

**“LUCIAN BLAGA” UNIVERSITY OF SIBIU
„VICTOR PAPILIAN” FACULTY OF MEDICINE**

DIN GEORGETA

SURGICAL THERAPEUTIC METHODS IN CERVICAL CANCER

Abstract of the PhD

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PREFACE

The quintessence and the accomplishment of this work would have never been possible without the combined efforts of several personalities to whom I would like to thank hereby.

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ABSTRACT OF THE PHD THESIS

1. INTRODUCTION

On global scale, cervical cancer ranks second after breast cancer in malignant tumors in women, representing 6% of all cancers, and nearly 10% of cancer deaths.

Without diminishing the undeniable progress in terms of etiopathogeny, methods of diagnosis and therapy, methods of preventions and early detection, we believe that stronger actions are needed to reduce the incidence and begin the treatment in the early and curable stages of the disease.

Despite the notable progress regarding the etiology, diagnosis and treatment of cervical cancer, the incidence and epidemiologic factors have not been influenced as expected. On the contrary, a recrudescence of these factors has been noticed, as well as a higher rate of mortality both in our country and worldwide. This is a cancer type that benefits from early detection and prevention methods, as well as from codified therapy, likely to offer healing.

The reality is difficult to justify and accept, as cervical cancer is the only cancer with known etiology, be it viral or sexually transmitted, and 100% curable in its early stages, by means of a complex and multimodal treatment.

One of the major achievements of modern medicine was the elucidation of the pathogenesis of the cervical cancer, namely its occurrence from a prior lesion, the cervical intraepithelial neoplasia. The precursor lesions occur almost exclusively in women that are sexually active. The association between cervical cancer and sexual activity has been known for over 150 years. Cervical cancer and its pathogenesis have improved significantly. Also, the researches through molecular techniques of detecting and analyzing HPV (Human Papillomavirus) have enriched our understanding to the extent of formulating new morphological criteria. The coexistence between the cervical lesion and the HPV is unquestionable. This viruses or their genome are encountered in a large number of precursor and malignant lesions. The coexistence is not mandatory, although 90% of the squamous carcinomas contain HPV genes with oncogenic functions.

It must be mentioned that 80% of the cervical cancer cases occur in women from underdeveloped countries. The screening programs using the Papanicolau test have significantly

reduced the number of invasive cancers, by means of early diagnosis and treatment of pre-cancerous lesions, such as cervical intraepithelial neoplasia. When the pre-cancerous lesions are diagnosed before evolving into cancerous forms and when early therapeutic methods are applied according to each grade, the survival rate can reach almost 100%. Still, in the case of invasive cancer, the prognosis is determined by the moment of the diagnosis of the precancerous lesion.

2. INCIDENCE

After cardiovascular diseases, cancer is the most frequent and lethal form of non-contagious diseases. Despite the fact that the results of the efforts made in the latest period in the treatment of cervical cancer are more and more obvious, the epidemiologic indicators are still high.

According to the US Center for Disease Control, the risk of infection throughout the entire life, for both sexually active men and women is at least 50%. Most of the infections with HPV are cured by the natural immune cellular response of our bodies.

Since initially only the superficial layer of epithelial cells undergoes malignant processes, we speak about an intraepithelial epithelioma. Thus, the cervical cancer knows a pre-invasive stage “in situ”, known as cancer in stage 0. If properly treated, the disease is perfectly curable in this stage and it can evolve to a perfect and permanent healing. A correct diagnosis is crucial in this instance, but although possible, it rarely happens.

Of all cervical cancers, 80-90% is located in the cervix. Cervical cancer represents the first cause of cancer mortality in women. It can be found at all ages, but the highest frequency is at the age of 40-60. The incidence of cervical cancer is also subject to large regional variations.

In Romania, 2.500-3.000 new cases occur annually, with an average of 2.800 new cases. There are recorded 1.400-1.500 deaths and there are more than 15.000 patients known to have cervical cancer. Within the last years, in Romania the incidence ranged between 21,90/100000 (1990) and 24,74/100000 (1996), ranking second in Europe as incidence and first as mortality caused by cervical cancer. In Europe, one woman dies at every 18 minutes because of cervical cancer.

Every year, in Romania over 3.400 women are diagnosed with cervical cancer. According to the European Health For All Database statistics communicated in July 2008, there has been an increase compared to previous years. Romania ranks first in Europe both in the incidence of cervical cancer (29.9 cases out of 100.000 women) as well as in the death rate due to this type of cancer (12 cases out of 100.000 women); this is 2 to 2.7 higher than the majority of Eastern and Central European countries, and 6 times higher than the average in the member states of the European Union.

It can also be noted a regional variation of the incidence of cervical cancer, with higher rates in the counties of Maramureș, Hunedoara, Arad, Constanța, Timiș, Mehedinți, which exceed 30 cases out of 100.000 women, while the lowest rates are recorded in the counties Ilfov, București and Vrancea, with values below 10 out of 100.000 women.

3. ETIOPATHOGENY

Many epidemiological studies conducted in the past two decades have demonstrated the implication of various etiological factors in the occurrence of intraepithelial cervical neoplasia and of cervical cancer. These risk factors have been ordered in terms of causality (among the

factors of direct causality there are HPV infection, which has a major role as it occurs in 90% of the cervical cancers; sexual behavior, biological and environmental factors, socio-economical and psycho-social factors, sexually transmitted diseases, such as chlamydia trachomatis, Herpes simplex virus type 1, co-infection with HIV/HPV), and their possibility of modification.

The HPV infection has also been suggested by Hausen as cause of the anogenital cancer (1976), but recently Syrjänen has searched for the prevalence of HPV in the invasive cervical cancers and reached to the conclusion that about 70% of them contained HPV DNA, especially types HPV-16, HPV-18, HPV-33. These HPV types have been encountered in the intraepithelial cervical lesions (CIN II-III), demonstrating their major oncogenic potential (Syrjänen *et al.*, 2000).

Latest discoveries in the field of immunology, medical genetics and molecular biology have allowed the validation of the major role held by HPV infection in the etiopathogeny of intraepithelial cervical lesions (CIN) and cervical neoplasia (CN). The local immune antitumor cellular response implies the intervention of the immunocompetent mononuclear cells which gather in the peritumoral tissue. These cells create what we know as tumor infiltrating lymphocytes (Tumor infiltrating Lymphocytes, TIL). Detailed information about TIL in the cervical cancer is crucial, as the initiation and the evolution of the disease are strictly related to the status of the immune cellular system. The mechanism through which the cells infected with HPV escape or survive the immune response evolving into invasive cervical carcinoma is represented by the implication of the cytokines and their local production or by the type and amplitude of the immune response.

The presence and persistence alone of the HPV infection are not enough for the development of cervical neoplasia. The etiologic co-factors (genetic, non-genetic) such as the mediated immune cellular response to the viral infection are determinant. The persisting HPV infection is a necessary condition, but not sufficient for the development of cervical cancer. There are **actual etiological factors** and **risk etiological factors** which contribute to the occurrence of cervical cancer.

3.1. Actual etiological factors

If etiology remains unknown or uncertain for most cancer types, cervical cancer is credited in an impressive percentage of 95% with a viral etiology. The incriminated factor is HPV (Human Papilloma Virus).

Among the HPV types, the following are to be remembered:

- The HPV types which may cause **low grade squamous intraepithelial lesions (LGSIL)** are 6, 11, 26, 40, 42, 53, 54, 55, 57 and 66.

- **The HPV types with medium risk** - 33, 35, 39, 51, 56, 58, 59, 68, 73, 82, 83 – they may cause low or high grade squamous intraepithelial lesions.

- **High risk HPV types** - 16, 18, 31, 45 – they cause squamous intraepithelial lesions with high oncogenic risk. They are identified in most cervical cancer types, as well as in many other types of cancer of the lower genital tract.

Identifying the various subtypes of HPV with a diverse oncogenic potential was an important step in establishing the exact relationship between HPV and cancer. Currently, over 200 types of HPV are known, out of which around 40 affect the genital tract. Early hybridization studies proved that mild dysplasia may be associated with any type of HPV, yet the most frequent are 6 and 11. Moderate and severe dysplasias and cervical cancers are mostly associated with types 16 and 18, which suggest that these specific types have a highest oncogenic potential.

Other types such as 31, 33 and 35 have been detected all over the precursor lesions, but they have also been associated with cervical cancers. There emerged the concept of low-risk, medium risk and high risk types in terms of oncogenic potential. The lesions L-SIL are associated with any type of HPV and they are generally self-limited benign processes which produce transmissible viral particles. Their DNA is normal (diploid) and the virus thrives separated from the host DNA (episomal). In contrast, high grade lesions H-SIL are characterized by nuclear atypias, an aspect that correlates with their aneuploid character. The lesions are frequently associated with oncogenic types of HPV and have a potential of becoming malign; thus, they are precursors of cervical cancer. In this case, the viral DNA is integrated into the DNA of the host cell.

3.2. Risk etiological factors

The genetic modifications can occur long before the histological ones, which at least in theory may allow the early diagnosis based on a set chromosomal pattern. Lately, some “types of population” with high risk of disease have been successfully identified.

As part of the uterus, the cervix undergoes repeated hormonal changes, over a long period of time, from puberty to menopause. At the same time, active genital life is dominated by multiple interventions of mechanical, physical, chemical and bacteriological nature, which cannot be disregarded and which are likely to become significant risk factors. Thus, the disease can occur in adolescence and continue to be met around the age of 65. In the same category fall the oral hormonal birth control methods which lead to endocrine disorders in women.

Poor sexual hygiene, increased number of sexual partners, smoking, and multiple births are all major contributing factors.

Numerous studies have highlighted the fact that vitamin C, beta-carotene, retinol and folic acid have a favorable effect by increasing general and specific resistance to cervical cancer.

It was noted and proved a much higher frequency of cervical intraepithelial neoplasia in women who underwent an immunosuppressive treatment and in women with a deficient immune system.

Smoking is a long-known risk factor for cervical cancer. The risk of cancer is twice higher in smokers than in non-smokers. The risk is related to the duration and intensity of smoking. In the cervical mucus of smokers there were revealed nicotine, cotinine and other mutagenic substances which the cervical tissue from the bloodstream.

As a risk factor, immunosuppression is sustained by the higher incidence of the HPV and CIN infections in women with renal or liver transplantation, in dialyzed patients, in HIV-positive women or in patients with lupus erythematosus. The therapeutic immunosuppression induces changes in the profile of the circulating antibodies. It is generally known that HPV infection is dependent of the interaction between the virus, the infected host cells and the host’s immune system. Therefore, patients subject to immunosuppression undergo periodic exams meant to detect precursor lesions (CIN), such as a semester smear cytotumoral and an annual colposcopic exam.

3.3. Epidemiological parameters in cervical cancer

a. Intrinsic factors:

✓ **Age:** most cases range in 35-65 of age (70%); almost 30% range under 35 years, and the incidents tends to shift towards younger ages.

