MANAGEMENT OF CERVICAL DYSPLASIA DIAGNOSED BY BIOPSY

GEORGETA GÎNFĂLEAN[1]

[1] *"Lucian Blaga" University of Sibiu*

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Abstract: *Progress made in the field of immunology, medical genetics and molecular biology have allowed demonstrating the central role of Human Papillomavirus Infection (HPV) in the etiopathogenity of cervical intraepithelial neoplasia (CIN) and, implicitly of cervical neoplasia (CN). When precancerous lesions are diagnosed before they develop into cancerous lesions, early and appropriate treatment are established for each grade and the survival rate can reach almost 100%. This study aims at standardizing the management of cervical dysplasia so as to lead to the optimization of the therapeutic results.*

Preinvasive disease concept was introduced in 1947, characterizing the existence of epithelial changes similar to cervical neoplasia, but limited to epithelium. The criteria for the diagnosis of intraepithelial neoplasia (CIN) are given by cell immaturity, cell disruption, cell abnormalities and increased mitotic activity.

Introduction of the Pap test as a screening method for cervical cancer reduced the mortality from this disease, but consecutively the number of diagnoses of cervical preinvasive lesions has increased. Although these lesions may regress spontaneously without any treatment, CIN is a lesion which can lead to cervical invasive carcinoma (table no.1).(1,2)

Table no. 1. Natural evolution of cervical dysplasia

	Regression (%)	Persistent (%)	Progression towards CIN_{III}	Progression towards invasive carcinoma (%)
CIN_I	60	30	10	1
CIN_{II}	40	40	15	5
CIN_{III}	30	55	-	>12

The natural evolution of cervical dysplastic lesions is related to the presence of HPV infection. HPV genome was demonstrated in all grades of cervical neoplasia.(3,4)

Although the number of HPV known genotypes are approaching 80, only certain types cause approximately 90% of intraepithelial cervical lesions with high-grade or cancer - representing the so called group of virus types with high risk of association with cervical carcinoma (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58). Type 16 is the most commonly encountered type of HPV in invasive cancer in CIN_{II} and CIN_{III}.(4,5)

Unfortunately, HPV type 16 is not very specific, and can be found in 16% of women with low lesions and 14% of normal smears. HPV type 18 is more specific, being found in 23% of women with invasive cancer, 5% of women with CIN_{II} and CIN_{III} and less than 2% of patients with normal cytology.(6) Infection with HPV is a common one and it is estimated that 25% of sexually active women have this infection, and a woman's cumulative risk of developing an HPV infection is about 80%. In most cases, viral suppression is produced, which is fast and without dysplasia, and only 7% of women will present abnormal Pap smears.

Ad a result, persistent HPV infection with high-risk serotypes is necessary but not sufficient for the development of invasive cervical lesions. Duration of HPV persistence increases the risk of CIN. Integration of transcriptionally active DNA of HPV in the host cell is mandatory for malignant development. Malignant transformation supposes the expression of oncoproteins E6 and E7 produced by HIV. The factors that seem to play a part in activating these oncoproteins are represented by smoking, contraceptive use, infection from other sexually transmitted diseases or nutrition.(3)

Currently, in the histogenesis of cervical cancer, it is widely accepted the hypothesis of lesion continuity, the relation between benign and malignant lesions. In the natural progression of dysplasia, it passes through successive degrees of severity, achieving a unitary continuous carcinogenic process. It is recognized that cervical cancer does not occur on a free cervix.

Colposcopic examination and especially, the cytological one allowed the differentiation between some anatomoclinical entities, especially the subclinical ones, representing intermediate stages in the uninterrupted lesional chain between the normal and cancerous epithelium. The sequence of these lesions is: normal epithelium - atypical epithelium - atypical aggravated epithelium (includes also CIE) - invasive carcinoma.(1)

Since, it is sometimes very difficult to establish a differential diagnosis between a serious dysplasia and an intraepithelial carcinoma, there has been suggested that all dysplastic changes evolving towards the last lesion to be included under the term of intraepithelial dysplastic neoplasia (CIN - grade I, mild dysplasia, CIN - grade II moderate dysplasia, CIN - grade III severe dysplasia).(7)

Carcinogenesis process starts initially by dysplasia. Mild or moderate dysplasia can regress or may develop in 60% of cases to severe dysplasia (CIN_{III}). If the process passes through the basal membrane and the infiltration goes beyond the depth of 3.5 mm, it is an invasive carcinoma. This process develops in about 15-20 years.

