Book Chapter

Vaccination Against Human Papilloma Virus Infection and Application of Screening Tests in Prevention, Diagnosis and Treatment of Cervical Cancer

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Abstract

Cervical cancer is one of the most common gynecological malignancies in women around the world. Most of these cancers are related to the human Papilloma virus, although other factors lead to neoplastic progression afterinfection. The majority of the younger population is affected by this cancer compared to other malignant diseases.

Cervical cancers are usually asymptomatic. The diagnosis is usually made on the basis of histological analysis of samples obtained during colposcopy. Changes in the cervix are less often noticed during the gynecological examination.

The clinical stage of the disease is crucial in deciding about the therapeutic modality. Early stages of the disease can be successfully treated surgically. For advanced stages of the disease, the primary therapeutic option is hemorrhage. The most important factor that influences on the prognosis and survival is stage of the disease. The early stages of the disease are often asymptomatic, which emphasizes the importance of cytology in screening. Abnormal uterine bleeding and vaginal discharge are the most common symptoms. A lesion localized on the cervix may clinically appear as a tumor growth or ulceration and lesions localized in the endocervical canal may be occult (hidden). The diagnosis of cervical cancer must be confirmed by biopsy.

In our paper, we explained the importance of cervical cancer prevention, which is based mainly on early diagnosis (screening) and treatment of severe cervical dysplasia and HPV vaccination. We also considered the etiology and risk factors for the development of cervical cancer. We explained the pathophysiological aspects for premalignant cervical lesions, clinical stages of cervical cancer, various therapeutic methods, application of sophisticated visualization diagnostic methods and treatment of invasive cervical cancer in pregnancy, as well as the

prognosis of the disease. Accordingly, we recommended regular screening examinations and HPV vaccination, in order to reduce the rate of cervical cancer in the future.

Keywords

HPV Vaccination; Cervical Cancer; Screening Tests in Prevention; Diagnostic Methods; Various Therapeutic Methods

Introduction

Cervical cancer is the third most common malignant disease in the world. Over 75% causes of death from invasive cervical epithelial cancer occurs in the economically less developed countries of the world. This is explained by the fact that in these countries the health care system is less developed, which affects poorer disease prevention and control. The incidence of invasive cervical cancer in Serbia is twice higher in relation to the European average. This cancer is in second place among malignant tumors of women in Serbia (after breast cancer), which is a consequence of the fact that with regular screening in our country began much later than in Western European countries [1]. Cervical cancer is far more common than all cancers in the genital region in men. Epidemiological research predicts that in 2050 there will be over a million cases cancer per year. From 60,000 cases of newly diagnosed cervical cancer per year level, half ends in death. In Serbia, the highest incidence of cancer is in the Branicevo, Zajecar and Moravian districts. Two-thirds of cervical cancers occurs after the age of 45, and one third in those under 45 years of age. Frequency of morbidity is lowest in the second decade of life. Risk factors for cervical epithelial dysplasia are: human papilloma virus infection (HPV), smoking, early sexual intercourse with multiple partners, use of oral contraceptives, herpes virus infection, other sexually transmitted diseases, immunosuppression [2]. In 1928, Georgios Papanicolaou recommended the taking a cervical swab and its microscopic analysis. Malignant cervical tumors are one of the most common malignancies in the female population. The incidence ranges from 8 to 30 newly detected cases per 100,000 women per year, depending on the country and region [3]. In the clinical material of the Institute of Oncology and Radiology in Belgrade, these tumors constitute approximately 50% of all

malignancies of the reproductive system of women. Most often, these tumors are discovered in the 5th and 6th decades of life. They rarely occur in people under the age of 20 years [4]. Many factors have been found to influence the malignancy to a greater or lesser extent: early coitus (before the age of twenty), promiscuity (multiple sexual partners, pregnancy in younger age, higher number of births, viral infection (HSV-herpes simplex virus), HPV (Papillomavirus), poor socio-economic status of women, and others [4,5]. The mechanisms by which highly oncogenic HPV viruses affect the onset of neoplastic changes and progression include the activity of two oncoproteins E6 and E7 which affect on cellular, tumor suppressor proteins, p53, and retinoblastoma protein (Rb). Alone HPV infection is not sufficient to lead to the malignant alteration, but various genetic and epigenetic factors have a important role in cancer development [6]. These additional factors (cofactors) of cervical tumorigenesis can be divided into infectious-such as co-infection with Chlamydia trachomatis or Herpes simplex virus and non-infectious-cigarette smoking, nutrients, genetic factors, hormonal contraceptives, parity, sexual behavior, early sexual intercourse relationships and number of partners [7]. Premalignant and malignant changes in the cervix are covered by the new name squamous intraepithelial lesion and are divided into two groups:

- Low−grade squamous intraepithelial lesions including cervical intraepithelial neoplasia (CIN1) and early condiloma (HPV−induced lesions),
- High−grade squamous intraepithelial lesions, which include cervical intraepithelial neoplasia (CIN2 and CIN3 with or without the characteristics of HPV lesions) [8].

The morphological criteria on the basis of which the squamous intraepithelial lesion is diagnosed and graded are: differentation, ie maturation or stratification of the epithelium, nuclear atypia and mitotic activity of the cell. Molecular−biological studies have shown that a low−grade squamous intraepithelial lesion differs from a high−grade squamous intraepithelial lesion by the type of ploidy. A low−grade squamous intraepithelial lesion has a diploid or polyploidy DNA content, wherefore the spontaneous regression is more common. It is important to point out that a

