

CLASSICAL AND MODERN TREATMENT APPROACHES FOR CERVICAL INTRAEPITHELIAL NEOPLASIA

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Keywords: cervical intraepithelial neoplasia (CIN), treatment
Abstract: Curing the cervical intraepithelial neoplasia consists of a complex treatment, both medical and surgical, avoiding the radical surgery methods and thus keeping the reproductive function.

Cuvinte cheie: leziune cervicală intraepitelială, tratament
Rezumat: Tratamentul neoplaziei cervicale intraepiteliale presupune un tratament complex, atât medical cât și chirurgical, care vor evita folosirea metodelor chirurgicale radicale, păstrându-se astfel funcția reproductivă.

Cervical intraepithelial neoplasia (CIN) is a benign lesion having an unknown prognostic and possibilities of regression (Christopherson, 1969).

In 1973, WHO classifies dysplasia into mild, moderate and severe.

This modification appears mostly at the level of the squamo-cylinder junction.

Anatomopathologists classify it into 3 grades:

- 1st grade CIN – mild
- 2nd grade CIN – moderate
- 3rd grade CIN – severe or “in situ carcinoma”

1st grade CIN or mild dysplasia

Changes of the maturation process of epithelial structure appear with this type of dysplasia. Nuclear anomalies and cytoplasm alterations appear as marked, even koilocytes can be visible. Cytological preparations for existing 1st grade CIN are characterized by mature cells and cytoplasm rich in **eosynophilies**. Nuclei are big and hyper chromatic and have a pyknosis tendency.(1)

2nd grade CIN or moderate dysplasia

Moderate dysplasia is characterized by an intensely proliferative activity of the basal cells, abnormal mitoses may also occur, nuclei are big, the chromatin is developed and basal membranes are abnormal. The nuclei – cytoplasm ratio results as bigger than in 1st degree CIN.(1)

3rd grade CIN or severe dysplasia

The 3rd grade dysplasia appears as a lesion with cytoarchitectural alterations similar to invasive carcinoma, but between the basal membranes limits. Frequent and abnormal mitoses, increased hyperchromic nuclei, irregular chromatin, numerous nuclear atypies, irregular nuclear membrane, anisonucleosis, modified nuclei – cytoplasm ratio appear.(2)

In 1988, following the Congress of the National Cancer Institute in Bethesda Maryland, the Bethesda system was

developed for the cytological classification, according to which premalignant squamous lesions classify into three categories:

- Atypical squamous lesions with an undetermined significance (ASCUS);
- Low – grade squamous intraepithelial lesions (LSIL);
- High – grade squamous intraepithelial lesions (HSIL)

Low – grade squamous intraepithelial lesions include CIN I (mild dysplasia) and high – grade squamous intraepithelial lesions include CIN II, CIN III (severe dysplasia and “in situ” carcinoma).

In 2001, ASCUS divide between ASC-US and ASC-H, which needs a different approach.

Cervix lesions associated to HPV are treated in order to prevent their evolution towards invasive cancer and to prevent the transmission of the virus to the sexual partner.(3)

Thus, the treatment of CIN HPV must be complex, both medical and surgical.

The medical treatment for CIN

This type of treatment targets the lesion directly (local treatment) or can stimulate immunity (general treatment).

Local medical treatment

1. 5-FLUOROURACIL is an antimetabolite cytostatic that inhibits the cell proliferation by blocking the DNA synthesis enzyme and forming an abnormally structured NRA.(4,5)
2. IMIQUIMOD belongs to the imidazquinoline family and is a first option solution as treatment of the lesion. It activates both the cell and humoral local immune response, by stimulating the local synthesis of alpha interferon, alfa TNF, and cytokine. 5% concentration Imiquimod induces the disappearance of condyloma lesions and decreases the viral force.

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General medical treatment

1. INTERFERON is a substance with a role in the unspecific protection against severe viral infections, by preventing the virus from multiplying at this level, and blocking the translation of the viral messenger NRA. It has an antiproliferative effect against condyloma but in 90% of the cases, recurrences have occurred.
2. IMMUNOMODULATORS stimulate cell immunity by activating the macrophages and T and B lymphocytes, thus inhibiting the replication and indirectly inhibiting the viral replication.
3. ANTI-HPV VACCINATION – as the connection between the cervical cancer and HPV has been proven, anti HPV vaccines were developed thus, reducing the incidence and increasing the curing rate.

