Treatment delay and pathology results in women with low-grade squamous intraepithelial lesions. A preliminary study

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Summary

Regression rate of CIN 1 (LSIL) can reach 85%. The purpose of this study was to investigate retrospectively pathology specimens in CIN 1 cases who delayed treatment > 2 years despite the persistence of the lesion.

One hundred and fifteen women diagnosed with CIN 1 were separated in two groups as follows: A) 92 women who underwent ablative treatment within three months after the completion of two years; B) 23 women who delayed ablative treatment for a mean interval of > 1 year after the completion of two years. Exclusion criteria were normal cytology and colposcopy results within the completion of two years. The chi-square, t-test and Kaplan-Meier method were used for analysis. Persistence of LSIL lesions was observed in 84% of the first group and persistence or regression of the lesion in 78% of the second one.

The study suggests the possibility of prolongation of the observation period after LSIL diagnosis. Prospective studies with close follow-up are needed for final conclusions.

Key words: CIN 1; LSIL; HSIL; Ablative treatment.

Introduction

The spontaneous regression rate of biopsy-proven cervical epithelial hyperplasia (CIN 1) can be as much as 85% and it occurs within or just after two years from diagnosis [1, 2]. Patients with satisfactory colposcopy can safely be observed every six months with cytology and colposcopy evaluation for two years after initial diagnosis. If, during this interval, the lesions persist or progress, ablative treatment is considered as the final solution to the problem.

The purpose of the study was to investigate pathology specimens of women diagnosed initially with CIN 1, in whom persistence of the disease was observed two years from the initial diagnosis, and who delayed treatment for more than two years. Links between delays in treatment and pathology specimens were investigated retrospectively.

Materials and Methods

Data were collected from the case notes of women diagnosed with low-grade squamous intraepithelial lesions (LSIL). Patients were included in the study if they had the following criteria: an initial Papanicolaou smear (Pap test) diagnosed as CIN 1, satisfactory colposcopy and biopsies confirming the cytology results and persistence or progression of the lesion within or just after two years from the initial diagnosis. Exclusion criteria were normal cytology and colposcopy results within the completion of two years. Most patients were informed about the possible benefits of quitting smoking and use of the condom or abstinence.

One hundred and fifteen women with the aforementioned criteria were included in the study and separated in two groups according to the time interval till final therapy. Time intervals were calculated from the dates of initial diagnosis of CIN 1 (low-grade squamous intraepithelial lesions/LSIL) till ablative treatment. First group - 92 patients who underwent ablative treatment within three months (mean 1.7, SD 0.8, range 0.5-3) after completion of the two years. Second group - 23 women who delayed ablative treatment from seven to 22 months (mean 15.1, SD 4.6) after completion of the two years. HPV infection was observed in 77 (84%) patients of the 1st group and in 18 (78%) patients of the 2nd group at the start of the study.

Characteristics of the women in both groups are shown in Table 1. Comparisons of quantitative data (ages) were done with the unpaired t-test and qualitative data (smoking, use of condoms, pathology results) with the chi-square test. Time intervals till final diagnosis (CIN 1 or high-grade squamous intraepithelial lesions/HSIL [CIN 2/CIN 3]) were compared with the Kaplan-Meier method and log-rank test, considering HSIL as the end-point.

Results

Delay of treatment was irrespective of medical instructions, and in most cases caused by personal or family reasons (illness of other member of the family, unplanned pregnancy, divorce, changing place of residence, "informed consent" of taking the risk, no explanation, etc.).

Characteristics of the women in both groups at the end of the study are shown in Table 2. Compared to Table 1, the standard deviation (SD) in age remained the same in

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Table 1. — *Ages of the women and percentages of smoking and regular use of condoms at the start of the study (CIN1 diagnosis) in both groups.*

	2 years (n = 92)		Delayed (n = 23)		
Age (mean; range)	32.5 (6.5; 21-43)		32.2 (6.3; 23-42)		ns*
Smokers** (n, %)	66	72	16	70	ns
Use of condoms (n, %)	05	05	01	04	ns

*non-significant; **more than 10 cigarettes/day.

the first group (because all patients "by definition" were about two years older) and in the second group changed marginally.

Cytology results at the end of the observation period are presented in Table 3. HPV infection was diagnosed in 70 (76%) of the 1st group and in 16 (70%) of the 2nd one at the end of the observation period. In the 2-year group, HSIL was diagnosed in cervical smears in the last Pap test (23-25 months after initial diagnosis) and in the "delayed" group 31-46 months after initial diagnosis.

In two patients of the "delayed" group, where planned treatment was postponed for 11 and 15 months, respectively (two years after diagnosis), regression of CIN 1 was observed in a Pap test after this interval which was confirmed by colposcopy. A new Pap test and colposcopy three months later confirmed normal epithelium of the cervix. These patients were withdrawn from further therapy.

