Abstract. Aim: To review the 22-year experience of the use of large loop excision of the transformation zone (LLETZ) for the treatment of cervical intraepithelial neoplasia (CIN). Materials and Methods: Design: Retrospective observational study. Setting: University Hospital of Ioannina, Greece. Period: January 1989 until December 2011. Population: Women undergoing excisional treatment with LLETZ for CIN. Women with invasive disease were excluded. Intervention: Excisional treatment with LLETZ. Women had post-operative surveillance with cytology and colposcopy at 6, 12, 18 and 24 months, and yearly thereafter. Outcomes: We assessed the histological outcomes and margin involvement, as well as the rate of treatment failures requiring a repeat conization. Results: A total of 3861 LLETZ biopsies were recorded during the study period. The histological evaluation of the cone specimens showed CIN1 in 897 (23.2%), CIN2 in 1129 (29.3%), CIN3 in 1322 (34.2%), microinvasive disease in 158 (4.1%), HPV lesions in 206 (5.3%) and normal histological findings in 149 (3.9%) women. The margins were reported as clear in 3166 (82%) cases, involved in 437 (11.3%) cases and uncertain in 258 (6.7%) cases. A total of 239 (6.2%) women underwent a second conization due to treatment failure. Conclusion: LLETZ remains the most popular conservative technique of treatment for women with precancerous cervical lesions. Post-treatment surveillance of these women is essential in order to detect residual or recurrent disease. New HPV biomarkers, introduced over the last two years, appear to be useful in the follow-up after treatment. A scoring system may allow for accurate prediction of women at risk of treatment failure and for tailored post-treatment surveillance.

Large loop excision of the transformation zone (LLETZ) is the most frequently used method of treatment for cervical intraepithelial neoplasia (CIN) worldwide (1, 2). This is attributed mainly to the fact that LLETZ is simple to learn and use, relatively cheap, of short duration and can be performed under local anesthesia in an outpatient setting; all these characteristics make it an appealing alternative to cold knife conization (CKC). Furthermore, being an excisional technique, it provides a cone-shaped specimen that allows for comprehensive histopathological evaluation of the lesion’s grade and an assessment of the excisional margins (3, 4). The aforementioned parameters are of paramount importance for the post-treatment management of those women who undergo treatment, determining the duration and intensity of the follow-up (5-7).

In addition, LLETZ has similar efficacy to other available therapeutic modalities and is associated with only minor intra- or short-term post-operative complications (1, 2, 8-12).
It has only recently been found that LLETZ is associated with long-term adverse obstetric outcomes and an increased risk of preterm birth. However, the obstetric risks associated with LLETZ are not as significant as those associated with other available excisional techniques, namely CKC or laser conization (13-16).

The purpose of this study is to present the 22-year experience of an academic colposcopic clinic on the use and outcomes of LLETZ for the treatment of precancerous or early invasive cervical disease, and to highlight the results of primary and secondary research driven from this experience in this particular setting (17).

**Patients and Methods**

The study was a retrospective case series with data collected from the colposcopy clinic of the University Hospital of Ioannina in Greece from 1989 until 2011.

Only women referred for colposcopy with abnormal cytology or positive HPV DNA test were included. As there is no national organized cervical screening program, the majority of women were either self-referred or referred by a private gynecologist and/or cytopathologist (18).

**Protocol and principles of management.** After colposcopic examination, a signed colpophotograph with the colposcopic impression and relevant plan of management was given to the patient.

Women with high-grade cytology and consistent colposcopy were advised to undergo treatment immediately after the end of their next menstruation. The appropriate timing for LLETZ was assessed in a departmental audit, which demonstrated that women treated during the first half of their cycle bleed less, both intraoperatively and in the post-treatment period. This observation was also subsequently confirmed in a randomized controlled trial (RCT) (12). The same treatment policy was applied for older women and women who had completed their family and who had low-grade cytology and low-grade colposcopy in six months was the preferred method of management rather than conservative surveillance.

Conservative management with repeated cytology and colposcopy in six months was the preferred method of management for young nulliparous women or for women who had not completed their family and had a low-grade cytology with consistent colposcopic findings (19, 20).

The management of young nulliparous women with high-grade cytology and low-grade colposcopy and vice versa was more challenging. In the majority of cases an expectant policy was adopted in colposcopy colposcopy mismatch cases, in close collaboration with the cytopathologists after review of the original smear.

The LLETZ procedure was also performed if there was suspicion of invasion, glandular lesion, persistent discrepancy between high-grade cytology and low-grade colposcopy, as well as in cases of treatment failure (21).

Pregnant women with cytological or colposcopic evidence of CIN underwent colposcopic examination every 2-3 months to exclude progression of the lesions and the final decision for further management, including treatment, was made eight weeks postpartum (22).

**LLETZ technique.** LLETZ was performed under colposcopic guidance using a local anesthetic. The cervical crater was cauterized to prevent immediate postoperative bleeding by the formation of a cauterized plaque on whole its surface and on the ectocervical lips with care to avoid an area of 3-4 mm around the new cervical os at the bottom of the crater. This technique was found to increase the possibility of satisfactory post-LLETZ colposcopy as shown in a RCT (8). The depth of the excision was decided after the clinical judgment of the lesion by expert colposcopists, based on the features of the lesion and the estimated cervical length. As a rule, the depth of the LLETZ was more than 7 mm to ensure eradication of cervical intraepithelial lesions that may involve the gland crypt, but less than 1 cm of depth if the patient was young, nulliparous or had not completed her family (23).

