and it was responsible for 311,365 deaths in the same year. Cervical intraepithelial neoplasia (CIN) is the most common premalignant lesion in women, and it is estimated that approximately 1-2% of women have CIN2 or CIN3 (referred to as CIN2+) each year. On the other hand, glandular pre-cancerous abnormalities — adenocarcinoma in situ (AIS) — are rarer than CIN and progress to cervical adenocarcinoma. AIS may co-exist with CIN.

The most significant cause of pre-cancerous abnormalities and cervical cancer is human papillomavirus (HPV) infection that is present in 99% of cervical tumors. The carcinogenesis mediated by HPV infection occurs at the transformation zone, which is an anatomic area that contains the transition from squamous epithelium of the ectocervix to the glandular epithelium of the endocervix. The gold-standard treatment of high-grade CIN (CIN2+) consists of excision of the transformation zone of the cervix (ETZ), previously known as cervical conization. Excisional treatment has been the preferred method since it enables the diagnosis of invasive lesions and points out resection margins. Ablative therapy on the transformation zone is also an alternative option in selected cases, such as those with (a) satisfactory colposcopy, (b) neither suggestion of micro-invasive or invasive disease nor suspicion of glandular disease, (c) corresponding cytology and histology, and (d) a patient who is able to follow up. This option is therapeutic only since it is a destructive method.

The main types of excisional treatments are cold knife conization, large loop excision of the transformation zone (LLETZ or LEEP), needle excision of the transformation zone (NETZ) and LASER conization. Cold knife conization has been replaced by the LLETZ and LASER techniques. LLETZ and NETZ are electrosurgical procedures where cutting and coagulation can be achieved depending on the current. In LLETZ, a wire loop electrode is used at the end of an insulated handle; a straight wire needle electrode is used in NETZ. LASER, an acronym for Light Amplification by Stimulation Emission of Radiation, is a technique that uses a highly focused beam to make an incision in the cervix. The operator delineates the desired circumferential incision in the ectocervix, including reaching the depth demanded. To obtain the preferred result, the operator usually uses small hooks and retractors to manipulate the zone to be excised. LASER can be used as a scalpel to cut or coagulate by defocusing the beam. This is usually performed in our center under local anesthesia. Protective eyewear is mandatory for staff in the operating room.

Although none of these techniques are new, few studies have been published that compare the different methods.

HYPERLINK \l "Mar13" [3] This study aims to determine which surgical procedure results in better outcomes, avoiding residual disease, thermal artifact, and peri-operative morbidity.

2. Material and Methods

This is a retrospective study of women who underwent excision of the transformation zone due to cervical dysplasia. It took place in a certified Portuguese cervical pathology unit in Centro Materno-Infantil do Norte, Porto, Portugal, between January 2016 and July 2017. All procedures were performed in the office setting under local anesthesia. It was carried out in accordance with the Declaration of Helsinki (revised in 2013).

A total of 301 women were subjected to ETZ during the target period: 201 using the LASER CO_2 method, 85 employing the LLETZ technique, and 15 using the NETZ procedure. Data files were consulted and complemented with the institutional medical record SClinico®.

Information was collected on the women's ages, parity, and smoking habits.

The ETZ motive was evaluated, and information about the cone was obtained (depth, lesion in margins, and presence of thermal artifact). Peri-operative bleeding and pain were analyzed as perturbing the execution of the surgery, and postoperative complications were searched. Cytology results at the 6th- and 12th-month follow-ups and a high-risk HPV test at the 12th- month follow-up were also studied.

Statistical analyses were achieved using SPSS® 25 software (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). Descriptive statistics were performed for demographic and clinical characteristics. Mean and standard deviations (SD) are presented for normally distributed variables. For group comparisons, parametric and nonparametric tests were used, as appropriate, for continuous variables, and Pearson's Chi^2 and Ficher's Exact tests were employed for categorical variables. All the results were considered significant if the p-value was <0.05, or they were evaluated at a 95% confidence interval.

3. Results

The age of the women who underwent ETZ varied from between 23 and 71 years old. The women in the NETZ group were significantly older (mean 46 years) than those in the LASER CO_2 (39 years) and LEETZ (38 years) groups. Most women were non-smokers (64.7%) and had one child. There were no statistical differences between the groups.