Surgical treatment for CIN

The therapeutic strategy nowadays consists of a conservative treatment which does not affect the reproductive function.

Between 1950 and 1960, the usual treatment for severe dysplasia was total hysterectomy.(6)

The treatment principles for CIN (7,8)

1. The transformation area must be totally excised;
2. A minimum 7 mm deep excision is recommended;
3. Dysplasia can also involve the glandular crypts, this is why the treatment also targets the tissue from under the glandular crypts;
4. All women patients suffering and being treated for CIN must be HPV tested;
5. The CIN progress depends on the lesion grade and extension and the age of the patient.

The surgical treatment methods include destructive techniques and excisional techniques.

1. Cryotherapy

This type of surgical therapy is a destructive method consisting of the usage of nitrogen oxide. The prescriptions of cryotherapy are low grade CIN that does not ascend endocervically, with a surface of less than 3 cm in diameter. Cryotherapy is not recommended for pregnant or aged women as it has an important disadvantage: hystopathologic exam cannot be made.(9)

2. Electrocauterization

This is a treatment method used when the anatomic limit of the lesion can be viewed during colposcopy. It is used without hospitalization and represents a method with very good results particularly in exocervical lesions. The most frequent complications are pain, uterus contractions, and cervical stenoses. This method is obsolete.(10)

3. Carbon dioxide laser vaporization

The laser converts into an energy radiant shape which is produced at a wave length specific to the laser type. Carbon dioxide laser produces energy at a 10.6 µg wave length. CO2 laser is attached to a colposcope and destroys the affected area under the direct visualization of the surgeon. The best results are obtained when the depth of the destroyed tissue is about 5-7 mm, and the vaporized area must be wider by 5 mm than the lesion and 4-5 mm of the endocervical channel area. Complications are rare: bleeding during the operation, minimum pelvic discomfort, or local infections. The results are very good if associated with a biopsy, loop electro-surgical

excision or conization. (The excised tissue will be sent to hystopathological examination).(11)

4. Conization and cold scalpel

This is an excisional therapeutic method more and more rarely used as it cuts either less or more than the affected area, bleeding during the operation occurs and it needs haemostasis with sawing wires. Vicious scars can appear.(12)

5. LASER conization

The size of the spot can be easily reduced and thus the fascicle power increases which leads to a more accurate resection of the cervical or vulva lesion. Complications after the operation: bleeding, infections, brown leakages, stenoses. The major disadvantage is the high cost of the process.

6. Loop electro-surgical excision and electrical conization

The diathermal loops were at first used to excise small or big lesions on the uterus cervix. Prendville and collabs. (1989) proved that using big autopsy loops can also turn into a treatment. Electrical conization is used when the lesion affects the endocervix too, and loop electro-surgical excision is used when the lesion is visible on the exocervix during colposcopy. This method has a low morbidity rate.(13) This method has been used in Polizu clinic since 1994 and it has great results. The method has three big disadvantages: it is a therapeutic and diagnostic method, and it keeps the reproductive function.(14)

Therapeutic method – the cervix lesion is fully excised;

Diagnostic method – the excised fragments are sent to the anatomopathologic examination.

For the high grade cervix lesions this therapeutic method keeps the reproductive function as it is a conservatory treatment method.(15)

7. Cervix amputation

This type of intervention was practiced in the past and has been replaced by conization. Cervix amputation involves a long stay in the hospital, general anesthesia and can frequently cause bleeding.(16)

8. Total hysterectomy

Total hysterectomy is a radical method currently recommended for women aged over 45, suffering from severe dysplasia and with no baby expectancy, women with associated tumoural pathology or “cancer phobia” women.

Conclusions:

1. The excisional conservative method of treatment is recommended for high grade cervical neoplasia, as it has the best long term results and a low rate of residual or recurrent lesions.
2. Avoiding radical methods for high grade lesions involves a high cost and an emotional stress as well.

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