

# Factors affecting outcome after incomplete excision of cervical intraepithelial neoplasia

E. Paraskevaïdis<sup>1</sup>, S. N. Kalantaridou<sup>1</sup>, M. Paschopoulos<sup>1</sup>, K. Zikopoulos<sup>1</sup>, E. Diakomanolis<sup>2</sup>, N. Dalkalitsis<sup>1</sup>, G. Makrydimas<sup>1</sup>, L. Pappa<sup>3</sup>, V. Malamou-Mitsi<sup>3</sup>, N. J. Agnantis<sup>3</sup>

<sup>1</sup>Gynecologic Oncology Unit, Department of Obstetrics and Gynecology, Ioannina University Hospital

<sup>2</sup>1<sup>st</sup> Department of Obstetrics and Gynecology, University of Athens, Alexandra University Hospital, Athens

<sup>3</sup>Department of Pathology, Ioannina University Hospital (Greece)

## Summary

**Purpose:** Conservative treatment for cervical intraepithelial neoplasia (CIN) by ablative or excisional techniques is widely used. However, women with incomplete excision have a variable risk of CIN recurrence. The aim of this study was to identify possible risk factors for recurrence of CIN after large loop excision of the transformation zone (LLETZ) with involved margins of excision.

**Methods:** All cases of women treated with LLETZ for CIN between 1989-2000, in whom histological evaluation of the excised specimen revealed extension of CIN to the excision margins, were retrospectively studied. A woman was considered to have recurrence when she had histologically confirmed CIN following a second LLETZ or hysterectomy during the follow-up period. The characteristics that were examined as possible risk factors were age, parity, smoking habit, grade of initial lesion and extension to the endo- or ectocervical margin.

**Results:** Treatment failure was diagnosed in 18 out of 65 (27.7%) women with involved margins. The only characteristic that reached statistical significance was age. The mean age of women with recurrence was 35.8 years, whereas the mean age of women without recurrence was 32.8 years ( $p = 0.044$ ). Also, a trend was evident in women with high-grade initial lesions (CIN II-III) ( $p = 0.168$ ) and involvement of the endocervical margins ( $p = 0.149$ ). No differences were observed between the two groups regarding parity and smoking habit.

**Conclusions:** Increased age is a risk factor for recurrence in women with incomplete excision of CIN after LLETZ. Larger studies are required for definite conclusions.

**Key words:** Cervical intraepithelial neoplasia; Large loop excision of the transformation zone; Involved margins; Recurrence; Risk factors.

## Introduction

Conservative treatment for cervical intraepithelial neoplasia (CIN) by ablative or excisional techniques is widely used. Outpatient excisional methods, such as large loop excision of the transformation zone (LLETZ), are becoming increasingly popular because they allow histological evaluation of the lesion along with excision margin assessment.

It is now well established that women with clear margins have a low risk of recurrence, approximately 5%, and can be monitored by cytology [1].

The management of women with involved margins of resection, on the other hand, remains unresolved, because these women have a higher and variable risk of recurrence [2-4]. Nevertheless, because the majority of these women will not present recurrence, incomplete excision of CIN does not represent treatment failure. Therefore, conservative management of these women is possible.

Although risk factors for recurrence following excision with clear margins have been identified [1], little is known about risk factors affecting the outcome after incomplete excision of CIN.

The aim of this retrospective study was to identify possible risk factors for recurrence of CIN after LLETZ with involved margins of excision.

## Material and Methods

All cases of women treated with LLETZ for CIN in our institution during the period 1989-2000, in whom histological evaluation of the excised specimen revealed involved margins, were retrospectively studied.

Women who defaulted follow-up or were followed-up for less than 18 months were excluded from the study.

Our treatment policy was selective "see and treat" without previous punch biopsies and the method of treatment was LLETZ [1]. The excision was performed under colposcopic guidance.

Indications for treatment were cytologic indications of CIN II-III along with colposcopic agreement or unsatisfactory colposcopy and persisting cytological and colposcopic impression of CIN I for more than six months. Human papillomavirus (HPV) associated findings only were not treated. The loop sizes were selected according to the extension of the lesion. When the lesion was extended towards the endocervix, a deeper loop excision, in a hat-top configuration, was performed and careful orientation of the second specimen was followed. Loop excision of the entire transformation zone was performed; however, satellite HPV lesions outside the transformation zone were not treated, since their inclusion in the conization would result in an excess removal of healthy cervical tissue. Following the exci-

sion, a diathermy ball was applied to the cervical crater for hemostasis and for destruction of possible residual nests of dysplastic epithelium. Initially, the entire crater was cauterized; however, after a study showing increased rates of cervical stenosis and unsatisfactory follow up colposcopy [5] this was avoided around the new cervical os. From each cervical specimen, 12-16 paraffin blocks were created and 4-5 sections were made and examined from each block.