The main reason for ETZ was CIN3 (35.9% of the total procedures) followed by CIN2 (32.6%). Also, CIN3 was the principal motive for the ETZ procedure in the LASER and NETZ groups. In the LLETZ group, CIN2 was the main reason for ETZ (table 1).

On average, LASER ETZ obtained cone biopsies with greater depth (mean 14.5 mm) compared to the other two procedures, and this depth is statistically different when compared to LLETZ (mean 12.1 mm, p=0,001). The mean depth of NETZ was 13.0 mm.

The primary aim of ETZ is the excision of the entire cervical lesion, that is, to obtain negative margins. Margins are considered positive when CIN2 or a greater grade of dysplasia is found at the margins of the excisional specimen. In our sample, less than 10% had positive margins: 9.5% in the LASER group, 9.4% in the LLETZ group, and 13.3% in the NETZ group. Although there was no statistically significant difference between the procedures, it was verified that the NETZ group had 1.5 times more positive margins than the LASER and LLETZ groups (table 2). It was in the cases of adenocarcinomas that the margins were positive more frequently. In eight cases, six had positive margins, followed by carcinoma in situ (three in six cases). Of note, there were no statistical differences found in the mean depth of the cones when comparing the margins, negative *versus* positive (13.7 vs. 14.0 mm, respectively, p=0.56).

Thermal artifact on an excisional specimen is an important fact to be examined because that can compromise or impair the evaluation of the margins. Twenty percent of the NETZ group conization specimens had thermal artifacts, which is about three times more than what occurred in the LASER (7.0%) and LLETZ (8.2%) groups (table 2).

Peri-operative morbidity was also evaluated. Bleeding as a morbidity factor was assessed as bleeding that disrupted the procedure or caused some increased intervention, namely, vaginal tamponade or a second surgery. Comparing the LASER ETZ group with the LLETZ group, there was no statistical difference, although there were about 1.7 times more cases of moderate bleeding from the LASER ETZ procedure (table 2). On the other hand, the NETZ method had a significantly higher risk of hemorrhage compared to both the LASER and LLETZ techniques [RR 3.50 (95% CI 1.07 to 11.36) and RR 5.85 (95% CI 1.54 to 22.22), respectively]. In the ETZ procedures, local cervical anesthesia with lidocaine is performed. Our study assessed pain by considering whether the woman was cooperative during the examination or if the procedure had to be interrupted due to the woman's pain intolerance. No case required suspension of the examination. However, it was found that women in the NETZ group experienced about three times more pain than the others. Also, postoperative complications were evaluated, such as an abnormal event that occurred during the procedure, admission to emergency service in the first postoperative month that was related to surgery, or any anomaly verified at a follow-up visit. Concerning postoperative complications, the LLETZ group had fewer complication events (4.7%) followed by the LASER group (7.5%). NETZ presented as the procedure with the most complications — 20% — and when compared to the other procedures, NETZ had three times more complications than LASER and five times more than LLETZ, which is a significantly higher risk (p=0.032) (table 2). Genital hemorrhage was the most frequently reported complication (nine of the total 21 situations registered) motivating the patient to go to the emergency department. However, no procedure required hospitalization, reintervention, or transfusion of red blood cells. Cervical stenosis was observed in four cases at follow-up visits: two after LASER, one after LLETZ, and one after NETZ.

At the 12th-month follow-up visit, cytology results and HPV tests were evaluated. This evaluation eliminated the cases re-intervened for a second conization to widen the margins and those who underwent a hysterectomy. We verified that most of the follow-up smear tests became negative at 12 months — 91.2% for LASER, 95.0% for LLETZ, and 83.3% for NETZ — with no statistical difference between them. The same was found for the high-risk HPV test, although to a lesser extent — 81.2%, 86.9%, and 69.2%, respectively. Although there was no statistical difference,

the NETZ group showed the worse results at follow-up visits compared to the other two groups, with twice as many abnormal cytology or positive high-risk HPV results (table 2).