✓ **Endocrine status:** the role of estrogens and progesterone in pathogenesis is yet to be established. According to some authors, they have a favorable role, whereas others consider they have a protective role. The diethylstilbestrol administered to pregnant women may generate cervical cancer to feminine products of conception. Hormone birth control pills are considered on one hand protective and favorable by others. It has been noticed that the development of cancer from non-invasive to invasive forms coincides with the period of “hormonal storm” preceding the menopause. This might as well confirm the role of some endogen hormonal influences.

✓ **Family and genetic factors:** Researches of genetics have confirmed the presence of chromosomal modifications in some dysplasias and in the intraepithelial carcinoma, proving the concept of malignity at a chromosomal level. These studies open the way to an early diagnosis from the histologic stage to the genetic one. The percentage in which specific chromosomes are present as markers in the dysplastic epithelia is overlapping with the one in which the dysplasias evolve towards intraepithelial carcinoma, and hence towards invasive carcinoma.

✓ **Alimentation:** women who consume reduced quantities of fruit and vegetables may have an increased risk. Also, overweight persons have a tendency to develop cervical adenocarcinoma.

✓ **Oral birth control pills:** long-term utilization of oral birth contraceptives increases the risk of illness proportional to the duration of administration. The risk decreases when consumption stops, thus in women using pills for over 5 years, the risk is doubled and it returns to normal after 10 years since the end of treatment.

✓ **Multiple births:** the multiparous with three or more term pregnancies have an increased risk of developing cervical carcinoma, but the mechanism of this process is yet to be elucidated. There are several theories concerning the repeated exposure to HPV, the hormonal changes that occur during pregnancies or the fragility of the immune system of the pregnant women.

✓ **First pregnancy at an early age:** women who had a term pregnancy before the age of 17 have a double risk to develop cervical cancer during their life compared to women who give birth after the age of 25.

✓ **The economic and social status:** poverty represents a risk factor due to limited access to screening and treatment.

b. Extrinsic factors:

✓ **Environmental factors:** the latest studies have confirmed there is little difference between urban (higher incidence) and rural environment in terms of exposure to environmental pollutants, higher natural radioactivity.

✓ **The role of sexuality in cervical carcinogenesis:** cervical neoplasia occurs only in sexually active women, fact which generated the idea of a carcinogen agent transmitted through sexual contact. Most modern authors incriminate a certain virus, namely the genital herpetic virus type II. Along other viruses, other possible oncogenic agents were analyzed, such as: bacterial infections and parasitic infections with mycoplasma, but it is generally considered that they represent an indicator of “sexual pollution” rather than a direct correlation to cervical neoplasia. Sexual intercourse is the main pivot in cervical carcinogenesis. Numerous parameters refer to this specific factor: early onset of sexual life, frequency of coitus, multiple sex partners, pollution and sexual promiscuity, contraceptives with various substances, as well as the number of births and abortions. The main risk parameter seems to be the early onset of sexual activity.

4. SYMPTOMATOLOGY

Cervical cancer is known as the “silent disease” because its the early stages can be completely asymptomatic. The symptoms usually occur only after the precancerous modifications become cancerous and invade the neighboring tissues.

The symptoms of the cervical cancer are quite poor, at least in the early stages, only to become characteristic, suggestive and irritating in the advanced stages.

The alarm signal that should alert every woman is bleeding. It is significantly reduced, at least in the beginning; it is fluctuating and variable, and mostly triggered by the sexual intercourse.

In parallel, the symptoms are competed with *leucorrhea*, whitish at first, and then pinkish and fetid at the end; *vaginal discharge* becomes more abundant and smelly, with blood clots; *the pain* occurs at the level of the vaginal pouches or at pelvic level with a low intensity at first, and then more penetrating. This trilogy signals the appearance of the associated inflammatory phenomena, with an extensive character.

In the invasive carcinoma, the symptomatology includes: constant, spontaneous or tactile *methrorragia*, sometimes abundant, *leucorrhea* with specific fetid smell with purulent discharge, often hemorrhagic (gravy aspect), and *pain*, which appears late in the advanced forms.

The symptomatology is progressively completed with general signs of neoplastic infection: anemia, loss of appetite, mental instability, characteristic facies with paleness, oscillating fever (in over infected forms), and other suggestive elements of tumor invasion.

As for the local modifications that occur in cervical cancer, the examination with valves shows obvious changes at macroscopic level, as follows:

- In the pre-invasive cervical cancer – usually the cervix has a normal aspect, but sometimes it takes the form of erosion;
- In the invasive cervical cancer – at the level of the cervix there occurs a slight growing at first around the external orifice of the cervix, of red color, well defined and friable, that bleeds easily on touch. This growing appears on the basis of “erosion” that has gained a new character: exophytic or eroded aspect, friability, or a rough consistency with an increased tendency to bleeding.

In a more advanced stage, the tumor grows and may take one of the anatomic-clinical forms:

- ✓ *The vegetant formation*: has the aspect of a cauliflower, it is friable and it easily bleeds on touch;
- ✓ *The ulcero-vegetant formation*: it has the form of a deep ulceration;
- ✓ *The infiltrative formation*: the affected area appears harsh and pale pink; it occurs in the endocervical area, and the cervix has the aspect of a “barrel”.

5. DIAGNOSIS

As far as the diagnosis is concerned, it implies a well-established procedure that must be followed in order to obtain the expected results: anamnesis; palpation of breast and axillary and supraclavicular region; examination of vulva and, if indicated, a biopsy; examination of vagina and cervix through colposcopy, cytology and biopsy; vaginal and rectal examination; examination of the lower limbs by comparatively noticing any signs of swelling; palpation of the abdomen and iliac fossa; tumor markers (SSC – squamous, CA-25-adenocarcinoma); renal

ultrasound; CT-scan; MRI scan; bone scintigraphy, laparoscopy, cystoscopy, rectoscopy, biopsy (the final term of examination which actually offers the certainty of the diagnosis).

For the more advanced stages of cervical cancer, the diagnosis implies the use of other diagnostic methods, apart from the already mentioned ones, namely the radiologic, imagistic and biologic ones, that will establish the evolutionary stage of neoplasia.

The anamnesis may provide the physician with clues regarding the possibilities of a certain patient to develop a cervical neoplasia at a certain point. Thus, three categories can be distinguished: low risk (women with no sexual activity or older than 60 years, and women who use barrier methods of birth control); medium risk (women with normal sexual activities, with multiple births or abortions); high risk (women with poor sexual hygiene, with multiple sex partners and early onset of sexual activity).

5.1. Clinical diagnosis

The clinical diagnosis involves the examination and palpation of pelvic organs, the valve examination, vagina examination and digital rectal examination included.

There are pre-clinical forms of cervical cancer, such as the cancer in situ, along with other types of cervical intraepithelial neoplasia (CIN_I – CIN_{III})

For the clinically manifested forms with specific symptomatology, the positive diagnosis is relatively easy to establish, while the challenge remains to determine the stage.

The valve examination – highlights an exocervical tumor growth, vegetant, friable, with irregular shape, and hemorrhagic.

- *In the exocervical ulcerous form*, the valve examination reveals a tiny loss of substance exterior to the external orifice of the cervix, with a budding pouch and covered with clots and necrotic accumulations.

- *In the endocervical form*, the valve examination does not show any useful information. However, on the hysteroscopy exam there can be noticed the irregularity of the endocervical cavity. The examination is followed by hemorrhage.

- *The vaginal examination* – a proliferative formation can be felt on palpation, and its consistency, friability and hemorrhagic character can be established. This technique allows the evaluation of the neoplastic infiltration of the vagina pouches, the juxta-cervical area of parameters and vagina walls.

- *Combined vaginal and rectal digital examination* – approaches the parameters and determines the degree of tumor infiltration, in which case in the place of a vacant spot between the cervix and the pelvic wall there will be detected an induration which may extend up to the wall.

5.2. The paraclinic diagnosis

The first evidence that made the connection between HPV and cervical cancer was the acknowledgment of specific cellular modifications due to a cytopathic viral effect. The introduction in practice of the exfoliative cervical cytology on a large scale by Papanicolaou and Traut allowed the study of microscopic cellular modifications. Koss and Durfee coined the term koilocytic atypia (from the Greek *koilos*=hole), in order to identify a frequent aspect of the cyto-tumor examination, until then known as dysplasia. Subsequently, it has been demonstrated that this particular aspect of the koilocytes was rendered by the cytopathic effect of HPV.

❖ **HPV test** – in the subclinical form, the HPV infection has the colposcopic aspect of the area with atypical transformation; the lesions are visible after the application of acetic acid and they are present outside the transformation area; they have a bright white aspect, with jagged edges, with a horizontal arranging of vessels (spider-web appearance) and they are iodine positive.

From a cytological point of view, the subclinical infection with HPV falls into the category of HGSIL (CIN_I). The specific pathological sign is the presence of koilocytes (squamous cells with irregular hyperchromatic nuclei, surrounded by a cytoplasmic halo); in the absence of koilocyte, the differentiation from CIN is made by the binuclear aspect of the cells, with a keratinization of the cytoplasm and the presence of mitotic figures.

HPV testing and viral typing was proposed as screening method and it was justified by

- Cyto-colposcopic diagnosis difficulties when viral lesions and CIN coexist;
- Cytologic categories considered to be suboptimal, LGSIL and ASCUS, have been shown to omit lesions with high grade of anomalies up to 20% of the cases;
- Cases with negative cytology but tested positive with HPV, with high oncogenic risk, have developed a form of CIN within the next two years;
- Patients with LGSIL și ASCUS (CIN_I) have evolved towards CIN_{III} in 9% of the cases; all these patients were tested positive for high risk HPV.

❖ ***Vaginal cytology***

Vaginal cytology has reached a high degree of accuracy in detecting cervical cancer. It is a valuable method of screening due to the following qualities:

- It is a simple unpainful examination technique, easy to perform and accepted by the examined woman due to its non-invasive character.
- It allows early detection of the disease (microinvasive carcinoma), and of the premalignant lesions; their detection and treatment permit a primary prophylaxis of the illness, especially in association with colposcopic methods;
- It has a significant grade of accuracy (sensitivity and specificity) up to 90-95%;
- It has an unlimited theoretical applicability and can include the entire female population at risk, which gives substantial value and recommendation as mass screening method;
- It is worth, since it addresses a type of disease with high morbidity and mortality rate;
- It may be repeated over a long period in a woman's life;
- It is one of the most inexpensive means of lab investigation, and it does not require special equipment.

Initially, the **Babeş - Papanicolau cytologic** revealed 5 categories of smears: C_I– normal cells with no atypias; C_{II}– cells with some atypias but with no suspicion of malignity; C_{III} – cells with atypias and suspicion of malignity which cannot be confirmed; C_{IV}– isolated cells with atypias and certain malignity, C_V– malignant cells in placards. Lately, the cytologic result tends to anticipate the histopathological diagnosis, by revealing various grades of CIN.

❖ ***Colposcopy***

Colposcopy allows the identification of certain pathology at the limit of the clinical perception (viral lesions, cervical dysplasia, microinvasive carcinoma) based on tissue and histochemical particularities which condition the colposcopic images. Also, it assesses the gravity of the lesions, allows the directed biopsy, and establishes the modality of therapy of the cervical lesions according to the type, topography and extent of the lesion, as well as the

patient's age and desire of maternity. The compliance between the colposcopic images, the cytologic reflection and the histopathological result represents the refined method of diagnosing the cervical and vaginal lesions.