The follow-up protocol included cytology and colposcopy at 4, 8, 12 and 18 months and annually thereafter (cytologic examination preceded colposcopy). Positive follow-up cytology was defined as any degree of dyskaryosis and positive colposcopy was defined as the presence of acetowhite epithelium giving the impression of CIN.

A woman was considered to have recurrence when she had histologically confirmed CIN or cervical cancer in a second LLETZ or hysterectomy specimen during the follow-up period.

The group of women with recurrence was identified and their characteristics (age, parity, smoking habit, grade of initial lesion, extension to the endo- or ectocervical margin) were compared to those of the group of women without recurrence.

Statistical analysis was carried out using the  $\chi^2$  test and the Student's t-test.

## Results

During the study period 79 women were identified with involved margins after LLETZ for CIN. Seven women were excluded because they defaulted follow-up and seven women have not completed 18 months of follow-up as yet.

Treatment failure was diagnosed in 18 of the remaining 65 women with involved margins (27.7%). In two women the diagnosis was made on a hysterectomy specimen and in the remaining 16 women on a second LLETZ.

The characteristics of women with recurrence (Group A) and women without recurrence (Group B) are presented and compared in Table 1.

The only characteristic that reached statistical significance was age. The mean age was 35.8 years in Group A and 32.8 years in Group B ( $p = 0.044$ ). No differences were observed between the two groups regarding parity ( $p = 0.541$ ) and smoking ( $p = 0.909$ ).

Seventeen out of 18 women had high-grade initial lesions (CIN II-III) in Group A (94.4%) compared to 38 out of 47 in Group B (80.8%) ( $p = 0.168$ ). Endocervical extension of the CIN was found in 16 women in group A and in 34 women in group B ( $p = 0.149$ ). CIN endocervical extension only was noted in 13 women in Group A and in 28 in Group B. Ectocervical extension only was

Table 1. — Comparison of women with recurrence (Group A) and women without recurrence (Group B) following incomplete excision of cervical intraepithelial neoplasia.

	Group A n = 18	Group B n = 47	p
Age $\pm$ Standard deviation	35.8 $\pm$ 4.6	32.8 $\pm$ 5.6	0.044
Parity	8 (44.4%)	25 (53.2%)	0.541
Smoking habit	7 (38.9%)	19 (40.4%)	0.909
Initial high-grade lesion	17 (94.4%)	38 (80.8%)	0.168
Endocervical extension	16 (88.9%)	34 (72.3%)	0.149

noted in two women in Group A and in 13 in Group B. Finally, extension to both margins was found in three women in Group A and in six women in Group B.

Table 2. — Histological grading of initial and subsequent lesions.

Initial lesion	Subsequent lesion		
	CIN I n (%)	CIN II n (%)	CIN III n (%)
CIN I n = 1	1 (100%)	0	0
CIN II n = 5	3 (60%)	2 (40%)	0
CIN III n = 12	3 (25%)	5 (41.7%)	4 (33.3%)
Total n = 18	7	7	4

The treatment failure was diagnosed within the first postoperative year in 16 out of 18 women (89%). Histological examination of the second cervical specimen revealed CIN I in seven cases (39%), CIN II in seven cases (39%) and CIN III in four cases (22%) (Table 2).

## Discussion

Incomplete excision of CIN does not represent treatment failure because only a small proportion of patients will eventually be diagnosed with residual or recurrent disease. One possible explanation for this phenomenon could be that the inflammatory response of healing may cause regression of the residual CIN at the cervical crater edges [2]. Another possible explanation could be that the thermal effect after laser or LLETZ may also play a role in the cure of CIN.

The reported rates of treatment failure following incomplete excision of CIN are variable, from as high as 44% to as low as 3.6% [2-4, 6]. The reasons for this discrepancy remain unknown. Information regarding potential risk factors for recurrence after involved margins has been limited and conflicting. Involvement of the endocervical margins has been suggested as a possible risk factor by some authors [4, 7], but has not been verified by others [3]. Simultaneous involvement of both endocervical and ectocervical margins has also been suggested as a risk factor [8], but, again, has been contested [3]. In addition, high grade of the initial lesion has been associated with recurrence [2, 4] but has not been confirmed [3, 7]. Furthermore, smoking has been suggested as a risk factor [2] but this remains controversial as well. Finally, it has been suggested that an important risk factor may be the grade of the lesion extending to the margins, and not the grade of the initial lesion [9].

In our study, treatment failure was diagnosed in 18 out of 65 (27.7%) women with involved margins. In the majority of the cases, treatment failure was found within the first postoperative year (89%).

