

**UNIVERSITY OF MEDICINE AND PHARMACY OF CRAIOVA
DOCTORAL SCHOOL**

DOCTORAL DISSERTATION

**THE SURGICAL TREATMENT OF SEVERE
CERVICAL DYSPLASIA**

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THE GENERAL PART

CURRENT STATE OF KNOWLEDGE

CHAPTER I

THE IMPORTANCE OF THE RESEARCHED TOPIC. OBJECTIVES OF THE DISSERTATION.

The cervical cancer is the second leading cause of female cancer worldwide. The onset of this cancer is preceded by abnormalities of the Malpighian epithelium, called cervical intraepithelial neoplasia (CIN), dysplasia or squamous intraepithelial lesions (SIL).

The aim of the study was the clinical-paraclinical and therapeutic re-evaluation of cervical intraepithelial neoplasia taking into account the grade of cervical lesion, the extension of the surface, the age of the patients and the desire for motherhood, as well as the pathology associated with cervical lesions.

CHAPTER II

CERVICAL DYSPLASIA. DEFINITION. INCIDENCE. RISK FACTORS.

The notion of cervical dysplasia or cervical intraepithelial neoplasia represents lesions of the squamous epithelium in the cervix, which are considered precursors of invasive cervical cancer.

The genital human papilloma virus (HPV) is the most common sexually transmitted infection. The HPV types are classified as high-risk (HR) or low-risk (LR) based on oncogenicity and association with cervical cancer.

CHAPTER III

SPECIFIC INVESTIGATIONS

CERVICAL CYTOLOGY

The Babes-Papanicolau cytological screening detects most cervical neoplasia in the early, occult, premalignant or malignant phases, when the evolution under treatment is optimal.

Following the processing and examination of the sample, the result is developed according to **the Bethesda System for reporting cervical cytology 2001** [96], the reported elements being the adequate character of the specimens and the anomalies of the epithelial cells.

HPV TESTING

A certain diagnosis of HPV infection can only be established by direct detection of HPV DNA. This can be performed histologically by PCR (nucleic acid amplification test), by hybridization or by other techniques [114].

COLPOSCOPY

The purpose of the colposcopy is to identify the invasive and pre-invasive cervical neoplastic lesions and their biopsy.

BIOPSY

The exocervical biopsy is performed under colposcopic guidance, by visualizing the suspicious lesions of the exocervix and collecting fragments with a special tool. **The endocervical curettage** is practiced in situations where the endocervical canal is not visualized by colposcopy and of course patients are not pregnant. The fragments obtained by exocervical biopsy or endocervical curettage are sent for histopathological examination, certainty examination for diagnosis

CHAPTER IV

THE MANAGEMENT OF CERVICAL INTRAEPITHELIAL NEOPLASIA

The goal of the treatment is to suppress the junction area including abnormal tissues by loop electrosurgical excision procedure and conization with laser or cold knife, or by tissues ablation, destroying it by cryosurgery or laser.

The ablative procedures are electro-surgery, cryosurgery, carbon dioxide laser. **The excision therapy** – consists of surgical excision with an electric loop, cold knife conization, CO₂ laser conization. **The hysterectomy** is an unacceptable therapeutic procedure for CIN 1, CIN 2 or CIN 3 lesions [133].

THE SPECIFIC PART

PERSONAL RESEARCH

CHAPTER V

MATERIAL AND METHOD

The study included a number of 328 patients with cervical dysplasia, between 2014 and 2018. During the 5 years, the patients were investigated, diagnosed and treated surgically in the Clinic II Obstetrics-Gynaecology, Clinic II General Surgery of the County Clinical Emergency Hospital of Craiova and Parc Medical Centre Craiova.

The investigations such as cervico-vaginal cytology, HPV testing and genotyping, colposcopy and fragmentary biopsy or conization were performed to determine the grade of lesions in the cervix, fractional biopsy curettage to identify associated lesions.

The HPV testing was performed in 242 patients, excluding 86 patients under 30 years of age. The HPV genotyping revealed 110 cases with low-risk HPV types (LR-HPV), in which types 61, 6, 81 were predominant, along with strains 11, 54, 42, 70 and 132 cases with high-risk HPV types (HR-HPV), in which types 16, 18, 45 were predominant, together with strains 52, 53, 68, 58, 31.

The colposcopic examination included the description of the examined cervix, the possibility of examining the junction area, the description of the normal and pathological colposcopic aspects, the appreciation of the possibility to examine the entire lesion area.