Table 1: Reason (in %) for excision of the transformation zone by procedure

	Laser CO_2	**Lletz**	**Netz**
Persistent CIN[1] 1	7.0	0	0
CIN2	31.3	35.7	26.7
CIN3/Carcinoma in situ	35.8	33.3	53.3
Squamous cell carcinoma	0.5	0	0
Adenocarcinoma	2.0	1.2	0
Discordance between cytology and biopsy	15.9	17.9	6.7
CIN and AIS[2]	0.5	0	0
Surveillance impossibility	3.5	6.0	6.7
Others	3.5	5.9	6.7

[1]CIN–cervical intraepithelial neoplasia; [2]AIS – adenocarcinoma in situ

Table 2: Comparison between procedures for outcomes (evaluation of relative risk)

	Laser *vs.* Lletz	**Laser *vs.* Neetz**	**Lletz *vs.* Neetz**
RR[1] (95% CI)			
Positive margins	1,02 (0,43-2,42)	0,69 (0,14-3,27)	0,68 (0,13-3,54)
Thermal artifact	0,84 (0,33-2,16)	0,30 (0,08-1,19)	0,36 (0,08-1,58)
Bleeding	1,67 (0,72-3,82)	0,29 (0,09-0,93)	0,17 (0,05-0,65)
Pain	0,84 (0,15-4,70)	0,25 (0,03-2,41)	0,30 (0,03-3,52)
Postoperative complications	1,62 (0,53-5,07)	O,32 (0,08-1,27)	0,20 (0,04-0,99)
Negative for lesion at 6th-month cytology	0,76 (0,26-2,16)	2,28 (0,58-9,06)	3,00 (0,62-14,43)
Negative for lesion at 12th-month cytology	0,55 (0,15-1,99)	2,08 (0,41-10,51)	3,80 (0,56-25,69)
Negative for HR-HPV[2] on 12m-testing	0,65 (0,28-1,51)	1,92 (0,55-6,67)	2,94 (0,73-11,90)

[1]RR – relative risk; [2]HR-HPV– high risk human papillomavirus

4. Discussion

ETZ is one of the most common gynecological procedures performed in Portugal as well as worldwide. Nonetheless, the optimal surgical technique for ETZ has not been established yet. To date, few randomized studies have been performed. In 2013, Cochrane published a meta-analysis of 29 randomized controlled trials, comparing seven surgical techniques for CIN treatment. Only four articles were used in the meta-analysis comparing the LLETZ and LASER methods; two articles were used comparing the LLETZ and NETZ procedures. Cochrane made no comparison between the LASER and NETZ techniques. Also, despite being a 2013 meta-analysis, this was carried out based on studies published between 1982 and 2004, which demonstrates the lack of comparative studies. The WHO Guidelines, which only compared three treatment techniques for CIN and AIS (cryotherapy, LLETZ, and cold knife conization), also refers to the lack of randomized trials and comparative studies between techniques. In the Cochrane review, no significant differences were demonstrated in terms of treatment failures or operative morbidity. However, it appears that LLETZ may be the preferred technique for ETZ because it is cheaper, faster, and has a shorter learning curve than LASER ETZ. The LASER procedure can be reserved for endocervical lesions and type 3 excisions.

In this study, the department's preference for the use of the LASER CO_2 procedure is evident; hence, there is a discrepant distribution in the types of procedures performed. Nevertheless, all medical doctors performed the three techniques. This is an obvious limitation to this study, namely, the heterogeneous distribution of the three ETZ procedures, corresponding to the low number of patients in the NETZ group. Also, since a randomization trial of patient allocation by the three ETZ techniques has failed and because the department is one that provides inpatient training for residents (whose learning curve for procedures should be considered), this study was only performed as a retrospective observational study. However, despite the lack of comparative studies between the LASER and LLETZ methods as well as between these two and the NETZ technique, this study provides some valuable insights.

Both the LASER and LLETZ techniques have similar results in this study. On average, only in the acquisition of excisional specimens was the depth greater in the LASER technique. This can be valued as a need for type 3 excision of the transformation zone. Our results are consistent with those presented in Cochrane's 2013 review except for the presence of bleeding during the procedure. In the Cochrane review, LASER ETZ was associated with a statistically significant increase in the risk of peri-operative severe bleeding compared to loop excision (RR 8.75, 95% CI 1.11 to 68.83). In fact, in our study, LASER ETZ showed a higher propensity for complicated procedures with bleeding, but this increase was not statistically significant and was lower compared to the Cochrane review — RR 1,67 (0.72-3.82).

