Frequency of recurrence after surgical treatment of cervical intraepithelial neoplasia grade 1-3

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Summary

Purpose of investigation: The objective was to demonstrate the frequency of invasive cervical cancer or recurrent CIN in patients treated by a previous diagnosis of CIN 1-3. *Methods:* We analyzed 1,397 records colpocytologic and medical records. Recurrence of CIN or invasive neoplasia of the cervix after treatment of CIN was assessed. The chi-square test was used for statistical analysis (significance level set at less than 0.05). *Results:* We obtained 696 CIN 1, 244 CIN 2, 451 CIN 3, and six squamous carcinoma. Regarding patients who relapsed, there were 6/690 (0.9%) patients had an initial diagnosis of CIN 1, 8/236 (3.4%) CIN 2 and 21/430 (4.9%) CIN 3 ($p < 0.0001$). Comparing the frequency of relapse among each group, we found: CIN 1 vs CIN 2: $p = 0.0073$; CIN 1 vs CIN 3: $p < 0.0001$; CIN 2 vs CIN 3: $p = 0.38$. *Conclusion:* Although the number of relapses when comparing CIN 2 and CIN 3 were not significant, the data suggest that CIN 2 has lower recurrence rates, so these patients require more conservative treatment if a desire of future pregnancy is expressed.

Key words: Post-treatment recurrence; Cervical intraepithelial neoplasia; Invasive cervical cancer.

Introduction

The incidence and mortality of cervical malignancy have substantially reduced with cervical screening programs [1]. The risk of recurrence of cervical intraepithelial neoplasia (CIN 2/3) after treatment may be associated with the degree of CIN, the type of treatment, and age [2].

CIN is the precursor lesion of cervical cancer. The triad of colposcopy, cytology and histology have confirmed the diagnosis of cervical premalignant and malignant lesions, and histology remains the gold standard which will define the treatment. The decision on choosing the most appropriate therapy for the treatment of cervical intraepithelial lesions depends on many factors such as location and extent of injury, patient age, the desire for pregnancy and adherence to follow-up [3-5].

Low-grade CINs should be followed up every six months with colposcopy and cytology since the rate of regression is high. Treatment is reserved for persistent lesions. The standard procedure for high-grade CIN is the loop electrosurgical excision procedure (LEEP) and its effectiveness depends on the status of the surgical margin, and extent and presence of endocervical lesions in multiple quadrants. The main techniques for removal of cervical lesions include local destructive treatments (cryotherapy, electrocautery, laser) and excisional treatments, which have the advantage of providing material for histological confirmation of the lesion and the margins [3-5].

The American Society for Colposcopy and Cervical Pathology (ASCCP) recommends for follow-up after treatment of CIN 2 and 3, a single HPV test for six to 12 months after treatment, two consecutive cytological tests with colposcopy or cytology), followed by routine check-ups if the usual screening tests are normal. The range for routine screening is nonspecific, but the guidelines indicate that a high risk of recurrence of CIN or invasive cancer persists for many years after treatment and the follow-up should continue for at least 20 years. Guidelines from the Agency of British Columbia Cancer at this time recommend colposcopy four to six months after treatment for CIN 2/3. If results are normal, cytological follow-up is recommended after 12 months of treatment [2].

The objective of the study was to demonstrate the frequency of invasive cervical cancer or recurrent cervical intraepithelial neoplasia in patients who were treated by a previous diagnosis of CIN 1-3 comparing age, pathological diagnosis and treatment.

Materials and Methods

A retrospective study was conducted at the Federal University of Triangulo Mineiro (UFTM). We analyzed 1,391 records (1994-2004) of Pap smears, colposcopy and epidemiologic data of patients diagnosed with CIN 1, CIN 2 or CIN 3 screened by cytology. These patients were treated and continued follow-up after treatment in the colposcopy clinic of the Discipline of Gynecology and Obstetrics, Universitary Hospital of UFTM (HU-UFTM). The record for each patient was obtained, numbered and cataloged according to diagnosis, age, treatment, and analyzed in conjunction with the Discipline of Special Pathology and IPON (Oncology Research Institute) - UFTM. Recurrence of cervical intraepithelial neoplasia or invasive neoplasia of the cervix after treatment of CIN 1 (when there was treatment), 2 or 3 was assessed. We also evaluated data such as age, parity and initial treatment, duration of follow-up (colposcopy and cytology every 6 months), diagnosis, treatment of relapse, and time after initial diagnosis of their appearance. Records not

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Table 1. — *Diagnosis, initial treatment, lesion in recurrence, recurrence time, treatment of recurrence and death.*