high−grade squamous intraepithelial lesion is characterized by aneuploidy. It is an indicator of malignant potential and low−grade aneuploid squamous intraepithelial lesions are true precursors of cervical cancer [9]. In persistent HPV infection from the appearance of initial, mild and moderate premalignant changes, ie. low−grade and high−grade squamous intraepithelial lesions to the appearance of cervical cancer passes the period time from 9 to 15 years. Due to the slower progression of the disease, it is considered that is possible to notice changes in time that can lead to the cervical cancer and prevent its occurrence [10]. This is achieved by secondary prevention measures by cytological diagnostics−Papanicolaou test, colposcopy and HPV typing. Primary prevention involves vaccination, which is carried out in a numerous developed countries around the world. The introduction of the Papanicolaou test as a cervical screening in the 1950s reduced the incidence and mortality from cervical cancer by about 60%. It has been considered that this test is one of the most effective, cheap and applicable for the general population, therefore it was introduced in the regular gynecological examination. Exfoliative cytology, as the basis of the Papanicolaou test is a diagnostic method that analyzes desquamated cells from the cervix and cervical canal, which reflect changes in the corresponding tissues [11]. Although, there are no clear parameters that indicate on the degree of dyskaryosis, the size of the nucleus and the distribution of chromatin in relation to the amount of cytoplasm are of the greatest importance in its assessment. With the severity of the lesion, the number of dyskaryotic cells increases and cell abnormalities become more pronounced (enlargement of the nucleus, hyperchromasia, irregular thickening of the nuclear membrane, nucleolus and mitosis). The finding of spindle cells, tadpole−shaped cells, extreme increased in the ratio of nucleus−cytoplasm, anisocytosis and pronounced hyperchromasia indicate on the appearance of more severe lesions and cancer [12]. Coliocytosis encompasses morphological changes of epithelial cells, which are characterized by a combination of nuclear atypia and cytoplasmic cavitation. Cytoplasmic vacuolization without nuclear atypia is not a specific lesion and occurs in normal epithelium as a consequence of increased amount of glycogen,

atrophy or infections of another nature. According to the degree of changes in the epithelial cells of the cervix, there are five degrees in the Papanicolaou classification: I−normal finding, II−inflammation, benign, reactive and reparative changes, IIIa−atypical cells of indeterminate significance (squamous and grandular), IIIb−mild grade dyskaryosis and moderate grade dyskaryosis, IV−severe grade dyskaryosis and V-malignant cells [13]. In addition to the great importance of Papanicolaou classification, it is insufficiently precise in defining of the third group due to the existence of dyskaryotic cells of varying degrees, does not reflect the current understanding of pathogenesis and has not equivalents in the diagnostic histopathological terminology. There is no possibility of diagnosing non-cancerous entities in Papanicolaou groups. The specificity of the Papanicolaou test is satisfactory and amounts from 91% to 99%, but the sensitivity is still inadequate and amounts from 32% to 78% [14]. Also, this test may have several potential errors, which refer to the gynecologist who takes the sample, the technique of taking and processing the sample and the interpretation of the findings by the cytologist. In order to reduce these potential errors and increases the overall sensitivity of the test, several new techniques have been developed in recent years, which have been proposed as complementary or replacement methods for Papanicolaou. These are liquid based cytology with a new method of technical sample preparation, computerized cytological analysis, HPV DNA typing and molecular markers (P16INK−4a, Ki67, PCNA, Mcm5, Cdc6) [15]. Papanicolaou test supplemented by colposcopy and histology still remains the basic method of secondary prevention of cervical cancer [16].

Etiology and Risk Factors for the Development of Cervical Cancer

A wide range of potential causes for cervical cancer is well known in modern medicine. If the factors act together over a longer period of time, the risk increases. In addition to factors, such as habits, lifestyle, inadequate socio−economic status, poor prevention policy and lack of organized screening, complex physiological, biological, psychological and genetic factors are

also extremely important [17]. These factors have the ability to initiate and promote the growth of altered abnormal cells, which by evading control mechanisms begin to divide without limits. Special attention should be paid to women in which these factors are identified. It is necessary to intensify control examinations, monitor and determine the nature of pathophysiological changes [18]. The most significant risk factor for cervical cancer is HPV from Zur Hausen's discovery until today. HPV is an epithelotropic virus, which possesses double−stranded deoxyribonucleic acid and primarily infects basal keratinocytes of the superficial epithelium of the skin and mucous membranes [19]. It contributes to the development of 4.5% of cancers worldwide. Over 170 HPV genotypes have been identified and all can be divided into two groups based on the likelihood of developing cancer. The low−risk group consists of genotypes 6, 11, 40, 42, 43, 44, 54, 61 and 72, while the high−risk group consists of genotypes 14, 16, 18, 31, 35, 39, 45, 51, 52, 56, 58, 66 and 68, which cause 99.7% of cervical cancer [20]. There is a significant predominance of HPV positivity in subtypes 16, 31, 35 and 52, when it comes to squamous cell carcinoma. It has also been observed that HPV 18, 39, 45 and 59 subtypes are more common in adenocarcinomas and adenosquamous cancers. Persistent and recurrent infection with high−risk HPV subtypes in an immunosuppressive environment potentiates the development of this tumor [21]. The cervico−vaginal microbiota is associated with local immune regulation and oncogenesis. It has been determined that invasive cancer develops in only 1% of cases from 90% of infected women. In immunocompromised patients, the percentage of invasive cancers is far higher. It is important to note that HPV infection heals spontaneously repaired even at 70% to 90% infected within one to two years [21]. Premalignant lesions are induced by changes in host DNA, which are a consequence of epigenetic and genetic mutations of oncogenes and tumor suppressor genes. E6 and E7 oncogenic viruses directly or indirectly disrupt cellular control mechanisms [22]. E6 inhibits cell cycle regulation and p53 transcription factor for apoptosis, while E7 regulates protein synthesis, which binds to the retinoblastoma tumor suppressor gene, allowing continued division of the infected cell [23]. The progression of premalignant changes in invasive cervical cancer is a process