The Lham – Schiller Test – is performed before colposcopy and it is based on the tinctorial affinity of the glycogen in normal the epithelial cells as compared to iodine. The lack of glycogen loading of the abnormal (and neoplastic) epithelium creates an incomplete colorless area (iodine negative), in contrast with the healthy brown colored epithelium. In the absence of colposcopy, this test may be used to justify biopsy.

The colposcopic images are conditioned in terms of aspect and intensity by a series of morphologic elements, among which the most important are: the thickness and the transparency of the coating epithelium, epithelium-stroma ratio, vascular particularities, allowing the evaluation of the gravity of lesions. Among the criteria of gravity assessment, one can mention: heavy congestion of subiacent stroma, abnormalities in the vessels' aspect and distribution, the polymorphic and/or associated character of the colposcopic images, the possibility of operating directed biopsies in the suspected areas.

❖ **Biopsy**

Biopsy is the most important method fused to diagnose the premalignant lesions of CIN and cervical carcinomas, and no therapeutic plan can be conceived in its absence. In dysplasia and micro invasive carcinoma, the biopsies facilitate the minute study of nuclei morphology and the ratio lesion-conjunctival tissue. The following conditions must be met: the fragment must contain enough conjunctival tissue; a nuclear fixation fluid must be used (Bouin's fluid fixation); the fragments must be well orientated in the paraffin block during the histologic procedure; an anti-inflammatory treatment must be followed in case of suspicion and the biopsy must be repeated.

The histopathological examination of samples can be done extemporaneous, by means of cryostat technique or by classical technique of paraffin embedding. After staining the sections with the usual staining techniques, a histopathological examination follows, along with interpretation and diagnosis. The histological exam will establish the final diagnosis.

In the clinical manifestation forms, cytology and colposcopy become useless, as the tumor is obvious. However, biopsy is mandatory in the differential diagnosis (syphilis, tuberculosis) and in order to assess the type of histologic lesion. *Cystoscopy and rectoscopy* are indicated in the case of a clinical suspicion of local-regional invasion. *Urography* is compulsory in the assessment of a possible compression of excretory pathways. *Tomography* and MRI are not particularly important. *Lymphography* is meant to highlight lymph nodes metastases and it has a high rate of false-negative results. Retroperitoneal pelviscopy allows the surgical evaluation of the interiliac lymph nodes.

❖ **Conization**

It may have double purpose, both as diagnosis and therapeutic. It is performed when there is an non-lesion cervix form clinical or colposcopic point of view and when there is a suspect etiology (C_{III}) or positive (C_{IV} - C_V), or when there is a suspect cervix in terms of clinical, and / or colposcopic and histologic, with a histopathology result of severe dysplasia (CIN_{III}).

5.3. Tumor extent assessment

Paraclinic diagnosis of lesion extension implies supplementary investigation methods meant to establish the extent of the neoplastic process. The evaluation of this invasion is done by means of imagistic examination:

Lymphography. Cervical neoplasia leads to metastasis especially on lymphatic ways. To highlight the lymphatic extension, a Lymphography is made by injecting lipiodol ultra fluid into a distal lymphatic vessel, which opacifies the lymphatic nodes. Lymph nodes hypertrophy with alteration of internal structure means neoplastic invasion.

Opaqueness remains present for a period of 8 months to 1 year, which allows the directed postsurgical radiotherapy, as well as the observation of nodes evolution under chemotherapy and radiotherapy.

Modern trend of limiting the radicalism of interventions in oncological surgery also applies in the case of cervical cancer. Lymphatic mapping and the biopsy of sentinel node represent one of the most revolutionary oncologic surgical techniques in the recent years.

Cystoscopy can show early changes of the bladder wall infections up to already constituted metastases.

Intravenous urography allows the assessment of the urinary tract injury, and the study of renal functionality. There can be revealed marks of the bladder walls, deviations, compressions or urethral stenosis, stasis, hydronephrosis, nonfunctional kidney that can cast a shadow over the prognosis.

Rectoscopy makes possible the early detection of the invasion on the rectal anterior wall in the tumor process.

Irigography and irigoscopy verifies the integrity of the rectum and the nearby upper portions from the large intestine, establishing its injury degree caused by the neoplastic process.

Venography allows the study of pelvic and extrapelvic venous network, providing indirect data on the status of nodal masses that are invisible lymphographic.

Computerized Tomography (CT) with i.v. contrast agents reveal the changes of the urinary tract (it may replace urography) and the pelvic nodes (with a specificity of 97% and sensibility of 25%), and the lombo-aortic lymph nodes (sensibility 75% and specificity 91%).

Thorax CT is indicated when lung metastases are present. Surgical assessment of pelvic and lombo-aortic lymph nodes invasion is optional, and the use of PET is still under study.

CT, abdominal or intravaginal echography and lymphography are not routine methods of investigation in the pre-therapeutic assessment of the invasive cervical cancer, but can be used optionally.

MRI (magnetic resonance imaging) is the most accurate method of examination of female pelvis, superior to CT in the evaluation of tumor extension, and capable to assess the lymph nodes insertion. Nuclear magnetic resonance provides exact data on the extension of

cancer and permits a perfect anatomic demarcation, which can be confirmed by contrast agents in MRI.

In many situations, the MRI provides information which cannot be visualized by radiography, ultrasonography or computerized tomography.

The specific MRI aspect of the uterus allows immediate identification of abnormalities. Also, it permits a precise detection of neoplasia. Thus, the pelvic MRI is frequently recommended when the results from the CT scan or echography are uncertain, and also in order to establish T radiologic staging.

Cervical cancer has an intermediate signal in T₂ (hypo-normal as compared to normal cervical mucous and hyper normal as compared to internal fibro-muscular stroma). The evaluation of cervical stroma irrigation is crucial for a correct diagnosis. The hypo signal makes the difference between the I_B stage from the II_B stage.

The search for the tumor extension in the vagina (best evaluated on axial and sagittal sections) is made in the T₂ and T₁ sequences, post contrast (makes a difference between the II_A and II_B). The next step is the inspection of the parameters to detect extra cervical extension of the tumor, T₁ sequences with no fat saturation free and T₂ and T₁ post contrast fat saturated. They are extremely sensitive in the parameter extension – stage III_B of disease.

The aimed sequences are those with undefined delimitation which infiltrate the hyper intense fat of parameters, respectively infiltrative hyper signal of parameter fat. The MRI assesses the status of urethras in axial and/or sagittal sections T₂ sequences for abnormal dilatations consecutive to neoplastic invasion – stage III_B.

In axial and sagittal sections T₂ and T₁ with contrast, it is considered the occupation and invasion of tissue plans that separate the cervix from the bladder or rectum – stage IV_A.

The inspection of pelvic sidewalls is done not only to specify the direct tumor extension, but also to determine the adenopathy. The invasion of parameters and the affecting of the stroma are also essential. The accuracy of the MRI stadialization ranges between 76 to 92%.

6. EVOLUTION AND PROPAGATION

The evolution of cervical cancer is progressive as it invades the neighboring tissues or organs, or it develops distant metastases.

The tumor extension at the cervix level can occur through the lymphatic or nervous vessels in the parameters structure.

The early stages of cervical cancer are generally defined as stages I - II_A, when the parametrial extension is not noticeable from a clinical point of view. Tumor parametrial invasion is always related to metastases in pelvic lymph nodes, as opposed to lymph nodes metastases which may occur in the absence of parametrial invasion. Parametrial invasion clinically evaluated does not correspond to the histologic stage. Thus, in stage I, the parametrial invasion is present in 18% of the cases, and in stage II it occurs in 34% of the cases. The tumor parametrial invasion may be discontinuous by the presence of isolated islands of tumor cells in an apparently unaffected parameter, which explains the appearance of recurrences in stage I.

In stages I_{B1}, the risk of parametrial invasion is reduced when the tumors are smaller than 2 cm, regardless of the histological type and grade of differentiation.

Pelvic lymphatic and para aortic metastasis can occur in 0-31%, respectively 0-21% in precocious forms of cervical cancer.

In 30% of the cases, pelvic lymph nodes can be affected even though there is no parametrial invasion, and the survival rate is of 71%, as opposed to simultaneous parametrial and lymphatic infection, in which case the survival rate decreases to 41%.

There are 3 ways of lymphatic propagation: the anterior lymphatic canal (it reaches the para cervical, obturator and iliac external lymph nodes), the posterior lymphatic canal (it ends in the hypogastric lymph nodes) and the sacral lymphatic canal (it ends in the sacral and promontory lymph nodes).

Lymph node groups can be divided into:

- *First lymph node station* – includes: urethral or para cervical lymph nodes, obturators, external and internal iliac (hypogastric lymph nodes) and sacral lymph nodes.

- *The second lymph station* – includes: aortic and inguinal common lymph nodes.

The introduction of the Sentinel Lymph Node concept (SLN) in incipient cervical cancer marked an important step in modern oncologic surgery. The concept of SLN is based on the hypothesis according to which the lymphatic basin drainage from the cervix is tiered; also the first affected lymph node acts as a filter in the way of tumor dispersal.

It is extremely rare that lymphatic metastasis should occur without affecting this particular lymph node. Levenback has shown that in cervical cancer, when the SLN is not invaded, there is a 95% chance that the other pelvic lymph nodes remain unaffected. The most frequent locations of SLN were identified in the external iliac group (43%), obturator (26%), parametrial (21%), and the rest of the groups (10%).

The lymph node groups which are often involved in the propagation process are the following: obturator lymph nodes, external iliac lymph nodes, hypogastric lymph nodes, those at the iliac artery bifurcation and the sacral lymph nodes.

In the cervical cancer the infiltrating process is limited to the pelvic area. Hepatic, lung or bone metastases are rare. In the evolution of the parametrial infiltrating process, it may extend to the pelvic walls, infecting the bladder and the rect.

The ureters are observed, but the tumor process leads to their stenosis by compression, causing hydronephrosis, urinary tract infections, and uremia (main cause of death in 60% of the cases). Another part of the patients die from vaginal bleeding.

7. PROGNOSIS

In determining the prognosis of the disease, a number of elements are taken into account, such as: age, location, histological nature, degree of cell differentiation, association with other pathological or physiological states, and last but not least stage classification.

The clinical stage represents the most important element of prognosis. In stage I the 5-year survival rate is around 90-92%; in stage II it is situated around 75-80%; in stage III the survival rate is around 40%, whereas in stage V it is exclusively exceptional. Other variables that influence the prognosis are: tumor size (the smaller the tumor, the better the prognosis); *parameters infiltration* (prognosis is better when parameter infiltration is reduced or absent), *lymph nodes* provide significant detail on prognosis (in stage I with no histologically confirmed adenopathy, the 5-year survival rate is of 92.8%; in cases with adenopathy the prognosis

percentage situates around 60%; in stage II the discrepancy is even deeper: 81.4%, respectively 14.3%); *degree of cellular differentiation* (spinocellular cancers with epithelial pearls have a better prognosis rather than the undifferentiated ones), *the age of the patients* (within the same study the prognosis is better if the disease occurs at an advanced age).