**Follow-up after LLETZ.** All patients were scheduled for follow-up examination after treatment at 6-12-18 and 24-month intervals with repeated cytology and colposcopy examination. During the past decade (2001-2010), we have also used HPV DNA test as an adjunct follow-up test (24, 25). Repeated LLETZ was performed in cases when there was both cytological and colposcopic evidence of residual high-grade disease or high-grade cytology in the presence of unsatisfactory colposcopy, as well as in cases of older women with positive endocervical margins for high-grade lesions (4, 7, 11). Women who had microinvasive disease on the LLETZ specimen were managed on an individualized basis, taking into consideration their age, parity and status of cone margins, as well as post-treatment HPV detection (21, 26, 27).

**Results**

We assessed 3861 women who underwent a LLETZ procedure over a period of 22 years in the colposcopy clinic of the University Hospital of Ioannina. The patients’ mean age was 36.24 years. Histological evaluation of the excised specimens showed 897 (23.2%) women with CIN1, 1129 (29.3%) with CIN2, 1322 (34.2%) with CIN3, 94 (2.4%) with microinvasive and 64 (1.72%) invasive disease, 206 (5.3%) with HPV lesions and 149 (3.9%) women who had normal histology.

From the sample of 3861 women with histological evaluation, 3166 (82%) women had clear endocervical margins, 437 (11.3%) of the cases had involved margins and uncertain margins due to diathermy artifacts were found in 258 (6.7%) cases. Treatment failure was diagnosed in 239 (6.2%) women who underwent a second conization. Out of the 239 repeat cone specimens, 131 (54.8%) revealed CIN1, 79 (33.05%) CIN2, 26 (10.9%) CIN3 and 3 specimens (1.25%) revealed microinvasive disease. Involved margins were confirmed in 12 (5%) cases, while in 227 (95%) cases the margins were clear after the repeat cone.

The majority (90%) of treatment failures were detected within 24 months of treatment. Women with involved margins were at higher risk of treatment failure compared to those with clear margins (18% versus 3%).
Discussion

The ability to identify pre-cancerous cervical lesions which require treatment in order to prevent their progression to cervical cancer, constitutes a significant challenge, especially for women who are nulliparous or wish to maintain their future fertility. In terms of residual disease after treatment for CIN and postoperative morbidity, evidence from the recent literature suggests that there is no superior surgical technique for treating such lesions (2, 10). Within that frame, a policy of see, think, select and treat is preferable in terms of effective management, limitation of complications and preservation of fertility in younger women (13-15, 28).

Cytology remains the mainstay in primary screening, while the HPV-DNA test also appears to have an important role in screening not only with improved sensitivity but also in the triage of women with atypical squamous cells with undetermined significance (ASCUS) and in post-treatment surveillance (19, 20, 24, 25, 29-32). However, HPV-related biomarkers such as high-risk (HR)-HPV DNA test, mRNA E6 and E7, or p16(INK4a) can be used as an adjunct test in the triage of women with low-grade squamous intraepithelial lesions (LSIL), as p16(INK4a) improves the specificity of HR-HPV DNA test in terms of identifying women at risk of developing high-grade lesions (CIN2+) (33-36).

There is evidence that the proportion of the cervical volume excised affects cervical regeneration. Thus, the larger the volume excised when treating CIN, the larger the deficit in cervical healing post-operatively. Subsequently, the assessment of the proportion of the cervical volume excised, after treatment of CIN, might determine the group of women who are at higher risk for preterm labour in future pregnancies (13, 14, 16, 23, 28, 37-44).

Although the excisional techniques with local anesthesia seem to provide an appropriate specimen for histological diagnosis of CIN, recent evidence has shown that the most effective way to prevent cervical cancer might be the combination of vaccination and screening, especially in younger women (45-48). Existing evidence supports that vaccination against HPV types 16 and 18 (responsible for up to 72% of cervical carcinomas) and screening with liquid-based cytology (LBC), or HPV DNA testing are effective ways to prevent cervical cancer and other HPV-related cancers, such as anal, oropharyngeal, and penile cancers. The combination of vaccination and screening is recommended for all women aged 9-26 years. However, data from the recent literature suggest that there is no significant reduction in the incidence of HPV-related cervical lesions in women who received the HPV vaccination alone, compared to women who received both vaccination and screening. Thus, vaccination alone is not sufficient to prevent HPV-related cervical lesions and screening with HPV DNA testing is recommended for all women aged 16-30 years. However, data from the recent literature suggest that there is no significant reduction in the incidence of HPV-related cervical lesions in women who received the HPV vaccination alone, compared to women who received both vaccination and screening. Thus, vaccination alone is not sufficient to prevent HPV-related cervical lesions and screening with HPV DNA testing is recommended for all women aged 16-30 years.

In an attempt to predict and prevent treatment failures, our group worked towards the development of a test of cure. Preliminary data has shown that after treatment of CIN, there is a significant reduction of positivity in all HPV-related biomarkers, while condom use in the post-treatment period reduces HR-HPV positivity rates (49). The different combinations of HPV-related biomarkers, various risk factors and individual characteristics, possibly in the form of a scoring system could allow for tailored surveillance after treatment of CIN and the possibility to predict treatment failure and allow the return to routine follow-up of women at low risk of recurrent disease (45, 49-51).

References


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