that can last from 10 to 30 years. Acute and chronic bacterial, fungal and other viral infections potentiate the development of cervical cancer, especially if they act in an environment of HPV coinfection. People infected with the human immunodeficiency virus (HIV) not only have a 2 to 12 times higher risk of developing HPV−mediated precancerous changes, but the progression to ivasive cancer is much faster [24]. Any type of immunodeficiency is a risk factor for cervical cancer. Also, irresponsible sexual behavior undoubtedly affects on the development of this tumor. It has been determined that women who early enter into unprotected sexual relations, they get sick more often. A large number of partners, but also the promiscuity of both partners, increases the chance of developing HPV 16/18 infection, as well as other infections [25]. People who have more than 10 partners have a six times higher risk for HPV 16/18. The cervical cancer can occur at women in pregnancy, due to changes in hormonal status, that can increase the body susceptibility to HPV infection or accelerate tumor growth. The risk increases after three and drastically after five or more pregnancies [26]. The first pregnancy in the period of early adolescence represents a special risk. The study, conducted by Chen, indicates the same incidence of HPV before and after pregnancy, while during pregnancy the greatest risk occurs in the third month. Back in 2004, the International Agency for Research onCancer proved that smoking, given the twice as high risk of disease is one of the main risk factors for the development of cervical cancer [26]. In female smokers, a significant concentration of carcinogenic substances and tobacco breakdown products can also be identified in the cervical mucus, where it damages the epithelium by various mechanisms [27]. Improper and inadequate diet can indicate on the development of this tumor, especially if it is rich in foodstuffs with a high percentage of fat and sugar with little fruit and vegetables, vitamins and minerals [28]. Nutrient−deficient food accelerate the progression of dysplastic changes toward invasive cancer. Pooralajal and coworkers have proven that being overweight is not a risk factor for cervical cancer. Women, who living in rural areas suffer more often from cervical cancer. In them, the tumor is detected in an advanced stage of the disease [29].

Prevention of Cervical Cancer and HPV Vaccination

So far, the prevention of morbidity and mortality from cervical cancer have been largely based on the diagnosis and treatment of preinvasive and early invasive forms of the disease. Universal cytological screening of all postpubertal women should also be performed regularly, until a better, more sensitive and specific way of screening is found [30]. Women at which have been diagnosed the preinvasive lesion on the cervix should be treated and followed according to the recommendations. It is also important to note that that cytological smears are of limited value in the diagnosis of disease and in some cases false negative findings are present in 50% of cases [31]. Sexual abstinence is an effective, but impractical invasive prophylactic measure. Education of young women about risk factors and the need for regular screening is crucial, as well as informational about the connection between HPV infection and smoking with the development of cervical cancer [32].

The vaccine for the prevention of HPV infection was approved in 2006 by the Food and Drug Administration. HPV infections are very common in women younger than 35 years and the most of them disappear spontaneously. Most people are exposed to HPV, when they become sexually active. The ideal way to prevent HPV infection would be through vaccination before exposure [33]. The development of the HPV vaccine may be a major step in cervical cancer prevention. The vaccine should protect against the most common types of high risk HPV 16 and HPV 18. It will take several decades that the effect of the vaccine on the reduction of incidence of cervical cancer be confirmed with certainty. Widespread screening for cervical cancer should continue even after the full implementation of the HPV vaccine program in order to detect and monitor abnormalities in unvaccinated and previously infected populations. Three HPV vaccines have passed the testing phase and are already being used in prevention [32].

CERVARIK (GLAKO SMITH BIOLOGICALS) **bivalent vaccine** protects against HPV16 and HPV18. **GARDASIL**

(MERK SHARP & DOHME) is a **quadrivalent vaccine**, which protects against Human Papillomavirus (HPV16 and HPV 18) and and two non−cancerous types HPV6 and HPV11 and has received approval from the Food and Drug Administration. It has been in use in the United States since 2006 in the female part of the population aged from 9 to 26 years. Recent studies have shown that the vaccine is quite safe, well tolerated, it is the immunogen and has an excellent efficacy in the prevention of persistent HPV infection and the development of cytologic atypia associated with the infection (Ault, 2006). **The 9-valent HPV vaccine** protects against HPV6, 11, 16 and 18, as well as five additional oncogenic types 31, 33, 42, 52 and 58. The Advisory Committee for Immunization recommends one of three HPV vaccines. All three vaccines have a good safety and protection profile with high−risk oncogenic HPV types 16 and 18 responsible for approximately 73% cases of cervical cancer in Europe. The effectiveness of the tetravalent vaccine that protects against HPV6 and HPV11 ranges from 75-90%, while its effectiveness against HPV16 and HPV18 goes up to 70%. In uninfected women, the effectiveness of the HPV4 vaccine (Gardasil) is 98% in the prevention of cervical cancer. Girls who are not infected with any of the four subtypes of HPV have the greatest benefit from vaccination [34]. It has been proven that the vaccine has practically 100% efficiency in the prevention of vulvar / vaginal precancerous lesions and warts caused by HPV subtypes target. The effectiveness of the HPV2 vaccine ranges from 96% to 98% in the prevention of cervical precancerous lesions. The vaccine includes two subtypes of HPV16 and HPV18 and is not effective in the prevention of genital warts−condyloma. The efficacy of the 9-valent HPV vaccine ranges from 87.5% to 98.6% for HPV 31,33, 42, 52 and 58; while 98% efficacy was found in HPV6, 11, 16, 18 after three-dose vaccination [35]. The vaccines are given in three doses over a period of six months. HPV vaccination is expensive and a three−dose regimen for six months is difficult to implement. Vaccination costs in some countries may result in their availability not being promoted. These are the primary reasons why coverage rates are low. Clinical trials have shown a significant difference in the efficacy of the bivalent vaccine at the four−year follow−up level, regardless of whether one or two

doses are administered in relation to the recommended three doses per protocol [36]. If this examination is confirmed, these findings will have a major impact on the costs and strategies for HPV vaccination programs. Vaccination coverage rates (first three doses) are optimal. Based on evidence from studies and data on sexual behavior from the United States, the American Cancer Society has developed the following guidelines about the HPV vaccination.

- Routine vaccination is recommended for girls from 11 to 12 years of age.
- Vaccination is also recommended for girls from 13 to 18 years of age to make up for missed vaccination [37].
- There is currently insufficient data to recommended vaccination for or against women aged from 19 to 26 years. Vaccination of these women must be based on the information of the doctor who takes into account the previous number of partners (eg previous risk).
- HPV vaccination is currently not recommended for women and men over the age of 26.
- Cervical cancer screening should be continued in vaccinated and unvaccinated women [38].