It can be said that the prognosis of cervical cancer is related to the biology of the disease in itself, as a resultant of the histological type, evolutionary rate, degree of aggressiveness, and the degree of extension.

8.PROFILAXY

In the current life and working conditions, cancer risk is continuously growing worldwide, due to developing factors and conditions which have a direct oncogenic influence, and favor or accelerate the emergence and the evolution of the epidemiologic process of the disease.

In this context, the organization of prevention methods has certain particularities and is often difficult to accomplish due to the various nature of risk factors, disease location, and the insidious and unspecific onset. Therefore, prevention and struggle against this disease at population level implies a complex of measures listed in the global actions of epidemiologic and clinical surveillance, as well as various lab screenings (cytological, immunological, serological, and radiological). All these actions are part of a national program of fighting against cancer.

Primary prevention continues to be the main economical and medical goal, yet hard to achieve and evaluate; the epidemiologic studies only are able to accomplish progresses in detecting and neutralizing the aggression working and environmental factors, and in detecting the population groups with high risk, endogen predilection or hereditary predetermination.

Cancer prevention is not limited to primary prevention, meaning to prevent the apparition of cancerous lesions by their removal or by limiting the action of the risk factors. The action has a much broader sense, including the simultaneous actions of disease detection in its early stages, in preclinical stages, in latent phase or just with a potential of malignization. This is the secondary prevention stage, which has known a relative development and has won the appreciation of oncologists, but it is likely to diminish the major importance of primary prevention with a tremendous medical, social and financial efficiency. Early detection of recurrences and metastases, when healing of life extension are still possible, represent the object of the tertiary prevention, still dominant in cancerous disease. This stage of prevention focuses on avoiding invalidity and social dependency of the patients. In order to be efficient, as compared to the other two forms, the tertiary prevention has a limited social and economic value, yet with important humanitarian implications and early diagnosis. Within national prevention programs, general actions are included, such as: revealing and neutralizing the risk factors; detection of premalignant stages; post-therapeutic hospitalization in order to prevent the apparition of recurrences and metastases. At the same time, anti-cancerous programs include particular methods and means of neutralization at population level of certain risk factors with known or possible malignant potential. National programs of fighting against cancer include many provisions referring to secondary prevention of malignant neoplasias. The organizing of screenings in order to detect and care for premalignant forms represents a significant process in the prevention and fight against cancer. The entire medical network is required to involve in this highly complex and important action, including the family physicians who have the possibility to discover the existence of these lesions by active population surveillance and whose contribution to the general action of cancer prevention must be increased.

Early detection of cancer is a major aspect of primary prevention, which is able to improve the prognosis and lead to prolonged survival.

Recent epidemiologic and ecologic studies have shown a pronounced disturbance of ecological balance which generated new and various causes in the occurrence of the disease. Based on the data provided by different combined epidemiologic international researches, there was revealed the complexity of the epidemiologic process and hence the appropriate disease prevention measures.

Cervical cancer prevention:

- Cervical cancer has a known cause;
- It can be prevented by screening and observation of each individual case;
- When detected in early stages, it can be cured.

The goals of chemo-prevention are inhibiting carcinogenesis, initiation and promotion of the malign process. The effectiveness of this action can be justified by data of the basic sciences, by the conclusions of the epidemiologic studies and by the clinical trials. Understanding the cellular factors incriminated in the forming and progress of neoplasia (cell proliferation and cellular differentiation control, the mechanisms of apoptosis, the mechanisms of tumor dissemination) and acting against these targets on molecular level are at a research level. **The major prophylaxis method is the administration of a recombinant quadrivalent vaccine against the Human Papilloma Virus types 6, 11, 16, 18.**

Vaccination of teenage girls against HPV types 16 and 18, along with a 3-year cytological screening for cervical cancer could actually reduce the incidence of cervical cancer with 94%, as compared with no action at all. (Goldie et al, 2004). Thus, there will be a significant decrease of abnormalities detected in screening tests, which otherwise would need medical surveillance over time. The effectiveness of screening increases in parallel with the frequency of testing. The aggressive forms and the premalignant lesions are more likely to be discovered when the testing interval is shorter. Yet, the additional benefits of every supplementary testing decrease progressively with the increase of frequency.

9.TREATAMENT

The treatment of cervical cancer is complex and it involves multiple therapeutic methods which have to succeed and combine with one another: irradiation, surgery, chemotherapy, adjuvant treatment. The timing of application for each method is dependent on the detailed analysis of each case, on the patient's local and general status. We are talking about a true therapeutic strategy. There is a common decision made by a complex team composed of gynecologist, oncologist, pathologist, radiotherapist, and chemotherapist.

Prior to determining a therapeutic strategy, it is required a general assessment that includes a complete gynecological examination (with clinic stadialization); a clinic general examination, pulmonary radiography, EKG, blood count with platelets, liver and urinary samples, VSH, glucose, echography, pregnancy test for young patients, and in advanced stages iv urography, cystoscopy, rectoscopy and lymphography.

The treatment aims primarily at the vital prognosis, sacrificing functionality in favor of oncologic radicalism, meaning the extension of surgical exeresis beyond the seeming boundaries of the tumor, with the massive removal of all propagation ways and lymphatic satellite stations.

The treatment of cervical cancer is a complex, individualized and stadialized. The following are used as therapeutic methods: surgery, radiotherapy, chemotherapy and immunotherapy. The only ones that have a radicalism intention are surgery and radiotherapy.

9.1 Principles of treatment

Surgical treatment is the main sequence of the therapeutic plan, and the results of the oncologic surgery of cervical cancer are directly and essentially dependent on the precocity of the applied treatment. One can refer to an actual healing if the treatment is applied in the early stages, namely stage zero or in situ.

Radicalism is the main goal of surgery but not always can it be achieved. In these conditions, even palliative interventions are made, depending on the conditions and complications that occurred during the evolution of the disease.

As a consequence, the surgical interventions in cervical cancer must be adapted to the stage of the disease. The surgical techniques can be divided into limited techniques (conization and excision, each with individual variables) and extended techniques (total hysterectomy or lympho-adeno-colpo-hysterectomy).

One of the most important principles regarding the therapeutic option in any form of cancer is the efficiency. On the secondary plan in the order of importance lies morbidity and mortality rate. In this respect, as assessed for stages II_A și I_B, the results of primary surgery and radiotherapy are similar.

The surgical treatment holds some advantages to radiotherapy:

1. The information provided by surgical and histopathological exploration is important to the prognosis and for the identification of cases with high risk of disease persistency. In these situations (around 20%), special diagnosis procedures are needed in order to select the proper adjuvant therapies.

2. The cases with high risk of recurrence must be differently hospitalized regarding the means and rhythm.

3. Surgical treatment provides exact information regarding the extension of cervical cancer, as well as other incidental lesion types, with no direct relation with the aim of the surgery.

4. In pre-menopause the normal function of the ovaries can be preserved. Maintained by means of preservation of one or both ovaries, the gonadal function can manifest up to regular age of menopause, even if radical hysterectomy has been applied. The ovary and the fallopian tube can be preserved in order to avoid vascular deficiencies, as they are unlikely to be invaded by metastases in stages I or II.

5. Interventions dictated by pathologic conditions developed at the level of annexes are rare. Yet, the final decision of ovaries preservation must be carefully analyzed. In post-menopausal cases annexectomy is, of course, compulsory. In pre-menopause, the conservation of ovaries offers benefits in protection against osteoporosis, cardiopathies, trophic tissue damage, and psychological stress.

6. Functional and anatomic changes induced by radiotherapy at the level of vaginal tract and their consequences on sexual life are not present after primary surgical treatment. Even if it is shortened, the vagina is still supple and functional.

7. After the primary surgical treatment, recurrences rate is low. This also applies to complications.

8. From the point of view of psychological benefit, it has been noticed that many patients would rather have their tumor removed and they are encouraged by the surgeon's position regarding the success of the intervention and the absence of the disease.

9. Correct indications and the completion of the technique in normal conditions assure a reduced morbidity of surgical therapy. This advantage becomes a fact when the operation is performed by experienced surgeons.

Tumor volume and parametrial state represent the main contradiction of surgical treatment, when they do not fall into stages I_B / II_A. In the absence of medical pathology, older women (over 70 years of age) can be operated if they are provided with competent ITA assistance and internal medicine, equipment and proper surgery technique.

Generally, oncologic pathology should be regarded as a systemic pathology with multiple progressive possibilities, with evolution and therapeutic results that differ depending on stadiality and applied type of therapy.

The complex radio-chemo-surgical therapy offers the best therapeutic and prognostic results, except the pre-invasive cancer (stage 0 or in situ), when surgical treatment alone is sufficient. For stages I and II there always must be applied a complex radio-chemo-surgical therapy. For stage 0, the surgical treatment consists in conization or cervix amputation in young patients who are willing to preserve reproductive function and total hysterectomy with or without annex preservation for patients for whom reproductive function is not necessary or patients over 40 years with associate pathology.

For stages I and II the therapeutic algorithm includes pre-surgery radiotherapy followed by surgery after 4-6 weeks. Surgical intervention must always be radical, involving radical hysterectomy with pelvic lymphadenectomy, resulting in tumor removal (uterus, parametrials, annexes, one third of the superior part of vagina) and the regional lymphatic territory (extern iliac lymph nodes, intern and obturator lymph nodes).

The individualization of treatment in cervical cancer is one of the basic principles in modern oncology. In case the reproductive functions are meant to be preserved, then pre-surgery radiotherapy is not recommended. The recommendation for radiotherapy is sustained by the loco-regional lymphatic invasion. In cervical cancer, pre-surgery irradiation in all stages has until recently represented a usual element in all therapeutic guides. Many studies have shown that complications triggered by specific radiotherapy complications have the potential to affect the success of the actual cancer treatment. Post-radiotherapy fibrosis, pathology related to bladder and rectal mucous irritation, vesicovaginal fistula are debilitating complications seriously affecting the life quality of patients with cervical cancer. They can be prevented by justified therapeutic indications and a proper irradiation technique.

Regardless of the chosen path, the surgery takes place in much better anatomic conditions and with lower risk of intra surgical complications if the patient has not been previously irradiated. Sometimes, postsurgical radiotherapy can trigger important tissue changes which may reduce the radical character of the intervention by uncontrollable bleeding, especially in overweight patients.

PART II – PERSONAL RESEARCHES

10. STUDY MOTIVATION AND RESEARCH OBJECTIVES

The introduction of the screening program in the USA and Western Europe countries, consisting of a clinical examination and cervical cytology, has determined a significant increase of morbidity and mortality caused by cervical cancer. As the examination of the cervix can be easily performed by paraclinic diagnosis methods such as cytology, colposcopy, and biopsy, cervical cancer can be detected in pre-invasive stages.

Yet, cervical cancer continues to be a pathology with increased incidence in our country (first place in Europe), and consequently in Sibiu county as well.