Regarding histogenesis, there are multiphasic and biphasic forms. Multiphase form is more common (85% of

[1]Corresponding author: Georgeta Gînfălean, Str. Moreni, Nr. 19, Sibiu, România, E-mail: rezultatemedicina@yahoo.com, Phone: +04723 254897
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cases). The events succeeding in invasive carcinoma are represented by the forms of: CIN_I, CIN_{II}, CIN_{III} and invasive carcinoma. Regarding the biphasic form, it is noticed a direct shift from CIN_I and CIN_{II} to invasive carcinoma. The biphasic form is more common in young women.

In clinical manifested forms, cytology and colposcopy lose interest, the tumour portion being evident. Instead, biopsy is mandatory for differential diagnosis (syphilis, tuberculosis) and to assess the histological type of the lesion.(1,2)

Biopsy is the sovereign diagnostic method of pre-neoplastic lesions of CIN and cervical carcinomas, no treatment plan can be conceived without a biopsy exam. In dysplasia and microinvasive carcinoma, biopsies should facilitate the thorough study of the nuclei morphology and the report of the lesion with connective tissue. In order to do this, the following conditions are necessary: the fragment should contain enough tissue; the fixative should be a nuclear fixative containing acetic acid (Bouin's fixative); fragments to be oriented in the paraffin block during the histological technique; anti-inflammatory treatment in case of doubt and biopsy repeat.

Histopathological examination of the sampled parts can be made extemporaneously, using the cryostat technique, or the classical technique can be used by paraffin embedding. After colouring the section with the usual colouring techniques, the histopathological examination, interpretation are performed, as well as the set up of the diagnosis by the histopathologist. Histological examination is the one that will determine the correct diagnosis.

Conization is performed clinically or colposcopically when there is a non-lesional cervical but with suspected etiology (C_{III}) or positive (C_{IV} - C_V), or when there is a suspected cervix clinically and/or colposcopically and cytologically and with a histopathologic result of severe dysplasia (CIN_{III}).(8)

Management of cervical dysplasia diagnosed by biopsy

1. CIN_I - Since a significant proportion of CIN_I lesions may regress spontaneously, most authors recommend the follow-up of these cases if the colposcopic examination was satisfactory. However, it should be recognized that some of these lesions may progress to invasive forms and therefore, the therapeutic approach of these cases is also accepted.

Surveillance protocols are represented either by repeated cytologies at 6 and 12 months, either by cytology combination with colposcopy. There are no studies to demonstrate the superiority of the follow-up method by colposcopy compared to the cytological surveillance.(1,2)

Currently, it is known that HPV infection testing at 12 months is an alternative to repeat two cytology examinations and that progression towards CIN_{III} assumes the persistence of HPV infection.(3) Under these conditions, the most widely accepted method of surveillance of the patients diagnosed with CIN_I is AND-HPV testing at 12 months. Persistence of HPV infection requires repeating colposcopy (figure no.1).

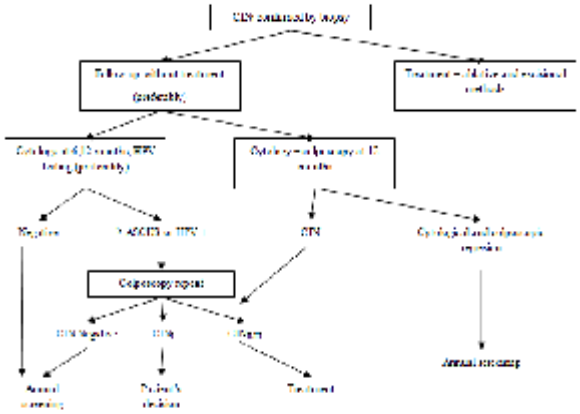
In the case of a $CIN_{II/III}$ diagnosis by biopsy, appropriate therapeutic conduct will be applied. In the case of a persisitent CIN_I result, it is recommended that the follow-up decision or therapeutic approach to be made based on the patient's informed consent.