The NETZ procedure was found to be associated more frequently with less favorable outcomes compared to the other two techniques, especially when evaluated for peri-operative hemorrhage where the risk of bleeding was more than three times higher compared to the LASER and LLETZ groups (RR 0.29, 95% CI 0.09 to 0.93 and RR 0.17, 95% CI 0.5 to 0.65, respectively). This finding follows what is described in the Cochrane review (RR 0.32, 95% CI 0.50 to 1.44), but it has a more pronounced difference than that described by Camargo *et al.* (RR 0.80, 95% CI 0.65 to 0.98). Although not statistically significant, it is important to highlight the greater registry of thermal artifacts at the specimen margins in the NEETZ group compared to the other two groups. However, this finding is different from

that achieved in Russomano *et al*., which found that the LLETZ technique had a higher risk of compromised or damaged margins in the surgical specimens compared to the NEETZ method (RR 1.37, 95% CI 1.01 to 1.84).

Evaluating the perception of the cervical pathology unit and considering the results obtained regarding morbidity, women in the LLETZ group usually had lower cases of severity (CIN2); they were also younger with type 1 or 2 transformation zones, which also reflects the lower depth of the cone (table 1). On the other hand, older women in the NETZ group had cases of greater severity (53% for CIN3); such a situation makes the procedure more difficult, namely, a type 3 transformation zone, the presence of vaginal atrophy, and a more inaccessible cervix. In these situations, the choice for NETZ concerns the ease of manipulating and drawing the cone with the needle. These features explain the increased morbidity associated with the NETZ technique compared to the LLETZ method.

The comparison between the LASER and the NETZ techniques is not straightforward. Given that both procedures allow delineation of the cone according to the situation, the depths of the excisional specimens were superior in the LASER group. However, several factors influence the success of the ETZ procedure, and a larger sample would be necessary for the group of women subjected to NETZ to be able to carry out a logistic regression to control these factors.

In this study, women in the NETZ group were more likely to maintain cytological changes and viremia for high-risk HPV. These findings are opposed to those obtained in Cochrane's meta-analysis, which concluded that the LLETZ method had a 10-fold higher risk of maintaining residual disease compared to NETZ and found no statistical difference between the LASER and LLETZ techniques.

5. Conclusions

In our study, there is no clear evidence that one of the three ETZ methods observed — LASER, LLETZ, and NETZ — is better than the others. It seems that the LASER and LLETZ procedures are both safe and effective ETZ options. However, the NETZ method should be reserved for obtaining excisional specimens with greater depth, such as type 3 ETZ, when the LASER procedure is not available.

6. Author Disclosure Statement

There are no financial conflicts of interest to disclose.

The authors have no conflict of interest.

7. References

1. Martin-Hirsch P, Paraskevaidis E, Bryant A, Dickinson H. Surgery for cervical intraepithelial neoplasia (Review). Cochrane Database Syst Rev. 2013; 12(CD001318).
2. Bray F, Ferlay J, Soerjomataram I, Siegek R, Torre L, Jemal A. Global Cancer Statistics 2018: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin, 2018.
3. Ferlay J, Colombet M, Soerjomataram I. *et al*. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer, 2018, 1133-45.
4. WHO Guidelines Approved by the Guidelines Review Committee. WHO Guidelines for Treatment of Cervical Intraepitheliel Neoplasia 2-3 and Adenocarcinoma in situ: Cryotherapy, Large Loop Excision of the Transformation Zone, and Cold Knife Conization. World Health Organization, 2014.
5. Marth C, Landoni F, Mahner S, McCormack M, Gonzalez-Martin A, Colombo N. Cervical cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017; 28((suppl_4)):iv72-iv83.
6. Hilal Z, Rezniczek G, El-Fizazi N, Tempfer C. Large Loop Excision of the Transformation Zone Versus True Cone Biopsy Electrode Excision: A Ransomized Trial. Journal of Lower Genital Tract Disease. Oct 2017, 21(4).
7. Portugal, Ministério da Saúde, Direção Geral da Saúde, Morbilidade Hospitalar. Serviço Nacional de Saúde - 2016, em Portugal Continental. Direção-Geral da Saúde, 2017.
8. Camargo M, Russomano F, Tristão M, Huf G, Prendiville W. Large loop versus straight-wire excision of the transformation zone for treatment of cervical intraepithelial neoplasia: a randomised controlled trial of eletrosurgical techniques. BJOG. 2015; 122(4):552-7.
9. Russomano F, Tristao M, Côrtes R, Camargo M. A comparison between type 3 excision of the transformation zone by straight wire excision of the transformation zone (SWETZ) and large loop excision of the transformation zone (LLETZ): a randomized study. BMC Women's Health, 2015, 15(12).