As a practitioner physician, the chosen theme offers me the opportunity to expand my knowledge and clarify aspects referring to epidemiology, risk factors, screening and surgical treatment of this particular neoplasia. The cases encountered throughout time have convinced me to deal with this subject that addresses to a specific segment of world population in general and Romanian population in particular, with profound economic and social implications given by the significant founding necessary for the treatment of each individual case.

The hereby study is based on the experience accumulated in the Gynecology Clinic in Sibiu with the significant help of Prof. Adrian Stretean, PhD. The present work is a comparative analysis of two types of classic and laparoscopic surgical approach in malignant pathology of cervical cancer. It is a retrospective study started in January 1998 and ended in December 2012. The study group included a number of 200 patients which were diagnosed, treated and observed in our clinic.

Personal researches refer to yet another two aspects, namely the surgical treatment of particular situations of cervical cancer, as well as the experience in using vascular clips with a hemostatic purpose (hypogastric arteries) in the surgical treatment of cervical cancer.

There were included in the study all women hospitalized in the Gynecology Clinic in Sibiu diagnosed with cervical neoplasm within the period January 1st 1998 – December 31st 2012; all these women underwent one of the two surgical procedures: classic or laparoscopic.

The study included a number of 200 patients operated by Prof. Stretean during the mentioned period.

The thesis also condenses recent data from literature and it aims at underlining the role and the place of laparoscopic surgery in the treatment of cervical cancer. There are rendered the diagnostic and therapeutic possibilities of this method and the stadial surgery indications.

We consider that the surgical stage in the treatment of cervical cancer is the landmark of its complex treatment which must be accomplished at the highest technical level, with special accuracy; its results must be consolidated and improved through the other therapeutic methods which should be applied according to a well-established plan. Taking all these aspects into account, the aim of the hereby research was as follows:

- Global assessment of surgical treatment and of its outcomes in malignant pathology of the cervix.
- Comparative assessment of obtained results by means of classic or laparoscopic surgery.
- Contribution to a more accurate stadialization of patients with cervical cancer depending on the surgical approaching methods.

- Utilization of the results in such way that they offer the possibility of implementing the laparoscopic surgical techniques in the therapy of cervical cancer, following all the classic therapeutic protocols, in the context of therapeutic algorithm.

The second part of the paper dedicated to personal research will render the results obtained from a retrospective analysis of the case studies that focused on the two types of surgical approach (classic and laparoscopic). These comparative studies were meant to analyze the epidemiologic and risk factors involved in the genesis of cervical cancer (age, environment, parity, smoking, blood types, associated genital pathology etc.) in relation to literature data concerning these aspects, as well as to mark the advantages of laparoscopic surgical approach in relation to intra-surgical and post-surgical complications, average time of hospitalization after surgery and survival rate. Also, the retrospective study of the cases tackled three important aspects of the paper: radical hysterectomy for cervical cancer – laparoscopy versus laparotomy, specific surgical therapeutic methods in cervical cancer and the surgical treatment of hemorrhagic complication by means of vascular clips in cervical cancer.

The study aims at answering some of the present key questions regarding cervical cancer:

1. What is the most representative profile of cervical cancer patients who will undergo surgical treatment?
2. What are the indications for surgical treatment?
3. What is the place and the role of laparoscopic surgery in the management and treatment of cervical cancer and can it be a part of the complex therapy by becoming an important and efficient therapeutic option for patients?
4. What method of surgical approach is the most efficient in terms of intra and post-surgery complications, post-surgical survival rate and surgically success?

11. PRESENTATION OF RESULTS

11.1. Material and methods of research

As a method of study we used both a minute analysis of clinical observation sheets of all patients included in the research group, with all the additional documents, and a thorough study of surgical protocols, individual record sheets from the cabinet of oncology, in order to consider the evolution of operated patients and the distant results of the applied treatment.

All the cases were treated surgically according to national therapeutic guides and protocols of diagnosis in force, with or without radiotherapy/neoadjuvant chemotherapy.

The study starts from the reality of the already installed and diagnosed disease (in outpatient setting or other medical units) and analyzes clinically and paraclinically the persons included in the group of enrolled patients; this made possible the attempt to shape a long-term prognosis of survival status, depending on when the surgery took place, along with the immediate and remote results, in relation to the influence of the risk factors and the application of other methods recorded in the defined therapeutic plan. The setting of the mechanisms for measurement and result evaluation was based on the frequency indicators showing the level, the intensity of the phenomenon on a certain period, and on the indicators of structure, which highlight the relation between part and whole.

The statistical analysis of data was completed by using the SPSS (Statistic Program for Social Science), version 19.

For descriptive analysis of data the following were applied:

1. Frequency tables showing the number of cases and the corresponding percentage for each of the studied variables;
2. In the case of numeric variables, the indicators of central tendency were calculated:

a. Average of values: $\frac{\sum_{i=1}^N x_i}{N}$ where N represents the total of studied cases and x_i represents the values of the studied variable;

b. Standard deviation: $\sigma = \sqrt{\sigma^2}$ where $\sigma^2 = \frac{\sum_{i=1}^N (x_i - \mu)^2}{N}$, this indicator provides information on the dispersion degree of values (x_i) as compared to the average (μ).

Parametric and non-parametric statistic tests were used, depending on the normality of variables distribution, in order to determine the significant differences between the two groups. Among these tests, we mention the following:

1. The T test, which offers information on the more or less significance between the averages of the two groups, in the case of two independent units normally distributed. The significance level of this test is the following: a lower value than 0.05 ($p < 0.05$) indicates a significant difference between the two groups, while a higher value ($p > 0.05$) indicates that the averages between the two groups do not differ significantly.
2. The Mann-Whitney test is used in the case of two independent units with abnormal distribution; in this case the more or less significant difference is measured between the group ranks. The significance level is interpreted similar to the T test.

For data representation, the following graphic charts were used:

1. The Pie chart which is used in the case of dichotomous or categorical variables with a smaller number of categories.
2. The bars chart was used in the case of categorical variables with a higher number of categories.

11.2. Clinic conduct in the diagnosis and treatment of cervical cancer

The first chapters of personal research render elements concerning the particular conduct of the Obstetrical and Gynecology Clinic in Sibiu in the diagnosis and in the surgical treatment of cervical cancer.

The emphasis is especially on the laparoscopic surgical techniques used in the clinic during radical hysterectomies with pelvic lymphadenectomy; there are also present aspects and specific technical methods that are preferred in the clinic, as well as certain changes and adaptations of techniques described in the literature in relation to the technical and possibilities and preferences of the main surgeon, Prof. Adrian Stretean. There are also rendered the criteria of selection of the surgical approach: classic or laparoscopic, as well as the preferred therapeutic indications.

The clinic conduct is also taken into account as far the pre-operative investigation and preparation of the patients, and post-surgery patient care is concerned etc.

• **STUDY I**

11.3. Radical hysterectomy in the treatment cervical cancer – comparative aspects of classical and laparoscopic surgical approach

The hereby study discusses and analysis the case studies of cervical cancer, which comprises a representative study group of 200 patients that were treated in the Clinic of Gynecology of the Emergency Hospital in Sibiu, thus forming a well-defined pathology chapter studying comparatively the advantages and shortcomings. This is a retrospective study that started in January 1998 and ended in December 2012.

The two comparative studies between the two surgical approaches aim at analyzing the epidemiologic and risk factors that are involved in genesis of cervical cancer (age, environment, parity, smoking, blood types, and associated genital pathology) in relation with these particular aspects debated in literature; in the same time it highlights the advantages of the laparoscopic surgical approach in relation to the intra-surgical and post-surgical complications, the average period of post-surgery hospitalization and the survival rate.

The experience within the clinic during 1998-2012 consists in the surgical treatment of 200 cases of cervical cancer. 37 cases were operated laparoscopic (18.5%), while 163 cases were operated with the classic method (81.5%).

The observation of cases with cervical cancer included in the group study for 15 years (1998-2012) indicates a smaller percentage in the period 1998-2000 (3-7 cases/year), followed by an increase in the period 2002-2010 (13-22 cases/year), and another decrease in 2011-2012 (6-7 cases/year).

The analysis of the results from demographic materials has shown the following:

11.3.1. In terms of clinical stadialization – in our group study it was possible the defined of less optimistic conclusions, taking into account the high incidence of the cases included in stage II – invasive stage, respectively 86 patients or 43% of the studied cases (table no. 1).

| Pre-surgery stadialization | Number | Percentage |
|----------------------------|------------|-------------|
| Stage 0 | 37 | 18.50% |
| Stage I | 73 | 36.5% |
| Stage II | 86 | 43% |
| Stage III | 2 | 1% |
| Stage IV | 2 | 1% |
| Total | 200 | 100% |

Table no. 1 Percentage and numerical global incidence of operated cases in relation with clinic stadialization

11.3.2. Distribution by age - the highest percentage of incidence occurred within the 46-50 year group, 29 cases representing 17.8% for the group where classic surgery was used; for the group with laparoscopic surgery the age group was 36-40 years, with a percentage of 24.3% 24.3% (table no. 2).

| Age groups | Classic interventions | | Laparoscopic interventions | | Total |
|------------|-----------------------|------------|----------------------------|------------|-------|
| | Number | Percentage | Number | Percentage | |
| 18-23 | 1 | 0.6% | - | - | |

| | | | | | |
|--------------|------------|-------------|-----------|-------------|------------|
| 24-30 | 8 | 4.9% | - | - | |
| 31-35 | 12 | 7.4% | 2 | 5.4% | |
| 36-40 | 22 | 13.5% | 9 | 24.3% | |
| 41-45 | 16 | 9.8% | 8 | 21.6% | 24 |
| 46-50 | 29 | 17.8% | 7 | 18.9% | |
| 51-55 | 24 | 14.7% | 5 | 13.5% | |
| 56-60 | 18 | 11% | 2 | 5.4% | |
| 61-65 | 18 | 11% | 1 | 2.7% | |
| 66-70 | 8 | 4.9% | 2 | 5.4% | |
| peste 70 | 7 | 4.3% | 1 | 2.7% | |
| Total | 163 | 100% | 37 | 100% | 200 |

Table no. 2. Numeric and percentage incidence of operated cases on age groups in relation with the surgical approach.

By analyzing the average age of patients no significant differences have been noticed between the two groups of studies (classic vs laparoscopic approach); average age was a particular element from the point of view of importance. Thus, **average age** when joining the study was 49.5 years for those operated classically, and 46.8 years for those who underwent laparoscopic surgery.

11.3.3. As for the origin environment of the patients – the results have shown a high incidence in urban areas, namely 126 cases, representing 63% of the studied cases. 74 cases were from the rural areas, representing 37% of the studied cases. (table no.3)

| Origin environment | Number | Percentage | Statistical significance |
|--------------------|------------|-------------|--------------------------|
| urban | 126 | 63% | p<0.05 |
| rural | 74 | 37% | |
| Total | 200 | 100% | |

Table no. 3 Numerical and percentage incidence of operated cases in relation to the origin environment.

11.3.4. Analysis of the education level of patients within the study group has shown high incidence in patients with elementary level of study, 98 patients (48%); 75 patients have middle school level of study (37.5%) and only 29 patients (14.5%) have academic studies. This incidence reveals the degree of training of Romanian population.