Diagnosis	n	Initial treatment	Lesion in recurrence	Time post-	Treatment of recurrence	Death
CIN 1	6	Cauterization	CIN 1, 2, 3	3 - 8 years	Conization, LEEP, hysterectomy or follow-up	0
CIN 2	4	LEEP, conization or hysterectomy	CIN 1, 3	1 - 4 years	Cauterization or follow-up	0
CIN 3	13	LEEP or hysterectomy	CIN 1, 2, 3, invasive cervical cancer	1 - 7 years	LEEP, cauterization, hysterectomy, chemotherapy or follow-up	0
CIN 1/2/3	3	LEEP or conization	CIN 1, 2, 3, adenocarcinoma in situ	2 - 9 years	Conization or hysterectomy	0
CIN 1/2	4	LEEP or conization	CIN 1, 2, 3	1 - 6 years	Conization, follow-up	0
CIN 1/3	1	conization	CIN 3	7 years	Hysterectomy	0
CIN 2/3	4	LEEP or conization	CIN 2, 3	1 - 6 years	Conization, hysterectomy	0
Invasive cancer	4	Wertheim-Meigs, Radiotherapy, Chemotherapy	CIN 1, 2, 3, invasive cervical cancer	2 - 16 years	Radiotherapy, follow-up	1
Total	39					1

Source: Data - Cytology (UFTM) 1994-2004.

pertinent to the work, such as other diagnosis, incomplete data and patients who did not undergo regular monitoring, were excluded.

Most patients who were lost to follow-up had a diagnosis of CIN 1 and were excluded from the study. Regarding patients with CIN 1, 288 women were lost to follow-up, and 143 women underwent follow-up irregularly.

Initially the records were separated according to cytological diagnosis, and when a patient had more than one, we considered it more complex. In our service there is no obligation to perform histology when there is a cytologic diagnosis of CIN 1. After confirmation of CIN 1 post Papanicolaou patients were referred to the Colposcopy Clinic for follow-up every six months and were discharged after three General Outpatient Clinic smears showed no CIN or HPV infection. However, for patients with a cytological diagnosis of CIN 2 or 3, it was compulsory to carry out pathological examination to confirm the diagnosis and direct the treatment. For patients with smear dissociation, we considered it a more complex diagnosis.

Cryotherapy or colpo-cytologic monitoring every six months (until there was no evidence of HPV infection) was the procedure for patients with CIN 1. Patients with CIN 2 and CIN 3 were treated with LEEP, conization, or hysterectomy. Hysterectomy was performed when there was no technical requirement for conization (flat or atrophic cervix).

Statistical analysis

X^2 test and X^2 test for trend were used for statistical analysis with the significance level set at less than 0.05. This research was approved by the Research Ethics Committee of the Federal University of Triângulo Mineiro.

Results

After rigorous analysis, 1,391 records of smears with CIN 1, 2 or 3 were selected. We obtained 696 CIN 1, 244 CIN 2, and 451 CIN 3. Thirty-nine patients relapsed after treatment of the initial diagnosis and one died after recurrence.

Table 1 shows diagnosis, initial treatment, lesion in recurrence, recurrence time, treatment of recurrence and death.

Table 2. — *Recurrence of CIN in each group.*

	Recurrence	Total
CIN 1	6 (0.9%)	690
CIN 2	8 (3.4%)	236
CIN 3	21 (4.9%)	430
Total	35	1,356

X^2 test for trend, $p < 0.0001$; X^2 test: CIN 1 vs CIN 2: $p = 0.0073$; CIN 1 vs CIN 3: $p < 0.0001$; CIN 2 vs CIN 3: $p = 0.38$.

Regarding patients who relapsed in each group, there were 6/690 (0.9%) patients with an initial diagnosis of CIN 1, 8/236 (3.4%) CIN 2 and 21/430 (4.9%) CIN 3 ($p < 0.0001$, X^2 for trend; Table 2). Four patients who relapsed had an initial diagnosis of invasive carcinoma.

The ages of patients who relapsed varied from 22 to 72 years, with a prevalence of 20-40 years (56.41%), and 43.58% of patients were over 40 years. Recurrence after initial diagnosis ranged from one to 16 years, and follow-up by Pap smear ranged from one to 18 years. Only one patient did not treat the recurrence of injury and another did not return to the clinic.

Regarding patients with CIN 1 who relapsed, the mean age was 38 ± 10.9 years, mean parity was 2.5 ± 1.9 children, four (66.7%) were white women and two (33.3%) were nonwhite women. In patients with CIN 2 who relapsed, the mean age was 40.1 ± 12.3 years, mean parity was 3.1 ± 2.9 children, two (25%) were white and six (75%) were nonwhite women. In patients with CIN 3, the mean age was 38.6 ± 11.2 years, mean parity was 2.5 ± 1.3 children, 17 (80.9%) were white and four (19.1%) were nonwhite women. Regarding patients with an initial diagnosis of invasive carcinoma, the mean age was 58.7 ± 15.7 years, mean parity was 3.7 ± 2.6 children, and all were white women.