The histopathological diagnosis was established on the basis of tissue fragments obtained by biopsy or cervical conization, endouterine fractionated curettage and excised operative piece

The surgical treatment of cervical intraepithelial neoplasia was established according to conditions, indications and contraindications and consisted of: conization, amputation, hysterectomy and triple Manchester operation.

CHAPTER VI

RESULTS

In the period of 5 years, 2014-2018, the 328 patients belonging to the study were distributed as follows: 39 cases (12%) in 2014, 53 cases (16%) in 2015, 64 patients (19.5%) in 2016, 80 patients (24.5%) in 2017 and 92 patients (28%) in 2018.

The cervico-vaginal cytological examination was reported in the Bethesda system. Thus, the following were found: ASC-US (atypical squamous cells of uncertain significance) in 97 cases (29.58%), ASC-H (atypical squamous cells that cannot exclude a high-grade

squamous intraepithelial lesion) in 14 cases (4.27%), L-SIL (low-grade intraepithelial lesion) in 83 cases (25.30%) and H-SIL (high-grade intraepithelial lesion) in 134 cases (40.85%).

HPV testing was performed in 242 patients, excluding 86 patients under the age of 30 from the study. HPV genotyping revealed 110 cases (45.45%) with low-risk HPV types (LR-HPV), in which types 61, 6, 81 predominated, along with strains 11, 54, 42, 70. HPV genotyping highlighted 132 cases (54.55%) with high risk HPV types (HR-HPV), in which types 16, 18, 45 were predominant, along with strains 52, 53, 68, 58, 31.

The Reid colposcopic index, calculated on the four parameters (lesion contour, lesion colour, vascularization, iodine impregnation) was 1 – 2 in 94 patients (28.65%), 3 – 4 in 126 patients (38.40 %), 5 – 6 in 72 patients (21.95%) and 7 – 8 in 36 patients (11%).

The histopathological diagnosis was established on the basis of tissue fragments obtained by biopsy or cervical conization. The results of the histopathological examinations of the removed fragments were: 168 cases (51.22%) of CIN 1 including lesions due to HPV infection, 93 cases (28.35%) of CIN 2, 67 cases (20.43%) of CIN 3.

Surgical treatment of cervical intraepithelial neoplasia was established in 236 patients, depending on the conditions, indications and contraindications and consisted of conization, amputation, hysterectomy and triple Manchester operation. The remaining 92 patients received other types of treatment: electrocautery, excision with diathermic loop. Surgical treatment was conservative in 192 patients (81.35%) – conization (93 cases, 39.49%), amputation (85 cases, 36%), in 14 cases (5.95%) triple Manchester operation was performed and radical in 44 patients (18.65%) – total hysterectomy. Depending on the grade of cervical intraepithelial neoplasia obtained by histopathological examination and the type of surgery, it was found that: the 93 patients who underwent conization had the HP result of CIN 1 (56 cases), CIN 2 (34 cases), CIN 3 (3 cases), the 85 patients with amputation were: 36 cases with CIN 2 and 49 cases with CIN 3. Patients with pathology associated with cervical lesions presented CIN 1 (20 cases), CIN 2 (23 cases) and CIN 3 (15 cases).

CHAPTER VII

DISCUSSIONS

The concordance of the diagnostic tripod: cytology – colposcopy – histopathological examination, the positive diagnosis of cervical dysplasia lesion, its grade and therapeutic conduct are drawn.

The cervical lesions generally have a polymorphic appearance. The systematic detection and treatment of precancerous lesions is the most effective means, perfectly demonstrated in the effective prophylaxis of cervical cancer.

HPV genotyping allows the identification of women at the highest risk and the detection of HPV strains becomes a tool for assessing patients' risk.

Colposcopy has a diagnostic interest and specifies the stage of preclinical lesions. Colposcopy allows a directed biopsy of the characteristic areas, in particular the areas closest to the squamous-cylindrical junction, the epicentre and the starting point of the dysplastic lesions. Colposcopy recognizes areas of pathological reshaping or atypical transformation. It assesses their contours and the severity of the lesions [156]. Colposcopy is of therapeutic interest, allowing, at the same time, the treatment of plurifocal lesions, of each of the affected areas, considerably reducing the risk of recurrence.