Worldwide, 67 countries have this vaccine in their national vaccination programs. HPV vaccines have been shown as effective in preventing cervical precancerous changes as well as other anogenital lesions (in women and men) caused by HPV serotypes with high carcinogenic potential, condyloma inducers. Studies show that there is a marked misunderstanding and negative attitude towards HPV vaccination more than other recommended vaccines. This applies in particular to the recommendation to vaccinate boys. Parents usually refuse and postpone the HPV vaccination process. The rate of complete vaccination in two or three recommended doses is significantly lower. Also, the rate of recommendations and willingness to discuss the topic of vaccination by the attending pediatrician is low [39]. The most important factors that contribute to the poor acceptance of HPVvaccinations are next:

- Parents do not accept that their child will soon be at risk of sexually transmitted diseases and want topostpone vaccination for later.
- Parents are worried due to manifestation of side effects of the applied vaccine.Parents do not understand why it is necessary to vaccinate boys.
- Parents think that non vaccinating of their children will not affect on others.
- Parents are not sure that benefits of the vaccine will outweigh the possible risks [40].

Pediatricians should use every opportunity to advise and emphasize the importance of this and as well as allvaccines that children should receive at school age with emphasis on the importance of age when vaccination is recommended.

Public easier accepts vaccination when instead of protection from a sexually transmitted disease is metioned the cancer prevention. It is especially important to cite examples from the environment of patients who have encountered with any type of cancer, as well as how it affects on the life of the patient□s family, what the life of a cancer patient looks like and the knowledge that there is now a possibility of preventing a certain type of cancer. In that sense, parents of patients should be educated about diseases (primarily cancers) that this vaccine prevents in adulthood and the importance of its use in the period of preadolescence - when the immune response is prompt and generous and there is no exposure to the virus, which is the best way to primary prevent. Despite the speech of the media and social networks, which are mostly negative, patients still trust the attending physician. For that reason, the education of health workers is most important for better communication with parents and adolescents [41].

Cervical Cancer Screening

The incidence of cervical cancer is decreasing thanks to organized screenings and increasingly developed preventive measures, mostly to the expense of squamous cell carcinoma. Cervical cancer screening aims to reduce morbidity and

mortality. It is important to start treatment on time with the most optimal therapeutic modality, in order to ensure longer survival, better disease control and quality of life [42]. Based on the European recommendations, which are also adopted by our country, it is envisaged that women aged from 20 to 30 years and women aged from 60 to 65 years will be covered by screening [43]. It should be performed the Papanicolaou test at every 3 years to 5 years. World Health Organization and European Guidelines for Quality Assurance for Cervical Cancer Screening suggest that the screening carried out mandatory and regularly in women between 39 and 49 years with indentified high−risk HPV subtypes, but also in women younger than 30 years, if there is a high grade squamous intraepithelial lesion−HSIL [44]. On the other hand, starting in 2014, the WHO proposes HPV testing at 3 to 5 years, colposcopy and analysis of cytological findings (Papanicolaou) at every 5 years. HPV typing is one of the basic screening tests . In case of a suspicious finding, the patient is referred for more detailed examinations, otherwise the next control is scheduled for 5 years. The WHO has developed a triple−intervention strategy to eradicate this tumor using scale−up vaccination, screening, treatment of precancerous changes, invasive cancers and palliative treatment in all countries until the year 2030 [44]. This should be potentially reduce the incidence of cervical cancer to 0.7 (0.6−1.6) / 100 000 women and mortality to 0.2 (0.2−0.5) / 100 000 women in 78 weak and middle−developed countries until the year 2120. Also, recommendations of US consensus are similar for treatment of abnormalities on cervix, which detecting by screening [45]. The goal of these strategies is increasing the availability of preventive vaccines and adequate HPV testing in underdeveloped countries. First generation preventive vaccines were bivalent and contained HPV 16 and 18 oncogenic subtypes, which are responsible for 70% of cervical cancers, while second generation vaccines were nine−valent and contained oncogenic subtypes of HPV virus, responsible for the occurrence of 90%of cervical cancers [45].

Pathophysiological Aspects of Premalignant Cervical Lesions

Premalignant changes of the cervix are most often identified during regular gynecological examinations or screening programs. They are defined on the basis of colposcopic and cytological findings [46]. Cervical intraepithelial neoplasia (CIN) represents a range of precancerous lesions from low to high grade. CIN−1 covers one−third of the height of the cervical epithelium and in more than 60% of cases is completely restituted during one year without treatment, thanks to a local immune response [47]. Higher grade changes of CIN−2 and CIN−3 affect two−thirds or the entire thickness of the epithelium and if left untreated progress to invasive cancer. Based on the Papanicolaou test, a diagnosis of low−grade squamous intraepithelial lesions (LSIL) includes CIN−1 is made [48]. High−grade squamous intraepithelial lesions (HSIL), which include CIN−2 and CIN−3 are diagnosed using the Papanicolaou test and often require colposcopic confirmation and biopsy. The existence of these changes requires more intensive monitoring and in a high percentage requires treatment [49]. Incomplete excision of precancerous changes occurs in 5 to 10% of cases. The risk of recurrent or residual CIN-2 is significantly increased if the resection edges are positive. HPV positivity after treatment is a more significant predictor of poor outcome than positive edge of resection. The incidence of cervical cancer is 39 ⁄ 100 000 women per year after precancerous treatment, which is three times higher risk compared to the general population [50]. Most intraepithelial and invasive cancers are defined as monoclonal, which supports the fact that there is an intraepithelial phase of the tumor, which precedes the formation of an invasive tumor. This observation contributed to the classification of cervical cancer as a group of “preventable tumors” When we talk about premalignant lesions of the cervix, we mostly think of lesions originating from squamous cells. Considerably less attention is paid to premalignant lesions of adenocarcinoma, which arises from endocervical gland cells [51]. Atypical glandular cells are found in about 0.1 to 2.1% Papanicolaou test samples. From 9% to 38% of women with this diagnosis have CIN−2, CIN−3 and adenocarcinoma in situ [52]. The endocervical epithelium shows

multistage precancerous changes, which begin in the form of endocervical dysplasia of low or high degree, reaching up to 2⁄3 of the height of the epithelium. The glands have an abnormal profile and irregular branching and budding [53]. Low−grade dysplasia represents a spectrum of changes that are by characteristics located between normal appearance and high−grade dysplasia [57].