11.3.5. Parity – regardless of the surgical approach, the results reveal that tertiparous women have the highest risk and incidence of cervical cancer. In our study, the numbers are 27.61% with the classic approach group and 48.65% with the laparoscopic approach group. On the other side, the nulliparous have a percentage of only 3.07%. For all the degrees of parity, the percentage of those operated through classical approach was not significantly different as compared to those with laparoscopic surgery. From the history of patients under study we noted that a number of 101 cases have had abortions, these particular patients representing an important percentage of 86.25% of the studied cases. (table no.4).

| Parity | Classic interventions 163 cases | | Laparoscopic interventions 37 cases | | Statistical significance |
|--------|---------------------------------|------------|-------------------------------------|------------|--------------------------|
| | Number | Percentage | Number | Percentage | |
| 0 | 5 | 3.07% | - | - | p>0.05 |
| 1 | 15 | 9.20% | 2 | 5.41% | p>0.05 |
| 2 | 40 | 24.54% | 6 | 16.22% | p>0.05 |
| 3 | 45 | 27.61% | 18 | 48.65% | p>0.05 |
| 4 | 21 | 12.88% | 4 | 10.81% | p>0.05 |
| 5 | 25 | 15.34% | 4 | 10.81% | p>0.05 |

| | | | | | |
|---|---|-------|---|-------|--------|
| 6 | 8 | 4.91% | 2 | 5.41% | p>0.05 |
| 7 | 2 | 1.23% | 1 | 2.70% | p>0.05 |
| 8 | 2 | 1.23% | - | - | p>0.05 |

Table no. 4. Numeric and percentage incidence of operated cases in relation to parity and surgical approach.

11.3.6. Smoking – the study reveals important statistic differences between the smoking and non-smoking patients, as follows: the number of smoking patients (141 cases – 70.5%) is significantly higher than the non-smoking patients (59 cases – 29.5%), within our study. The results reinforce the conviction that smoking has a crucial etiologic role in the occurrence and development of cervical cancer, and their distribution in within the two groups was different, as shown in table no. 5.

| Case distribution in relation to smoking | Classic interventions | | Laparoscopic Interventions | | Total | | Statistical significance |
|--|-----------------------|-------------|----------------------------|-------------|-----------------|-------------|--------------------------|
| | Number of cases | Percentage | Number of cases | Percentage | Number of cases | Percentage | |
| Smoking | 115 | 29.4% | 26 | 29.7% | 141 | 70,5% | p<0.05 |
| Non smoking | 48 | 70.6% | 11 | 70.3% | 59 | 29,5% | |
| Total of cases | 163 | 100% | 37 | 100% | 200 | 100% | |

Table no. 5. Numeric and percentage incidence of operated cases in relation to smoking

11.3.7. Blood types – statistic data based on this parameter revealed a high incidence of those with A_{II} blood type, 78 patients representing 39% of the studied cases (table no. 6).

| Blood type | Number | Percentage | Statistical significance |
|-----------------------|------------|-------------|--------------------------|
| Type 0 _I | 65 | 32.5% | p<0.05 |
| Type A _{II} | 78 | 39% | |
| Type B _{III} | 34 | 17% | |
| Type AB _{IV} | 23 | 11.5% | |
| Total of cases | 200 | 100% | |

Table no. 6 Numeric and percentage incidence of operated cases in relation to blood types.

From the very beginning of the study, this chapter reveals unsatisfactory aspects which should alert public health organizers.

Statistical processing of epidemiologic characteristics allows the outlining of the most representative profile of patients treated for cervical cancer within the Gynecologic Clinic of the Emergency Clinic Hospital in Sibiu, regardless of the surgical approach. In the following table it is charted the profile of the cervical cancer patient, as resulted from the series of treated patients: (table no. 7).

| Epidemiologic characteristic | Profile | % |
|------------------------------|-----------------------------------|-------|
| Age group | 46-50 | 18% |
| Origin environment | Urban | 63% |
| Educational level | Elementary level of studies | 48% |
| Obstetrical history | Miscarriages or request abortions | 86,5% |
| Parity | Tertiparous | 31,5% |
| Life conditions | Smoking | 70,5% |
| Blood type | A _{II} | 39% |

Table no. 7. The profile of patient with cervical cancer within the series of treated patients

11.3.8. In terms of associated genital pathology – the conclusions of the study reveal that the highest percentage of pathologic association was the uterine fibroids (in 20 of the cases,

representing 10%); the ovarian cysts were involved in 16 cases (8%), and genital prolapse was present in 10 cases (5%) of the total study.

It has been studied the distribution of associated diseases in terms of clinic stage and surgical approach and the outcomes were that the distribution of associated diseases was met in advanced clinical stages which were operated classically; within the laparoscopic group these were encountered in incipient stages. The explanation lies in the selection for the laparoscopic surgical approach of cases with a reduced associated pathology. (table no 8).

| Associated genital pathology | Classic interventions 163 cases | | Laparoscopic interventions 37 cases | | Total |
|------------------------------|------------------------------------|---------------|--|---------------|-----------|
| | Number | Percentage | Number | Percentage | |
| Uterin fibroid | 18 | 10.7% | 2 | 5.4% | 20 |
| Ovarian cysts | 10 | 5.9% | 6 | 16.2% | 16 |
| Genital prolapse | 6 | 3.5% | 4 | 10.8% | 10 |
| Cervical polyps | 10 | 5.9% | 2 | 5.4% | 12 |
| Endometriosis | 2 | 1.2% | 2 | 5.4% | 4 |
| Total of cases | 46 | 28.22% | 16 | 43.24% | 62 |

Table no. 8 Numeric and percentage incidence of operated cases in relation to associated genital pathology and surgical approach

11.3.9. Treatment – in terms of global analysis of result, the exclusively surgical treatment was applied to a number of 39 patients, 19.5%, and it consisted in total hysterectomy with bilateral annexectomy in 37 patients with in situ carcinoma, representing 18.5%. This intervention was done mainly laparoscopic due to its benefits, and it was also applied in two cases in stage I_{A1}, where cervix conization with pelvic lymphadenectomy was performed, as the patients were young women who requested the preservation of reproductive function. Thus only 20% of the cases were treated in the pre-invasive stage.

For the other 161 operated patients, (80.5%), the combined radio-surgical treatment was chosen. This shows a high incidence of cervical cancers in invasive stages. It would be desirable that the percentage of the two therapeutic methods be reversed. This would be possible by means of early detections and increase of the educational level of female population in our country.

As for the types of applied surgical treatment in relation with clinical stadialization, some aspects must be mentioned. In terms of clinical stage, the surgical treatment was performed in the above mentioned conditions. In terms of surgical approach, for stage 0 the laparoscopic approach was preferred in 18 patients (48.64%) and classical approach in 19 patients (11.65%).

For stages I and II, the surgical interventions were performed by both methods of approach. Out of 73 stage I operated cases, 15 cases were operated laparoscopic (40.5%). The other 58 cases (35.5%) underwent classical surgery.

Out of the 86 patients with stage II, only 2 cases were operated laparoscopic (5.40%), while 84 cases (51.53%) were operated by classic method. Thus it is revealed the necessity of an early diagnosis in order to increase the number of laparoscopic surgical approach. Moreover, laparoscopy was used in a IV_A stage case with lymphadenectomy and laparoscopy of stadialization, with lymph nodes biopsy. This conduct demonstrates the preference for mini-invasive surgical approach in order to complete suboptimal interventions in patients that have undergone surgical treatment in a short period of time. Laparoscopy may represent the favorite surgical method in patients with incipient carcinoma, stages 0 and I.

11.3.10. The number of removed lymph nodes – final analysis of removed lymph nodes in studied cases with invasive carcinoma (163 cases) has revealed the following: in the case of

performed interventions, it has been removed a number of 2363 lymph nodes, while the average number was M=16.36(SD=8.94); the minimum number was one lymph node, and the maximum number per operated case was 36 lymph nodes. (tab. no. 9).

| Removed lymph nodes 163 cases with invasive carcinoma | |
|---|-------------|
| Average /operated case | 16.36 |
| Standard deviation | 8.94 |
| Minim/operated case | 1 |
| Maxim/operated case | 36 |
| Total of removed lymph nodes | 2363 |

Table no. 9. Global number of removed lymph nodes in studied cases (163 cases).

Global analysis of removed lymph nodes showed the following:

- in **laparoscopic interventions (19 cases)**, of a total of 355 removed lymph nodes, the average number on operated case M=18.68 (SD=9.72), the minimum number was one lymph node, while the maximum number was of 34 removed lymph nodes.
- In **classic interventions (144 cases)**, out of a total of 2008 removed lymph nodes, the average number per operated case was M=14.04 (SD=8.17), the minimum number – one lymph node, and the maximum number – 36 removed lymph nodes. These values are significantly smaller than the laparoscopic group (p=0.024<0.05) (table no.10).

| | Removed lymph nodes | | P=0.024 |
|-------------------------------------|-----------------------------------|-------------------------------------|---------|
| | Classical interventions 144 cases | Laparoscopic interventions 19 cases | |
| Average /operated case | 14.04 | 18.68 | |
| Standard deviation | 8.17 | 9.72 | |
| Minim/operated case | 1 | 1 | |
| Maxim/operated case | 36 | 34 | |
| Total of removed lymph nodes | 2008 | 355 | |

Table no. 10. Incidence of average number of removed lymph nodes in relation to the classical or laparoscopic surgical approach.

11.3.11. Tumor invaded lymph nodes - in 13 cases (7.9%of the studied cases with invasive carcinoma) we have noticed the presence of tumor invaded lymph nodes.

Depending on the surgical approach, the distribution of cases with tumor invaded lymph nodes was as follows: in 12 cases the approach was classical (8.33%), and one case was laparoscopic operated (5.26%) ou ot the total of the studies cases with invasive carcinomas (163 cases) (table no 11).

| Total of cases with invasive carcinoma 163 (81.5%) | Classical interventions 144 cases (88.3%) | | Laparoscopic interventions 19 cases (11.6%) | |
|--|---|------------|---|------------|
| | Number | Percentage | Number | Percentage |
| Total of cases with tumor invaded lymph nodes | 12 | 8.33% | 1 | 5.26% |

Table no. 11. Numeric and percentage incidence of cases with tumor invaded lymph nodes histopathological confirmed depending on the surgical approach: classical or laparoscopic.

11.3.12. Cases with incomplete lymphadenectomy – our study revealed that out of the 163 cases of cervical cancer, in those specific cases of invasive carcinoma with pelvic lymphadenectomy, in 9 cases the removal of lymph groups could not be done (5.52% of mentioned cases).