Therapeutic options therapy are represented by ablative methods (cryotherapy, electrofulguration, laser ablation), which are recommended for patients with colposcopy involving exclusion of invasive lesions, as well as excision methods (loop electrosurgical excision, laser conization) indicated in cases of persistent or recurrent CIN.

Total hysterectomy is burdened by increased morbidity and mortality, reason for which it is not justified as a therapeutic method of first choice in cases of CIN_I

Patients with CIN_I and unsatisfactory colposcopy require an excisional diagnostic method, such as loop electrosurgical excision or conization.(4,5)

Figure no 1. Management of CIN_I cases diagnosed by biopsy



2. CIN_{II} - CIN_{III} - The natural evolution of these lesions is mostly towards persistence or progression, and not towards spontaneous regression, justifying the therapeutic intervention in these cases. In patients with satisfactory coloscopic examination, the therapeutic procedures used are varied: ablative methods (cryotherapy, electrofulguration, laser ablation), or excision methods (loop electrosurgical excision, laser conization) or hysterectomy.

To be effective the method chosen must remove the entire transformation area regardless of the focal colposcopic location of the lesion. Because of the potential presence of microinvasive lesions or even really invasive, most authors do not prefer the ablative methods.(2) For patients with unsatisfactory colposcopic exam, an excision diagnostic method is required, such as conization. The absence of free margins of the excised tissue increases the risk for recurrent/persistent CIN by about 4 times compared to the situation where the margins are negative. However, it is accepted that the presence of pathological edges is not an independent predictor factor for the residual disease.(2)

As a general rule, it is recommended that in case of some positive margins to continue treatment, according to the patient's age and desire to preserve fertility, opting between expansion excision by conization or hysterectomy.

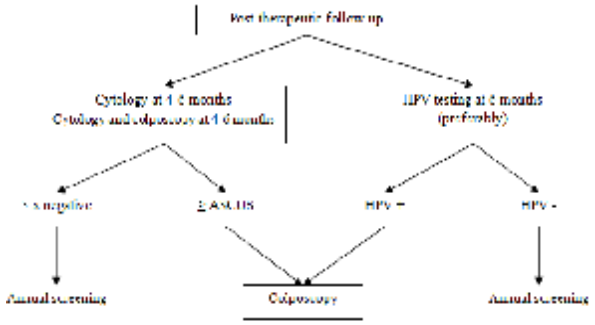
Surveillance protocol after the treatment for a $CIN_{II/III}$ lesion, may be the repeated by cytology examinations at 4-6 months or by combining cytology with colposcopy. It is accepted that after 3 negative cytological examinations, to perform annual screening.(2)

Cytological detection of some ASC-US lesion or more severe requires colposcopy. Recent studies have shown eradication of cervical HPV infection in the case of an effective treatment of dysplastic lesion and that in the post-intervention follow-up of women with negative HPV, no persistent/recurrent CIN was detected unlike those with positive HPV presenting persistent or recurrent CIN in 50-73% of cases.(1)

As a result, AND-HPV testing is the right way of following-up the women treated for $CIN_{II/III}$ cervical lesion (figure no. 2).

HPV persistence requires colposcopy with biopsy. Hysterectomy is the method of choice in treatment of persistent/recurrent $CIN_{II/III}$ lesions, confirmed by biopsy.

Figure no. 2. Post-therapeutic management of $CIN_{II/III}$ lesion



Conclusions:

Lately, there is an increased incidence of precancerous cervical lesions, probably due to higher accuracy of diagnostic methods. Also, there has been succeeded to correlate the intraepithelial cervical diseases with oncogenic HPV infection, which opened up new prospects for treatment. Currently, there is a well established correlation between diagnostic and therapeutic protocols.

With the required rigor, cytology has now become the most practical method of detecting dysplastic and malignant cervical lesions.

Colposcopy may not be a definitive method of diagnosis, but its corroboration with cytology and histology especially and viral typing becomes very useful in setting up the therapeutic conduct.

Advances in recent years have led to a standardization of cervical dysplasia management enabling the optimization of the therapeutic outcomes. Recent studies suggest the introduction of oncogenic anti-HPV vaccines in future protocol with a view to find their proper place in current practice.

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