If these changes persist for a long time, they later progress to adenocarcinoma in situ, which is rarely diagnosed in clinical practice, mainly in women aged between 39 and 46 years [51] .

Diagnostic Aspects of Cervical Cancer

The goal of all diagnostic procedures in discovery of cervical cancer is to detect the disease in the preinvasive phase, when the treatment options and treatment outcome are more favorable. The initial diagnosis begins with a clinical examination, which consists of inspection, palpation of the inguinal and supraclavicular lymph nodes, gynecological examination, bimanual rectal examination and the findings of laboratory analyzes [54]. Based on the examination in the preclinical phase of the disease, changes are not noticed on the cervix. The macroscopic appearance of the change depends on the origin and size of the tumor, the degree of necrosis and the mode of growth [55].

When the changes in the squamous epithelium become clinically visible during the gynecological examination, they are mostly already extended to the outer mouth of cervix. Infiltrative cancer causes enlargement, irregularity and hardening of the cervix and adjacent parametrium [55]. There are endophytic tumor growth in which the barrel enlargement of the cervix is characteristic and exophytic tumor growth in which the lession appears as a friable cauliflower outgrowth on the vaginal part of cervix. The exophytic type of cervical cancer grows outside the plane of the cervical epithelium as a soft papillary and polypoid formation of an irregular surface, which bleeds in contact. The endophytic type infiltrates the surrounding rather than the superficial structure and is characterized by a firm fibrous consistency,

while the cervix is completely retracted [54]. The necrotic type is characterized by massive necrosis with secondary infection and hemorrhage with destruction of the cervix and proximal part of the vagina. Premalignant and malignant changes on the cervix are most often manifested in the form of erosions or erythematous plaques, which are Lugol positive when performing the Sciller test. After coating all parts of the cervix, the inspection is performed under the colposcope with a magnification of 20 times [56]. Suspection lesions are worse stained, because the color binds weaker to the cells, which have less glycogen. The sensitivity and specificity of colposcopy increase, when applied with Papanicolaou and HPV tests. American Society of Colposcopy and Cervical Pathology suggests that colposcopy is mandatory in HPV−positive women with atypical squamous cell undetermined significance and low−grade squamous intraepithelial lesions or in a situation where there is more than a 4% probability of CIN−3+ [57]. It is possible to obtain positive cytological results even though there is a negative colposcopy finding [56]. A high risk of developing CIN−2 and CIN−3 corresponds to the characteristics of a positive cytological finding and does not always correspond to a colposcopic finding, which usually occurs in the presence of high−risk HPV genotypes [58]. HPV genotyping is performed in order to identify the HPV subtype, as well as to distinguish between low and high-risk subtypes. In clinically unclear cases, the examination is continued with targeted biopsy, conization and endocervical curettage [59]. In persons who have an increased risk of developing cervical cancer with a positive cytological finding, it is necessary to take tissue biopsies from all four quadrants of the cervix and make pathohistological verification of all clippings. Endocervical curettage is suggested for women over the age of 45 with HPV infection or women aged from 30 or more years with a highly squamous intraepithelial lesion, or when it is not possible to determine the exact nature of the lesion with certainty [59]. A biopsy is advised in all cases, when it is necessary to determine the nature of the changes in the cervix. It is recommended to be performed under the control of a colposcope. After a biopsy or curettage of the cervical canal, pathohistological and immunohistochemical analysis is required. Conization of the cervix is a diagnostic and

therapeutic procedure for HSIL and LSIL changes [60]. Conical excision of the cervix is performed by removing the lesion and the inside of the transformation zone with the help of a scalpel [59]. Indications for this procedure are CIN−2⁄3, carcinoma in situ and squamous cell carcinoma stage 1A1 in persons who have a desire to preserve fertility. In patients with an abnormal cytological finding, a deep excision of the large loop of the transformation zone can be conducted, which is performed with the help of a diathermy electrode with minimal damage to the surrounding tissue [61]. Liquid biopsy identifies free circulating cellular DNA, based on the detection of DNA of normal and tumor cells. The level of circulating DNA in plasma as a predictive factor may be related with the response to the applied treatment and may indicate on the further course of the disease. Annual testing of the presence of Human Papillomavirus DNA, during the first two years of follow−up may single out patients with higher risk from disease relaps. [62] Available tumor markers are not routinely analyzed, considering they are not specific for cervical cancer [63]. Squamous cellular carcinoma antigen (SCCAg) and carcinoembryonic antigen (CEA) markers are with the highest sensitivity, but are low specific [64]. Pre−therapeutic SCCAg levels correlate with disease stage, poorer prognosis and and tumor radioresistance, whereas a post−therapeutic jump in SCCAg levels may indicate disease relapse [65]. Septins which constitute the family of guanosine tri−phosphate binding proteins participate in the formation of the cytoskeleton, cellular division and tumorigenesis. Increased protein methylation has been confirmed in many tumors. It has been proven that hypermethylation of septin 9 with a high degree of sensitivity and specificity can indicate on the occurrence of cervical cancer [66]. Overexpression of this protein in the tumor indicates on the tumor radioresistance. Down−regulation of the SET−domain protein 3 affects on the occurrence of radioresistance, which adversely affects on the treatment outcome [67]. Ulceration is the primary manifestation of invasive cervical cancer. In the early phase, it is often superficial and similar to ectopia and chronic cervicitis. With the progress of the disease, the ulcer becomes deeper and necrotic with indured dilapidated edges, which are prone to bleeding [68]. Vaginal fornix can be affected by a pathological process. Then it

comes to the infiltration of the parametrium, which causes nodular thickening of the ligaments (sacrouterine and cardinal) and leads to the filtration of the cervix. Infection with Human Papilloma virus is considered a primary risk factor for cervical cancer [69]. Synchronous cancers localized in the area of the cervix, vagina, vulva and anal mucosa are also possible [4]. It is necessary to make a detailed examination of all the mentioned organs. Cervical lesions can be clinically reminiscent of other pathological processes such as: leiomyoma, cervical polyp, vaginitis, cervical erosion, cervicitis, abortion, herpetic cervicitis, chancre, uterine prolapse, polyp and like this. The bimanual gynecological process can be used for assessing the degree of involvement of the tumor process of the uterus and other structures inside the small pelvis. Bones, lymph nodes, ureters, bladder and rectum can be affected in the later stages of the disease [70].