The mean interval from the date of initial diagnosis of CIN 1 till ablative treatment was 25.7 months (SD = 0.8) in the 2-year group and 39.1 (SD = 4.6) in the delayed group (p = 0.0001). This comparison is better presented by Kaplan-Meier curves (Figure 1) and better estimated by the log-rank test (p = 0.002) because final diagnosis was not the same in all patients (CIN1 or progression to HSIL). The almost "vertical" appearance of the Kaplan-Meier curve in the 2-year group is due to the fact that "by definition", these patients completed therapy in a 2-year period (24-27 months).

Table 2. — *Ages of the women and percentages of smoking and regular use of condoms (or abstinence) at the end of the observation period in both groups.*

	2 years (n = 92)		Delayed (n = 23)		
Age (mean; range)	34.6 (6.5; 23-45)		35.4 (6.3; 26-45)		ns*
Smokers** (n, %)	47	51	09	39	ns
Use of condoms (n, %)	52	57	18	78	ns

*non-significant; **more than 10 cigarettes/day.

Table 3. — *Cytology and pathology results at the end of the observation period in both groups.*

	2 years		Delayed		
	n	%	n	%	
		Cytology			
LSIL (CIN 1)	79	86	16	70	ns*
HSIL	13	14	05	22	ns
Normal epithelium	–	–	02	09	ns
		Pathology			
LSIL (CIN 1)	77	84	16	70	ns
HSIL	15	16	05	22	ns

*non-significant.

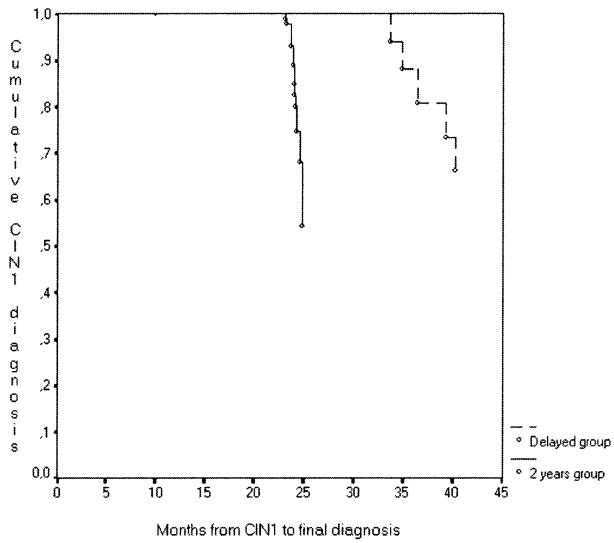

Figure 1. — Kaplan-Meier curves of the groups in the study related to the interval from initial CIN1 diagnosis to final diagnosis after ablative treatment. Steps of the curves correspond to HSIL diagnosis.

Loop electrosurgical excision was performed in 78 (85%) and laser conization in 14 (15%) women of the 1st group and in 17 (81%) and four (19%) patients of the 2nd group.

The pathology results of all patients in the 2-year group and the remaining 21 patients in the delayed group are presented in Table 3.

Comparisons of subgroups are not presented (eg., laser conization and loop electrosurgical excision, smokers and non smokers, etc. because this kind of division left very few patients in each subgroup.

Discussion

Although there is an agreement that all CIN 2 and CIN 3 lesions require treatment, in CIN 1 lesions there is the choice of observation. We must take into account the high spontaneous regression rate of CIN 1 and that all therapeutic approaches carry a recurrence rate of up to 10% [3]. Although ablative therapy of intraepithelial lesions carries a minimal risk of intraoperative or postoperative hemorrhage and cervical stenosis, these complications cannot be totally ignored, especially in young women. The ablative approach of CIN 1 lesions includes the removal of the entire transformation zone along with varying amounts of the cervical canal. In young women, this kind of therapy can prove to be a serious problem causing impaired fertility. Thus, a conservative approach to these lesions, at least in young women, is desirable.

Links between delays in treatment and pathology specimens were investigated retrospectively in our study because a prospective study of this kind could be unethical for patients without the assurance of a close follow-up.

The comparison of pathology results between groups were probably not affected by smoking because percentages of quitting smoking were similar in both groups at

the end of the observation period. Comparison of pathology results between groups may have been marginally affected by condom use or abstinence which was higher in the delayed group at the end of the observation period.

Prospective studies of longer (and very close) observation of CIN I lesions could be proposed in women who quit smoking and use exclusively barrier methods of contraception or abstinence. Cytology and colposcopy together can be more reliable in the follow-up because cytology alone is not suitable to exclude CIN; a closer correspondence was found between colposcopy and the result of histological samples after punch biopsy in CIN detection [4].

The possible prolongation of the safe interval of observation of LSIL lesions could be beneficial in very young, nulliparous women or women planning a pregnancy. Disadvantages of this approach could be feelings of worry and anxiety in cases of remaining disease [5].

The progression to HSIL lesions in 16% of the 2-year group and in 22% of the delayed group is not an argument against the prolongation of the observation period because it is already known that persistence or progression of the lesion is expected in 15-40% of the cases [3] and in our study progression to HSIL was observed almost exclusively in patients who continued to smoke or have intercourse without condoms.

Conclusion

The study suggests the possibility of a safe prolongation of the observation period after LSIL diagnosis. Prospective studies with close follow-up are needed for final conclusions.

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