In a number of cases, colposcopy allows, at the same time, the treatment of the observed lesions. The advantage of the diagnostic condition with a cold knife is to have a complete histopathological analysis of the lesion, the only examination that specifies the existence and degree of dysplasia, to treat at a low cost in simple and fast conditions, without major psychological implications for the patients. These treatments under colposcope are resections adapted to lesions allowing a good quality healing, with a good prognosis in 95-98% of the cases. Conization is also applied when the squamous-cylindrical junction is located totally in the endocervix, existing the risk of its escape at a convenient directed biopsy.

Histopathological biopsy remains the gold standard in making the diagnosis, even if the biopsy is unpleasant for patients and waiting for the result is stressful.

Conization was the most common surgery (39.40%), followed by amputation (36%), taking into account the age of the patients and the desire for motherhood.

In the case of associated genital pathology, total hysterectomy (18.65%) and triple Manchester operation (5.95%) were performed.

Conization with diagnostic and therapeutic role was performed in 77 patients, whose histopathological result was CIN 1, CIN 2 and CIN 3.

In 16 cases, a fractional biopsy of the cervix was performed, prior to conization. We found that there was concordance only in 9 cases, in 4 patients the histopathological diagnosis established at fractional biopsy was overestimated, and in 3 cases the lesions were underestimated.

In patients who underwent amputation of the endovaginal portion of the cervix, the histopathological examination, initially, was established based on the targeted biopsy.

In the 44 cases of total, extra or intracapsular hysterectomy, the initial histopathological examination was established based on the targeted biopsy.

By the same targeted biopsy procedure, the diagnosis was made in the 14 cases in which the triple Manchester operation was performed.

Although epithelial cellular changes were observed in 111 cases (33.84%), their type could not be established with precision and the smear was included in the class of atypical epithelial cells (ASC): 97 cases with atypical squamous cell of undetermined significance

(ASC-US) and 14 cases with atypical squamous cell where a high-grade lesion (ASC-H) cannot be ruled out.

The concordance between the cervical-vaginal cytological examination and the histopathological diagnosis established by examining the conization fragments was partial, being present in 86 patients (77.48%), which confirms the studies in the literature according to which the cytological examination is a test with high sensitivity and specificity in the detection of cervical intraepithelial neoplasia and cervical cancer in infraclinical phases, but with little value in terms of the degree of squamous lesion or invasion.

Regarding amputation, the indication was broader than in the case of conization, meaning a wider excision of the exocervical epithelium to the level of the healthy epithelium, but also of the endocervical epithelium, up close to the internal cervical orifice.

Amputation was performed in 85 patients, 36% of the cases. The histopathological results were: CIN 2 in 36 patients and CIN 3 in 49 patients.

Cold knife conization was practiced in 59 cases and in 34 cases electric scalpel conization. It is preferable to use a cold knife conization, because the healthy edges of the exocervical epithelium are clear, without other abnormal changes and can be examined histopathologically very correctly [162].

Electric scalpel conization, even if it is preferred by some surgeons, because it ensures a very good concomitant haemostasis, for the remaining exocervical epithelium, the histopathological examination is more difficult due to the artefacts consecutive to the electrocautery.

Simple hysterectomy involves the removal of the uterus and cervix, but does not involve excision of the parameters and the paracolpos.

It is a surgical procedure that can be indicated for benign gynaecological pathology, preinvasive cervical neoplasia and stage IA1 of cervical cancer.

Although hysterectomy is an unacceptable procedure for CIN 1, 2, 3 lesions [163], the surgical treatment of patients over 40 years of age who have had uterine polyfibromatosis, endometrial hyperplasia, adenomyosis, and who have completed pregnancy planning, after performing the biopsies and establishing the diagnosis, benefited from a total hysterectomy.

The histopathological result of the operative pieces resulting from hysterectomy showed uterine leiomyofibromatosis, adenomyosis, simple endometrial hyperplasia with or without atypia associated with cervix lesions such as CIN 1 (11 patients), CIN 2 (18 patients), CIN 3/CIS (15 patients). Of the 44 total hysterectomies, in 36 cases total extracapsular hysterectomy was performed (81.82%) and in 8 patients total intracapsular hysterectomy was performed (18.18%).

Postoperatively, as a distant prognosis, many surgeons prefer total intracapsular hysterectomy because it preserves the suspension and support system of the endopelvic floor,

preserved by maintaining the cervical capsule, parametric lateral ligaments, pubocapsular and sacrocapsular ligaments, thus avoiding vaginal prolapse.

In general, electrocautery is practiced in mild cervical dysplasia, in severe cases conization, amputation, total hysterectomy are practiced.