Application of Sophisticated Visualization Diagnostic Methods

The introduction of new, more sophisticated diagnostic procedures has contributed to better diagnostics and individualization of treatment. The minimum initial diagnostic methods necessary for assessing the extent of the disease are two−way chest radiography, ultrasonography, computed tomography and magnetic resonance imaging ofthe abdomen and small pelvis [71]. Aditional diagnostic procedures include CT urology, intravenous urography or ultrasound examination of the kidneys, cystoscopy, rectosigmoidoscopy and CT of the chest. The application of all methods is based on defining of the presence and extensiveness of tumors, assessing the status of regional lymph nodes, evaluating of the therapeutic response and detecting disease recurrence [72]. The CT method with intravenous contrast helps to differentiate of healthy tissue from the field of necrosis and ulceration. Malignantly altered cervix is an enlarged hypointense zone with or without invasion of the proximal part of the vagina and parametrium. A superior method compared to CT is MRI, due to better contrast resolution and multiplanar possibilities for cervical analysis [73]. This method more precisely defines the outer edges of the tumor and the

presence of infiltration of the surrounding soft tissues and the status of the lymph nodes. The T2 sequence provides a detailed analysis of normal uterine and cervical anatomy, endocervical changes and gives the information about the extent of the disease. The altered cervix is characterized by an amplified signal on the sequence, which is limited by the surrounding stroma. MRI is reliable in detecting invasion of parametrium in 95% of cases [74]. Good resolution is a significant benefit, when it comes to delineation of residual tumor tissue. The possibilities of modern MRI devices can be used during the planning of transcutaneous radiotherapy (external beam radiotherapy) and 3D brachytherapy [71,75]. Cervical cancer is detected in the early stage with a sensitivity of 52%. For the local advanced stage of the disease, the sensitivity is significantly higher and amounts to 88%. Tumor growth on MRI may indicate on survival length and locoregional disease control. This high-sensitivity diagnostic modality can detect positive pelvic and paraaortic lymph nodes [76]. The use of positron−emission computed tomography with fluorodeoxyglucose (^{18}FDG−PET−CT) helps to differentiate the change based on increased aberrant glucose metabolism, which limits the tumor and the affected lymph nodes [77]. This method is more sensitive than CT (computed tomography) and MRI (magnetic resonance imaging). ^{18}FDG−PET−CT integrates anatomical and functional imaging [76]. The presence of metastases in the lymph nodes is one of the most important factors, which influences on the choice of the treatment and the prognosis of the disease. The positivity of lymph nodes is determined based on their diameter over 10 mm. In modern oncology, ^{18}FDG-PET-CT is of exceptional importance in radiotherapy planning, because it can single out the affected lymph nodes or distant metastases with high specificity [77]. ^{18}FDG may potentially indicate on the regions, where dose escalation is required during of the application of radiotherapy [71]. The latest recommendations of National Joint Cancer Network suggest the use of ^{18}FDG−PET−CT for monitoring cervical cancer patients according to PET criteria for assessing the response of solid tumors after treatment, given the reliability in differentiating of the locoregional or distant recurrence of the disease [77].

Differential Diagnosis

A number of lesions localized on the cervix can be replaced with cancer . Clinical conditions that cannot be ruled out are ectopia, chronic cervicitis, condyloma, cervical tuberculosis, ulceration in sexually transmitted diseases (syphilis, granuloma inguinale, lymphogranuloma venerum, soft ulcer), actinomycosis, abortion of cervical localized pregnancy, metastatic choriocarcinoma and other types of carcinoma. Hystological examination is usually sufficient in differentiation [30].

Biopsy

Histological analysis of a biopsy sample imoplies the change on cervix. It is the primary diagnostic procedure in the diagnosis of cervical cancer. The Papanicolaou test is used in screening on cervical cancer [78]. The sensitivity of this test ranges from 53% to 80% in the detection of high−grade lesions. Invasive cervical cancer exists in addition to the negative cytological fundings due to the appearance of abundant necrosis of malignant cells and the overlap of the sample with the inflammatory cells [31]. It is necessary to biopsy all suspected cervical lesions, regardless of the results of cytological analyzes. A biopsy, whether of Schiller positive areas, ulcerative parts, nodular or papillary lesions, allows diagnosis in most cases. Colposcopically guided biopsy and endocervical curettage or conization of the cervix may be indicated in cases where reports are qualified as suspicious or in the presence of invasive lesions and where the lesion is not clinically present. Colposcopic image indicates the existence of early invasive cancer and the presence of a distinctly irregular capillary networks [32].

Conization

In the case when the biopsy sample contains elements of cancer in situ and the presence of invasion cannot be ruled out, or in the case of negative colposcopic finding and a positive cytological finding, conization is indicated to determine the presence or absence of invasive lesion [31]. If the microinvasion (<3mm) is

determined in the biopsy sample, conization is necessary to determine the definitive depth of invasion [64]. The conical incisions must be marked by a pathologist, in order to determine the location and extent of the lesion and the relationship to the edges of the resection. Conization for lesions, which are observed macroscopically is not indicated. The diagnosis in such cases is almost always reliable in biopsy specimens [32].