The main causes that led to incomplete pelvic lymphadenectomy were: obesity (3 cases, 1.84%) and lymph nodes adherence to important blood vessels (6 cases, 3.68%). 4 cases of the latter had pelvic lymph nodes fixated on the external iliac vein and 2 cases had the nodes in the obturator fossa. (table no 12).

| Total of operated cases | Incomplete PL | Cause of incomplete PL | | Classical interventions | Laparoscopic interventions |
|-------------------------|---------------|------------------------|--|-------------------------|----------------------------|
| | | Obesity | Lymph nodes adherence to important blood vessels | | |
| 163 | 9 | 3 | 6 | 7 | 2 |
| Percentage | 5.52% | 1.84% | 3.68% | 77% | 23% |

Table no. 12. Cases with incomplete lymphadenectomy depending on cause and surgical approach (classical or laparoscopic)

11.3.13. Residue of tumor tissue after radiotherapy and chemotherapy histologically confirmed, in relation to the surgical approach – our study emphasizes within the 163 cases with invasive carcinoma a number of 26 cases (15.95%) with histopathological confirmation of tumor tissue residue. The surgical approach was classical in 24 cases (16.6%) and laparoscopic in 2 cases (10.5%).

The evolutionary stages in the classic surgical treatment were different: 7 cases in stage II_A (4.86%), 5 cases in stage I_B (3.47%), 11 cases in stage II_B (7.63%) and one case in stage III_B, stage reconverted to operability (0.69%). Laparoscopy was used in just two cases, one in I_B and one in stage II_A, representing 5.26%.

11.3.14. Incidence if cases in relation to the tumor histologic type – within our study, the histopathological analysis of surgery piece within the 163 cases with invasive carcinoma established that, regardless of the surgical approach, the squamous carcinomas were predominant; their presence was revealed in 152 cases (93.25%). Adenocarcinomas were identified in 11 cases (6.74%) of the cases with laparotomy. Our results proved to be similar to those in literature, which mention percentage for adenocarcinomas between 6 and 10 %, and squamous carcinomas between 80-90%. (table 13).

| Histological type | Total of cases with invasive carcinoma 163 (81.5%) | Classic interventions 144 cases (88.3%) | | Laparoscopic interventions 19 cases (11.6%) | |
|-----------------------|--|---|-------------|---|-------------|
| | Number of cases | Number of cases | Percentage | Number of cases | Percentage |
| Squamous Carcinoma | 152 | 133 | 92.36% | 19 | 100% |
| Adenocarcinoma | 11 | 11 | 7.63% | - | - |
| Total of cases | 163 | 144 | 100% | 19 | 100% |

Table no. 13. Numeric and percentage incidence of cervical cancer in relation to tumor histological type and surgical approach, classical or laparoscopic.

13.15. Rate of intra-surgical complications in relation with the two surgical methods – the situation is the following: with laparoscopic operated patients, the complications occurred in 5

cases (13.51%). They consisted of: massive intra-surgical hemorrhage in one case (2.70%) and visceral lesions in 3 cases (8.10%), out of which: 2 cases of incomplete lesion of the sigmoid colon (5.40%), one case of incomplete lesion of the bladder wall (2.70%), and one case of incomplete ureteral lesion by ligature (2.70%).

In the classical surgical approach, the intra-operative complications occurred in 35 cases (21.47%). They consisted in: massive bleeding which required ligature of hypogastric arteries in 21 cases (12.9%), out of which in two cases the pelvic tamponade was needed for hemostatic control (1.2%), 11 visceral cases, 6.74%, out of which: 7 cases of incomplete lesion of sigmoid colon (4.3%), one case of unilateral lesion of ureter (0.6%), one case of complete ureter lesion, where bladder implantation was performed (0.6%), two cases of incomplete lesion of bladder (1.2%). It has been noticed one case of damage to external iliac vein, representing 0.6% of the classically operated cases. (table no.14).

| Intra-surgical complications | Classical interventions 163 cases | | Laparoscopic interventions 37 cases | |
|--|-----------------------------------|---------------|-------------------------------------|---------------|
| | Number | Percentage | Number | Percentage |
| Massive bleeding requiring tamponade + LAH | 2 | 1.2% | 1 | 2.7% |
| Major bleeding requiring hypogastric arteries ligature | 21 | 12.9% | - | - |
| Incomplete lesion of the bladder | 2 | 1.2% | 1 | 2.7% |
| Incomplete lesion of the sigmoid rectum | 7 | 4.3% | 2 | 5.4% |
| Incomplete ureteral lesion by ligature | 1 | 0.6% | 1 | 2.7% |
| Complete ureteral lesion with bladder re-implantation | 1 | 0.6% | - | - |
| Damage of external iliac vein | 1 | 0.6% | - | - |
| Total | 35 | 21.47% | 5 | 13.51% |

Table no. 14. Numeric and percentage incidence of intra-operative complications in relation to the surgical approach – classical or laparoscopic .

11.3.16. Post-operative complications – the situation is as follows: for laparoscopic operated patients, the post-operative complications occurred in 3 cases (8.10%): two cases of urinary infections (5.4%) and one case of pelvic cellulite (2.70%).

In classical surgeries, the post-operative complications occurred in 35 cases (21.47%): 12 cases of urinary infection (7.4%), pelvic cellulite in 3 cases, 1.8%; 11 cases (6.6%) of post hemorrhage secondary anemia, which required blood transfusion; one case of vesicovaginal fistula (0.6%), one case of partial vaginal dehiscence (0.6%), and 7 cases of suppuration with parietal dehiscence (4.3%) (table no. 15).

| Post-surgical complications | Classical interventions 163 cases | | Laparoscopic interventions 37 case | |
|--|-----------------------------------|---------------|------------------------------------|--------------|
| | Number of cases | Percentage | Number of cases | Percentage |
| urinary infection | 12 | 7.4% | 2 | 5.4% |
| Pelvic cellulite | 3 | 1.8% | 1 | 2.7% |
| Severe anemia requiring blood transfusions | 11 | 6.6% | - | - |
| Vesicovaginal fistula | 1 | 0.6% | - | - |
| Partial vaginal dehiscence | 1 | 0.6% | - | - |
| Suppuration with parietal dehiscence | 7 | 4.3% | - | - |
| Total of complications | 35 | 21.47% | 3 | 8.10% |

Table no. 15. Numeric and percentage incidence of post-operative complications in relation with the surgical method of approach: classic or laparoscopic.

11.3.17. Average period of post-operative hospitalization of patients – average global period of post-operative hospitalization of studied patients was of 6.05 days. For 37 of the patients operated laparoscopic the hospitalization period was only 3.8 days. The 163 classically operated patients were hospitalized after surgery for 8.3 days. In general, the laparoscopic operated patients can be discharged after 48-72 hours after surgery, lest there should be any complications. (table no.16).

| Average duration of post-surgery hospitalization | Number of days | Statistical significance |
|--|----------------|--------------------------|
| Global | 6.05 | p<0.05 |
| Laparoscopic surgery | 3.8 | |
| Classic surgery | 8.3 | |

Table no. 16 Average duration of post-surgery hospitalization.

11.3.18. Average surgery time for the two surgical approaches – in our study, for classic interventions the average duration of a radical surgery was 155 minutes (2 hours and 35 minutes), and the average duration for laparoscopic surgery was of 205 minutes (3 hours and 25 minutes).

11.3.19. Intra-surgery bleeding in the two surgical methods – in the cases with invasive carcinoma, there were 21 cases of massive intra-surgery bleeding which required surgical sanction for its control (12.9%); there were performed ligatures of the hypogastric arteries with hemostatic purpose. The success of this particular surgical procedure in bleeding control was of 90.4%. The bleeding stopped in 19 cases, out of which two cases pelvic hemostatic tamponade was needed.

Average intra-operative bleeding was 405 ml per intervention in classical surgery, and 250 ml per intervention in laparoscopic surgery. Taking into account that we are referring to ample surgical interventions, we do not consider this to be an quantitatively important bleeding.

11.3.20. Post-surgery survival rate

The survival rate of patients who underwent surgery during an observation interval of 1-5 years was similar regardless of the surgical approach: 83.94% no matter what the clinical stadialization, 87% in stage I, and 67% in stage II. This data is similar to those in literature, and no statistically significant differences were observed between the two surgical approaches.

| Stages I and II of disease | | Laparoscopic approach | | | | Classical approach | | | |
|----------------------------|-------|-------------------------|----------------------------|-------|-----------|-------------------------|----------------------------|-------|-----------|
| | Total | Total of operated cases | Patients under observation | Alive | Survivors | Total of operated cases | Patients under observation | Alive | Survivors |
| St. I | 73 | 15 | 15 | 15 | 100% | 58 | 39 | 32 | 84.05% |
| St. II | 86 | 2 | 2 | 1 | 50% | 84 | 46 | 32 | 69,50% |
| Total | 159 | 17 | 17 | 16 | | 142 | 85 | 64 | |

Table no. 17. Survival rate on an observation period between 1-5 years, in terms of clinical stage of the patients under observation

The assessment for postoperative survival was made for the patients who remained under observation, in clinical stages I and II, with tumor invaded lymph nodes, as shown at the post-

operatory HPE. Out of the total of 159 patients operated in stages I and II, in 12 cases there were noticed tumor invaded lymph nodes (7.54% of the studied cases).

Survival period was negatively influenced by the presence of tumor invaded lymph nodes. Survival rate decreased to 84% in stage I and to 60% in stage II. Obtained data for the two surgical methods are not statistically significant, especially due to the small number of laparoscopic surgeries.

The deceased patients had pelvic tumor recurrences, with ureteral compression and uremia (table no 18).

| Survival study in cases with tumor invaded lymph nodes | | | Classical interventions | | Laparoscopic interventions | |
|--|---|----------------------------|-------------------------|----------------|----------------------------|------------|
| Clinical stage | Total of cases with tumor invaded lymph nodes | Patients under observation | Alive | Percentage | Alive | Percentage |
| I | 2 | 2 | 1 | 100% | 1 | 100% |
| II | 10 Lost 1 | 9 | 5 deceased 4 | 55.5% 44.5% | - | - |

Tabel nr. 18 Supraviețuirea bolnavelor operate rămase în evidență, la un interval de urmărire între 1 și 5 ani, în raport cu stadiul clinic și prezența ganglionilor invadați tumoral.

Analysis and discussion of obtained results was constantly made comparatively. The global results were compared with those obtained by laparoscopy and laparotomy; also the two surgical approaches were compared, as well as other similar recent studies from literature.

• *STUDY II*

11.4. Specific surgical therapeutic methods in cervical cancer

The study aimed the assessment of surgical therapeutic possibilities, laparoscopic in particular, and our experience in atypical clinical situations in cervical cancer, when the treatment was integrated to a complex radio-chemical-surgical treatment in compliance with the oncologic principles.

Particular situations requiring atypical therapeutic actions are: occult invasive cervical cancer, discovered by means of post-operative HPE, after hysterectomy or cervix conization; cervical cancer associated with 3rd degree genital prolapse; cervical cancer on residual bunt after HST; advanced cervical cancer (stage III).

The study conducted in the period 2001-2011 within the clinic comprises a total number of 22 atypical cases: 14 cases of cervical cancer diagnosed after total hysterectomy, two cases of cervical cancer after conization, one case of genital prolapse of 3rd degree and cervical cancer in stage II_A, three cases of cancer on residual cervix, two cases of cervical cancer in stage III, with pelvic lymphadenectomy as adjuvant method of treatment.