The triple Manchester operation is the type of intervention in which at least 3 concomitant pathologies are resolved: uterine prolapse, urinary incontinence on exertion, the presence of severe exo- and endocervical dysplasia [165].

The intervention was performed in a relatively small number of cases (14 patients, 5.95%), especially when the patients requested the resolution of the three associated diseases at the same time, and preoperative investigations showed that it is possible to perform this type. of interventions.

CHAPTER VIII

CONCLUSIONS

1. Early diagnosis and treatment of dysplasia is a real breakthrough, being the most effective method to prevent cervical cancer.
2. The highest share of patients studied, by age groups, was 31-40 years (47.6%).
3. The differences are significant between the patients from the urban area (64.3%) and the rural area (35.7%), considering the much wider accessibility of the patients from the urban area to the specialized consultation, at the performance of paraclinical investigations such as: cytology, colposcopy and targeted biopsy under colposcope.
4. From the point of view of the obstetric antecedents, we found a higher incidence of cervical dysplasia in multigravidas (81.1%) and multiparous (87.5%).
5. Cytological screening is a test for precancerous lesions and early cervical cancers in asymptomatic women. The cytological examination revealed a predominance of patients with H-SIL (40.85%), followed by ASC-US (29.58%) and L-SIL (25.30%).
6. The HPV testing shows an approximately equal share of high-grade (54.55%) and low-risk (45.45%) HPV strains. The HPV genotyping allows the identification of women at highest risk and the detection of HPV strains becomes a tool for assessing patients' risk.
7. Colposcopic examination allows the identification of suspicious lesions following cervico-vaginal cytology, being able to specify the location, extent and severity, orients the biopsies and is an essential element in the cyto-colpo-histological triad. The category of patients whose colposcopy received a Reid index of 3 – 4 was the most common (38.40%), the lowest category was the one with a Reid index of 7 – 8 (11%).
8. Biopsy with histopathological examination remains the gold standard in establishing the diagnosis. The histopathological examination, performed on the fragments taken by targeted biopsy and conization, reveals on the investigated group the presence of

low-grade cervical intraepithelial neoplasia (CIN 1) in proportion of 51.22% and of high-grade cervical intraepithelial neoplasia (CIN 2 and CIN 3) in proportion of 48.78% (CIN 2 – 28.35%, CIN 3 – 20.43%).

9. The decision on the management of cervical dysplasia took into account the degree of the cervical lesion, the extension of the surface, the age of the patients and the preservation of reproductive, menstrual and sexual functions, as well as the pathology associated with cervical lesions.
10. Conization was the surgical therapy of choice for patients (39.40%) with cervical intraepithelial neoplasia, under 40 years of age, who wanted to preserve fertility and had no other gynaecological lesions.
11. Cold knife conization is a safe method of diagnosis and treatment in cervical intraepithelial neoplasia. Compared to fractional biopsy, conization provides the advantage of a diagnostic certainty by fully excision of the lesion and detailed histopathological examination.
12. Conization is a necessary method especially in discordant cytology, colposcopy, fractional biopsy and in situations that require a long follow-up and additional investigations. It is a method that establishes the histopathological diagnosis of endocervical lesions associated with or concomitant with CIN due to the fact that the excised piece contains both the lesion and the adjacent area.
13. While the use of electric current for surgical excision can cause histological artefacts by partial thermal compromise of the resection edges, cold knife conization is preferable because it provides borderless tissue samples for histopathological examination, successfully applied especially in patients with an increased risk of invasive cancer, CIS, CIN 3, AIS, extensive lesions and a high grade of malignancy.
14. Amputation was performed in 36% of the cases, after performing the fractional targeted biopsy that showed lesions such as CIN 2 and CIN 3.
15. Hysterectomy was the surgical treatment for patients (18.65%) over 40 years of age, with completed pregnancy planning and associated genital pathology (uterine polyfibromatosis, adenomyosis, severe endometrial hyperplasia) of cervical intraepithelial neoplasia.
16. The triple Manchester operation is a conservative surgical procedure, effective in women under 45, multiparous, with genital activity present, with cervical dysplastic lesions and cystocele (5.95%). It solves at the same time, cystocele, cervical dysplasia, hypertrophic elongation of the cervix and grade I, II descent.
17. Although surgical conduct is the most effective way to treat severe dysplastic cervical lesions, an important role in the prophylaxis of dysplastic lesions and cervical cancer is vaccination against HPV, the most effective vaccine today being the one with 9 serotypes (16, 18, 31, 33, 45, 52, 58, 6, 11).