Increased age was the only factor found to be statistically significant in the group of women with recurrence. This may be due to the endocervical transposition of the transformation zone that occurs in older women and results in higher unsatisfactory colposcopy rates.

Although high-grade initial lesions (CIN II-III) and involvement of the endocervical margins did not reach statistical significance, it should be pointed out that a trend was evident. This can be attributed to the fact that incomplete excision is more likely with high-grade CIN and involvement of the endocervical canal [6]. Larger studies are required to determine whether high-grade CIN and involved endocervical margins may play a role in recurrence.

Parity and smoking did not seem to have any association with recurrence.

It is now accepted that incomplete excision of CIN should be managed with follow-up and not with immediate retreatment [10, 11]. However, follow-up with cytology only, as suggested in the case of complete excision of CIN [1], is not adequate following incomplete excision of CIN and, thus, colposcopy should be added to the postoperative protocols [12]. Of course, this management results in higher financial costs and longer waiting lists [10].

Well-designed larger studies should be conducted, completed, analyzed and validated in order to identify risk factors for recurrence following incomplete excision of CIN. The identification of these risk factors and the subsequent adjustment of follow-up will decrease both costs and waiting lists, without increasing the cases of undetected CIN recurrences. However, until these trials clearly identify risk factors for recurrence following incomplete excision of CIN, recommendations cannot be given.

## References

- [1] Paraskevaïdis E., Lolis E., Koliopoulos G., Alamanos Y., Fotiou S., Kitchener H.C.: "Cervical intraepithelial neoplasia outcomes following loop excision with clear margins". *Obstet. Gynecol.*, 2000, 95, 828.
- [2] White C.D., Cooper W.L., Williams R.R.: "Cervical intraepithelial neoplasia extending to the margins of resection in conization of the cervix". *J. Reprod. Med.*, 1991, 36, 635.
- [3] Vedel P., Jakobsen H., Kryger-Baggesen N., Rank F., Bostofte E.: "Five-year follow up of patients with cervical intra-epithelial neoplasia in the cone margins after conization". *Eur. J. Obstet. Gynecol. Reprod. Biol.*, 1993, 50, 71.
- [4] Lapaquette T.K., Dinh T.V., Hannigan E.V., Doherty M.G., Yandell R.B., Buchanan V.S.: "Management of patients with positive margins after cervical conization". *Obstet. Gynecol.*, 1993, 82, 440.
- [5] Paraskevaïdis E., Koliopoulos G., Paschopoulos M., Stefanidis K., Navrozoglou I., Lolis D.: "Effects of ball cauterization following loop excision and follow-up colposcopy". *Obstet. Gynecol.*, 2001, 97, 617.
- [6] Lopes A., Morgan P., Murdoch J., Piura B., Monaghan J.M.: "The case for conservative management of 'incomplete excision' of CIN after laser conization". *Gynecol. Oncol.*, 1993, 49, 247.
- [7] Narducci F., Occeilli B., Boman F., Vinatier D., Leroy J.L.: "Positive margins after conization and risk of persistent lesion". *Gynecol. Oncol.*, 2000, 76, 311.
- [8] Reich O., Lahousen M., Pickel H., Tamussino K., Winter R.: "Cervical intraepithelial neoplasia III: long-term follow-up after cold-knife conization with involved margins". *Obstet. Gynecol.*, 2002, 99, 193.
- [9] Jansen F.W., Trimbos J.B., Hermans J., Fleuren G.J.: "Persistent cervical intraepithelial neoplasia after incomplete conization: predictive value of clinical and histological parameters". *Gynecol. Obstet. Invest.*, 1994, 37, 270.
- [10] Murdoch J.B., Morgan P.R., Lopes A., Monaghan J.M.: "Histological incomplete excision of CIN after large loop excision of the transformation zone (LLETZ) merits careful follow up, not retreatment". *Br. J. Obstet. Gynaecol.*, 1992, 99, 990.
- [11] Paraskevaïdis E., Kitchener H., Adonakis G., Parkin D., Lolis D.: "Incomplete excision of CIN in conization: further excision or conservative management?". *Eur. J. Obstet. Gynecol. Reprod. Biol.*, 1994, 53, 45.
- [12] Dobbs S.P., Asmussen T., Nunns D., Hollingworth J., Brown L.J., Ireland D.: "Does histological incomplete excision of cervical intraepithelial neoplasia following large loop excision of transformation zone increase recurrence rates? A six year cytological follow-up". *Br. J. Obstet. Gynaecol.*, 2000, 107, 1298.

Address reprint requests to:  
S. N. KALANTARIDOU, M.D.  
Kosti Palama, 3  
45221 Ioannina (Greece)