All the above mentioned cases required an atypical therapeutic action as compared to the usual procedures. The results were assessed from all the already mentioned point of views.

For the first three situations, we consider that the suggested therapeutic action is the correct and the only possible one, as it is imposed by the general therapeutic protocols in cervical cancer, as long as it is adapted to the given atypical situation.

For stage III of cervical cancer, routine laparoscopic lymphadenectomy as a mini-invasive method could alleviate the evolution and the prognosis. This possible benefit is to be further studied, on an extended case study.

In terms of particular surgical therapeutic methods in cervical cancer, our study has reached the following conclusions:

- cervical occult carcinoma after total hysterectomy discovered at post-operative histopathological examination requires the re-application of the oncologic treatment with the performance of pelvic lymphadenectomy preferably laparoscopic, of parametrectomy and removal of one third of the superior part of the vagina, as well radiotherapy and chemotherapy pre and post-surgery, depending on the lymph nodes status;
- invasive cervical cancer associated to 3rd degree genital prolapse is a rare association and calls for radical hysterectomy on vaginal path, colpectomy, myorrhaphy of anal levator plate, laparoscopic pelvic lymphadenectomy, and post-surgery radiotherapy and chemotherapy in relation to the lymph nodes status;
- Cervical carcinoma on residual cervix requires the removal of the cervix, of parameters, of the superior 1/3 of vagina, laparoscopic pelvic lymphadenectomy, pre- and post-surgery radio and chemotherapy;
- Laparoscopic pelvic lymphadenectomy may be useful in stage III of cervical cancer, in association with radio and chemotherapy.

Following the post-surgery histopathological examination, the analysis of the medical particularities of the studied cases has revealed the ensuing aspects:

| Medical particularity | Laparoscopic interventions 9 cases | Classical interventions 7 cases |
|---|---|--|
| Average number of removed lymph nodes | 18 | 14 |
| Tumor invaded pelvic lymph nodes | - | - |
| Cervical vaginal tumor residue | - | - |
| Tumor invaded parameters | - | - |
| Average duration of interventions (minutes) | 125 (1h 25min) | 110 (1h 10min) |
| Average duration of hospitalization (days) | 4.2 | 8.5 |
| Local tumor recurrences or distant metastases | - | - |
| Survival rate in post-operative observation on a 1-5 years interval | 100% | 100% |

Table no. 17 Analysis of medical characteristics of operated cases

Post-surgery complications were represented by urinary infections in three cases, in one case after laparoscopic intervention and in two cases after classical surgery. Pelvic cellulite occurred in only one laparoscopic case, while the pelvic lymphocele with clinical manifestations occurred in two cases, one for each surgical approach (table no.18).

| Specific post-surgery complications | Laparoscopic interventions 9 cases Nr.(percentage) | Classical interventions 7 cases Nr. (percentage) |
|--|---|---|
| Urinary infection | 1 (11.1%) | 2 (28.5%) |
| Pelvic cellulite | 1 (11.1%) | - |
| Pelvic lymphocele (clinic) | 1 (11.1%) | 1 (14.2%) |

| | | |
|-----------------------|--|--|
| manifestation) | | |
|-----------------------|--|--|

Table no. 18. Post-surgical complications in the studied cases with occult cervical cancer discovered by HPE

• **STUDY III**

11.5. Surgical treatment of hemorrhagic complications through vascular ligatures in cervical cancer

We consider that in oncologic surgery in radical hysterectomies with pelvic lymphadenectomy bleeding may occur from dissected structures (obturator fosses, prevesical venous plexus, certain vessels etc.). Therefore, the aim of this study is to present the possible surgical techniques which allow the amelioration of evolution and prognosis in complicated cases of cervical cancer.

In the operated cases within our clinic, out of 200, only 21 (10.5%) needed ligatures of hypogastric arteries (HAL) unilateral or bilateral. Of these cases, on one patient with stage III converted to operability the radical surgery was not possible. In this particular case, completion pelvic lymphadenectomy was performed, with bilateral ligature of hypogastric arteries, in order to prevent possible bleeding.

The rest of 2R cases were stage I and II cervical carcinoma on which it was performed radical hysterectomy and pelvic lymphadenectomy. Here, the intra-operative bleeding was important (obturator fosses, prevesical venous plexus, peritoneal limits, etc.). In 16 cases the hypogastric arteries ligature was made bilateral (76.1%), and in 5 cases (23.8%) unilateral (23.8%) due to important bleeding to one of the obturator fosses.

From the total of 21 cases with bilateral ligature of hypogastric arteries, in 2 cases (9.5%) it was required the appliance of hemostatic tampons in obturator fosses. In the rest of the cases, the bleeding stopped once the ligature was completed.

No intra-operative incidents regarding the damage of ureters or other iliac vascular elements occurred.

In cases with advanced stages of cancer with ligature of hypogastric arteries, the bleeding was reduces during the observation interval.

In one case of cervical cancer stage II_B, with radical hysterectomy and pelvic lymphadenectomy there was an accidental damage of a few millimeters of the external iliac vein, in the process of dissecting some lymph nodes adherent to the vascular package. To reduce bleeding at this level, a bilateral ligature was performed in order to decrease the arterial flow and vein turning. The small vascular laceration was patched with a hemostatic and adhesive material wrapped around the external iliac vein.

The rate of “hemostatic success” – if considering the 21 cases – was of 90.4%, namely in 19 cases. (table no.19).

| | Number of cases | Performed ligature type (LAH) | | | | Rate of hemostatic success | |
|----------|-----------------|-------------------------------|------------|-----------------|------------|----------------------------|------------|
| | | unilateral | | bilateral | | | |
| | | Number of cases | Percentage | Number of cases | Percentage | Number of cases | Percentage |
| Operable | | | | | | | |

| | | | | | | | |
|---------------------------------|----|---|-------|----|-------|----|-------|
| cervical cancer (I, II and III) | 21 | 5 | 23.8% | 16 | 76.1% | 19 | 90.4% |
|---------------------------------|----|---|-------|----|-------|----|-------|

Table no. 19. Hypogastric ligatures performed in the treatment of hemorrhagic complications in cervical cancer and rate of hemostatic success.

12. GENRAL CONCLUSIONS

1. Cervical cancer is high incidence pathology in our country (ranked 1st in Europe) and implicitly in Sibiu County. The issue of cervical neoplasm is extremely complex and it addresses not only to Gynecology or Oncology department, but also to all medical specializations, and society as well, as it represents a major problem of public health.

2. Ever rising incidence of the disease in the latest years especially in young women implies advancement of sanitary educational level of population and organizing efficient screening programs that include the female risk population.

3. The results of descriptive epidemiological evaluation highlight the high prevalence of risk factors that may influence the occurrence or unfavorable development of precancerous lesions in the female population in our area. The detected risk factors are: age of 45-50 years, urban environment, multiparity, smoking, blood type A_{II}.

4. The hereby work marks the role, the value and the importance of surgical treatment, as an essential step in the treatment of cervical cancer, aiming at oncological radicality.

5. The thesis offers a generous amount of space to the surgical act. The types of interventions are mentioned, as the team has suggested extended lymphadeno-colpo-hysterectomy on most studies cases. The interventions are accompanied by specific illustrations of particular cases. Radical interventions were possible even in cases with advanced stages of cancer already known pre-operatory.

6. The treatment of this disease (except stage 0) is a radio-surgical complex. The surgical approaches were laparoscopic (national premiere) and classical ones.

7. The comparison of the two surgical methods allowed the identification of the shortcomings and advantages as far as intra and post-surgery complications, and post-surgery survival rate are concerned.

8. Surgery in cervical cancer has the tendency of becoming less aggressive, in the sense of preserving the patients' life quality (function, esthetics, reproduction). Since incidence in young women seems to be rising constantly, the laparoscopic technique of radical hysterectomy represents an absolute progress in the field of mini-invasive surgery in the oncologic surgery of the latest decade. In this context, laparoscopic radical hysterectomy becomes an important therapeutic possibility provided to patients.

9. There is now a consent that laparoscopic surgery specific treatment of gynecological malignancies is not yet standard therapy, but that these methods must be integrated into a comprehensive arsenal of genital cancer therapy.

10. Surgical trauma is minimal, the risk of complications is reduced; the level of post-surgery pain is minimized, while the hospitalization and social reintegration period is significantly shortened. Classical surgery is unable to provide these advantages.

11. Resulting from the conducted researches, the incidence the complications, the post-surgery evolution and the survival rate for the studied patients were similar to literature data concerning the mentioned aspects.

12. Hemostatic vascular ligation (ischemia) is a relatively simple surgical procedure, but extremely useful in major bleeding that may occur in gynecologic oncology surgery; it allows successfully hemostasis where all other medical or surgical methods have failed.

13. In cancer surgery (radical or palliative) hypogastric artery ligation is an effective way to stop or prevent serious bleeding which sometimes makes the difference in the patient's vital prognosis. The efficiency in achieving a sufficient hemostasis ranges between 50-90% of the cases where it was applied.

14. Mortality rate is not necessarily higher as compared to classical surgery, and morbidity and complications proved to be even more reduced. The 5-year survival rate is similar to that after classical interventions.

15. Small duration of the period of hospitalization, minimal postoperative surgical trauma, rapid recovery and fast social and professional integration of patients operated laparoscopic justify the use of these minimally invasive techniques.

16. Bearing in mind that radical hysterectomy with pelvic lymphadenectomy is a prototype of intervention for cervical cancer, we found that average survival rate was higher in the cases with laparoscopic surgery, namely 12 years after HRVAL, as compared to 5.54 years after HRLP.

17. The study confirms the feasibility of carrying out pelvic lymphadenectomy in laparoscopic manner, as the average number of lymph nodes excised from some groups (in our study the obturator fossa lymph) is significantly higher than average number of lymph nodes excised by classic open approach, while the average number of nodes lymph nodes excised from other groups is approximately equal in both surgical approaches.

18. The laparoscopic approach of this pathology will only be performed in centers specialized in advanced laparoscopic surgery, with surgeons endowed with surgical abilities and adequate experience; the same clinics are able to apply other therapeutic procedures implied by the treatment protocols. Laparoscopic surgery of cervical cancer should be included in standard therapeutic protocols of the disease; it will be integrated in the complex algorithm of radio-chemo-therapy and it will be performed according to therapeutic protocols and research.

19. Radical hysterectomy with laparoscopic colpoassisted pelvic lymphadenectomy can constitute an alternative to laparotomy radical hysterectomy in incipient clinical stages (0, I, II_A), due to its advantages (short period of hospitalization, rapid post-surgery recovery, lower hospitalization expenses). It will have to be included in standard therapeutic protocols of the disease.

20. The thesis thoroughly answers the question regarding the place and role of laparoscopic surgery in the management and treatment of cervical cancer and whether it can join the complex therapeutic arsenal, thus becoming important and effective treatment option offered to patients.

21. The paper emphasizes the essential value of minimal invasive surgery, and the overall conclusion is that, through the many advantages it offers, both for patient, for the health system and also for society, the laparoscopic surgical technique can and should be implemented in the algorithm treatment of this pathology.

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