Comparing the frequency of relapse among each group, we found: CIN 1 *versus* CIN 2: $p = 0.0073$; CIN 1 versus CIN 3: $p < 0.0001$; CIN 2 versus CIN 3: $p = 0.38$.

Discussion

Patients with CIN and microinvasive carcinoma usually have no specific symptoms. The careful choice of primary therapy for cervical carcinoma is crucial, because treatment of recurrent disease is more difficult.

In patients over 40 years, most of the initial diagnoses were CIN 2 or 3 (64.7%), and recurrence also occurred in more complex lesions or invasive carcinoma. Melnikow *et al*. demonstrated that the recurrence of CIN 2/3 increases with age, grade of intraepithelial neoplasia and early treatment of disease [2].

Regarding tumor recurrence, only two cases had recurrence as invasive, and in both the initial diagnosis was invasive carcinoma. Thus, we can not conclude that there is a greater predisposition to invasive neoplasia, if the initial diagnosis was a high-grade CIN. Therefore it confirms the importance of prolonged follow-up since relapse occurred after four and 13 years of colpo-cytologic monitoring.

Some recurrences occurred in the short term, other long-term recurrences occurred during follow-up with Pap smears and colposcopy. Thus it is not possible to predict the ideal time in which the patient should return for routine annual check-up.

Age, CIN grade and type of treatment are important factors related to rates of recurrence of intraepithelial lesions or invasive neoplasia [2]. This is in agreement with our results, which also showed an association between recurrence and grade of CIN. Women with CIN 3 who were not treated had an increased risk of developing cervical cancer [6, 7] while the risk was very low in women treated conventionally [6]. Although wide excision of the transformation zone is an effective treatment in high-grade intraepithelial lesions, approximately 15% of patients will have persistent or recurrent disease at follow-up. Furthermore, patients who tested positive for HPV DNA at follow-up seem to have a considerably higher risk of recurrence of intraepithelial lesions than those with these negative tests [7].

Melnikow *et al*. demonstrated overall rates of CIN 2/3 declined rapidly for the first two years after treatment, but during the first six years of follow-up, these rates were 14.0% for women treated for CIN 3, 9.3% for CIN 2, and 5.6% for CIN 1 [2]. In our study, these rates were 0.9% for CIN1, 3.4% for CIN 2 and 4.9% for CIN 3. The ASCUS/LSIL Triage Study (ALTS) demonstrated women with initial low-grade squamous epithelial lesions who were referred for early colposcopy had rates of subsequent CIN 2/3 of 8% to 13% during a 24-month follow-up [8]. Other studies demonstrated residual or recurrent disease ranged from 7.6% to 17.9% in women treated for high-grade squamous intraepithelial lesions [9-11].

HPV infections in adolescents have a high rate of spontaneous regression [5]. Some will progress to HSIL or LSIL, but rarely is there a progression to cervical cancer. Excisional techniques could disturb the future pregnancy outcome of these patients, so a conservative approach can be done in these cases [4, 5]. The available data have shown an increased risk of overall preterm delivery, preterm delivery after premature rupture of membranes, and low birth weight infants in subsequent pregnancies [12-16].

When a woman expresses a desire for future pregnancy, even the type of excisional treatment should be thoroughly evaluated. When comparing LEEP with cold-knife conization, obstetric complications such as miscarriages and preterm pregnancies are more frequent with cold-knife conization [17].

Epidemiological evidence has demonstrated that the biological behavior of CIN 2 is closer to CIN 1 than to CIN 3, and the risk of progression to invasive carcinoma in cases of CIN 1 and CIN 2 is low [18, 19]. Castle *et al*. estimated a fraction of cervical intraepithelial neoplasia 2 (CIN 2) that may regress if untreated using data from the ALTS study and approximately 40% of undiagnosed CIN 2 will regress over two years, but CIN 2 caused by HPV-16 may be less likely to regress than CIN 2 caused by other high-risk-HPV genotypes [20].

Our study showed a low frequency of recurrence of CIN 1 (0.9%). This confirms that follow-up every six months is safe for patients with this diagnosis. When comparing the different degrees of CIN, there was a trend towards increased frequency of recurrence with worsening of the injury. Thus maybe the option of more conservative treatment could be performed in patients with CIN2 or even in adolescents with CIN 2 and CIN 3.

Conclusions

Although it did not significantly affect the number of relapses when compared with CIN 2 and CIN 3, the data suggest that CIN 2 has lower recurrence rates, so patients with CIN 2 who require more conservative treatment, such as those with a desire for pregnancy, may be subjected to less invasive treatment. These patients may be advised to have close follow-up, since the frequency of recurrence is lower, preventing a higher rate of premature rupture of membranes, premature labor and of prematurity.

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