The Clinical Image of Cervical Cancer

The initial phase of cervical cancer usually goes unnoticed, since the manifestations are usually discrete and nonspecific. Patients report to doctor, due to the appearance of abnormal bleeding, which can be postcoital, postmenstrual, irregular and continuous [79]. Chronic bleeding can last for years before visiting a doctor. It is often accompanied by severe weakness and anemia with the disturbed general condition of the organism. Fragile tumor blood vessels can easily cause heavy and persistent bleeding due to injury during sexual intercourse, during gynecological examination or spontaneousseparation of necrotic tumor mass [79]. Sometimes bleeding can be life−threatening. In the early stages of the disease, pain is a nonspecific symptom and patients attribute it to various other diseases and conditions. When pain occurs as a result of cervical tumor growth,it can progress to the hypogastrium, pelvis, lumbosacral or gluteal region. In the advanced stages of the disease, the tumor spreads from the cervix and parametria to neighboring organs, most often the bladder and rectum [80]. Patients will have dysuric problems that are often accompanied by hematuria, if the tumor infiltrates in the bladder. Lateral tumor growth causes urinary retention in the proximal parts of the urinary tract, due to obstruction of the ureter, which can progress to hydronephrosis of the kidney [80]. Infiltration by the rectum initiates the appearance of rectorage, which is accompanied by exhaustion, general weakness, cachexia or discomfort during defecation. The tumor of the cervix usually spreads first to the neighboring lateral parametriums by direct invasion through the loose connective tissue, so the regional lymph nodes are affected very quickly. The tumor can infiltrate the lymph nodes without affecting the parametrium. Across the obturator fascia, the spread can

continue towards the pelvic wall, the upper third and the vaults of the vagina, as well as towards the body of the uterus [81]. In advanced stages of the disease, the tumor directly infiltrates the wall of the bladder, rectum or sigmoid. The presence of distant metastases is most common in the iliac and paraaortic lymph nodes. By way of ductus thoracicus, metastases spread to the mediastinal and supraclavicular lymph nodes. After invading venous blood vessels, tumor cells travel to distant organs. In the metastatic phase of the disease, the most common metastatic foci are located on the brain, bones and lungs [82].

The Radiological Image of Cervical Cancer

Chest radiography is necessary in all patients in which diagnosed the cervical cancer. Also, intravenous pyelography (IVP) and computed tomography (CT) of the urinary tract are recommended to determine ureteral involvement [64]. Magnetic resonance imaging, computed tomography, lymphangiography, positron emission tomography (PET) scanning may indicate the spread of the tumor process inside the small pelvis and involvement of paraaortic lymph nodes, as well as other organs. The sensitivity of CT, MR and PET scanning in the detection of lymph node metastases ranges from 45%, 60% and 80%, respectively. Although, PET is not recommended in the clinical stage of the disease, it can be of great importance in treatment planning (scope of radiotherapy or radical surgical intervention) [31].

Pathohistological Classification of Cervical Cancer

In accordance with the WHO recommendations from 2014, malignant tumors of the cervix are divided into tumors originating from squamous epithelium, glandular epithelium and other types that are much rarer. The new classification was changed on the basis of immunohistochemical analyzes and integrated neuroendocrine tumors. Immunofluorescent and immunohistochemical staining are used for more precise sample analyzes [83]. Squamous cell subtypes make about 80% of all cervical tumors, but with the introduction of increasingly

high−quality prevention measures, their frequency is decreasing. Based on the degree of invasiveness, in situ cancer and early invasive cancer are distinguished. Unlike the WHO classification, which is based exclusively on the morphological characteristics of tumors, the New International Criteria for the Classification of Adenocarcinomas combine the etiology, biological nature and morphological image of the tumor [84]. Recently, the incidence of invasive adenocarcinoma has increased and ranges up to 25% of all cervical cancers. The main etiological factors for the development of this tumor are the use of contraceptives, but also HPV infection, which is variable represented and depends on the geographical region, tumor subtype and method of detection. The early stage of the disease is asymptomatic, when only an abnormal cytological finding can indicate on the changes in the glandular epithelium. Neuroendocrine tumors account for about 0.9 to 1.5% of all cervical tumors [85]. These tumors belong to the group of rare and aggressive tumors with an extremely poor prognosis. Manifestations of paraneoplastic syndrome are common (Cushing's syndrome, carcinoid syndrome, hypoglycemia and syndrome of inadequate secretion of antidiuretic hormone). The diagnosis is made on the basis of immunohistochemical analyzes and histological presentation. Tumors of mesenchymal origin are rarely diagnosedon the cervix. They are characterized by an extremely poor prognosis and therapeutic possibilities are limited. Secondary cancers occur in 1 to 2% cases of all cervical cancers. They most often occur as a consequence of the spread of tumors in the gynecological region per contimuitatem or metastasis of breast and lung cancer [4]. In Table 1 is shown the histological classification of malignant tumors of the cervix.

Table 1: Histological classification of malignant tumors of the cervix (WHO from 2014).

Histological type	Histological subtype
Epithelial tumors	**Squamocellular (keratinizing, non−keratinizing, basaloid, verrucous,papillary like lymphoepithelioma), Early invasive (microinvasive) squamocellular, Squamous cell carcinoma in situ**
Glandular tumors	**Adenocarcinoma (endocervical, intestinal and viloglandular, mucinous,endometroid, clear cell adenocarcinoma, mesonephric adenocarcinoma) Early invasive adenocarcinoma, in situ adenocarcinoma, other epithelial tumors (carcinoid of primary cervical origin, glassy cell carcinoma, cysticadenoidand basal cervical adenoid and basal cervical adenoid carcinoma) Neuroendocrine tumors (atypical cervical carcinoid, small cell carcinomaof the cervix, large cell neuroendcride carcinoma of the cervix) Undifferentiated cervical cancer**
Mesenchymal tumors	**Leiomyosarcoma, low−grade endometroidstromal angiosarcoma**
Mixed epithelial and mesenchymal tumors	**Carcinosarcoma (malignant Mullerian's mixed tumor, adenosarcoma, Wilms' tumor**
Lymphoid and hematopoietic tumors	**Malignant lymphoma and B−acute lymphoblastic leukemia presenting as a cervical malignancy**
Other tumors	**Tumors of germ cell origin**
Melanocyte tumors	**Primary cervical malignant melanoma**
Secondary tumors	**Metastases**

In Table 2 is shown the international criteria for classification of adenocarcinoma.

Table 2: International criteria for classification of adenocarcinoma.

HPV status of adenocarcinoma	Adenocarcinoma subtype
Endocervical adenocarcinoma associated with HPV	
Endocervical adenocarcinoma which is not associated with HPV	**Gastric type, clear cell, endometroid, mesonephric, miscellaneous and other non−specific types**

Clinical Stages of the Disease

Determining the clinical stage of the disease is important because of the prognosis and treatment plan. The clinical stage also provides data for comparing treatment methods for different stages of the disease in the world. The most commonly used staging system is the International Federation of Gynecology and Obstetrics (FIGO). Staging of the disease is performed by clinical examination of the bladder, ureter and intestines [86]. If the lesion is limited to the cervix, additional methods that are necessary in this case are chest radiography and assessment of the ureter (IVP or CT) and in these cases it is possible to determine the clinical stage of the disease. If it is possible to assess the local spread of the disease on an outpatient basis, it is necessary to perform an examination with the use of anesthesia using chitoscopy and rectoscopy. Significant information can be obtained by CT, MRI, lymphangiography, PET scan, which affect on the treatment plan. Before making a definitive decision on the therapeutic treatment of a change in the cervix, it is necessary to ensure a reliable diagnosis of the disease and the degree of its spread [86].

Criteria for Defining the Stage of the Disease

In previous decades, the extent of the disease was determined on the basis of a clinical examination. Today, the stage of the disease is assessed clinically, but also on the basis of diagnostic

visualization methods. The disease is staged according to the criteria of the VIII edition of Tumor−nodus−metastasis (TNM) and the classification of the International Federation of Gynecology and Obstetrics from 2018 [87]. Regardless of the fact that the therapeutic course and the prognosis of the disease are most often considered with the help of the FIGO classification, the stage of the disease should be determined in both ways [88]. Using the help of the new FIGO classification, the stages of the disease have been redefined and the attitudes about therapeutic options have been modified accordingly [89]. In the case of locally advanced cervical cancer, substages IIIC1 and IIIC2 were singled out within the third stage of the disease, which classify pelvic and paraaortic lymphadenopathy into special groups, which influences on the choice of the treatment [90]. Objections to the new way of staging relate to the neglect of the number and size of pathologically altered lymph nodes,because these parameters affect on the prognosis of the disease and the long−term survival of patients. Clinical examination with a high degree of certainty may indicate on the approximate size of the tumor, involvement of the parametrium and the lateral walls of the pelvis. In patients with the poor prognosis, more aggressive treatment is applied [90]. In Table 3 is shown the FIGO stages of cervical cancer from 2018.

Table 3: FIGO stages of cervical cancer from 2018.

Stages of the disease	Description
I	**The cancer is strictly limited on the cervix**
IA	**Invasive carcinoma that can only be diagnosed microscopically with a maximum depth of invasion < 5mm**
IA1	**Measured stromal invasion depth < 3mm**
IA2	**Measured stromal invasion depth ≥ 3 mm and □ 5 mm**
IB	**Invasive carcinoma depth of invasion ≥ 5 mm,lesion limited to the cervix**

IB1	**Invasive carcinoma ≥ 5 mm of stromal invasion depthand □ 2 cm in the largest dimensions**
IB2	**Invasive cancer ≥ 2 cm and □ 4 cm in the largestdimension**
IB3	**Invasive cancer ≥ 4 cm in the largest dimension**
II	**The cancer spreads outside the uterus, but does not affect the upper third of the vagina or the pelvic wall**
IIA	**Tumor spread is limited to the upper third of thevagina without spreading to the parametrium**
IIA1	**Invasive cancer □ 4 cm in the largest dimension**
IIA2	**Invasive cancer ≥ 4 cm in the largest dimension**
IIB	**Tumor affects the parametrium, but does not spread tothe pelvic wall**
III	**The cancer affects the lower third of the vagina with orwithout spreading to the pelvic wall with or without hydronephrosis or renal dysfunction and / or involvement of the pelvis and / or paraaortic lymphnodes**
IIIA	**The cancer affects the lower third of the vagina withspreading to the pelvic wall**
IIIB	**Spreading on the pelvic wall and/or hydronephrosis or renal dysfunction in the absence of another sample**
IIIC	**Involvement of pelvic and/or paraaortic lymph nodes,regardless of tumor size and extension**
IIIC1	**Presence of metastases in pelvic lymph nodes**
IIIC2	**Metastases in paraaortic lymph nodes**

IV	**The cancer spreads to the small pelvis or involves (as confirmed by biopsy) the mucosa of the bladder or rectum (bullous edema such as is not a criterion for theclassification of stage IV)**
IVA	**Spreading to pelvic organs**
IVB	**Spreading to distant organs**

If there is a doubt, a lower stage of the disease is assigned. Imaging and pathology can be used, if they are available, as supplement to clinical findings, given the size and extension of the tumor at all stages. Involvement of vascular / lymphatic spaces does not change the stage of the disease. Lateral extension of the lesion is not considered. If the imaging indicates metastases in the pelvic lymph nodes, the stage of the disease would be IIIC1r and if it is confirmed by pathological findings, it would be stage IIIC1p. The type of imaging modality or pathology technique must always be documented [90].

Methods of Treatment in IA1 and IA2 Stages of the Cervical Cancer

The basic treatment of IA1 stage of cervical cancer is surgery. In patients with IA1 stage and healthy margins at conization requires no further treatment. The decision on the type of the treatment is made on the basis of thepatient's desire to preserve fertility. Conization is applied in women with negative peritumoral lymphovascular invasion, which have a goal to preserve the fertility. The treatment is completed in the case of planocellular carcinoma and the top and edges of the cone are without histopathologically visible signs of a malignant lesion or atypia. Classifical (extrafascial) hysterectomy is performed in all other cases. Intracavitary radiotherapy is used when surgery is contraindicated [91]. If peritumoral lymphovascular invasion is present in IA1 stage of cervical cancer, conization or radical trachectomy with pelvic lymphadenectomy should be performed, if a woman wants to preserve fertility [91].

In all other cases, a modified radical hysterectomy with pelvic lymphadenectomy is used. Intracavitary radiotherapy is used when surgery is contraindicated. Postoperative radiotherapy (without concomitant chemotherapy) is applied from 3 to 5 weeks after surgery, if the regional lymph nodes are positive or there are other unfavorable prognostic factors [92].

The basic treatment of patients with IA2 stage of cervical cancer is surgical and necessarily includes lymphadenectomy. If the regional lymph nodes are positive or there are other unfavorable prognostic parameters, postoperative concomitant chemo−irradiation is applied from 3 to 5 weeks after the operation. In patients with IA2 stage of cervical cancer for whom surgery is contraindicated, radical external radiotherapy and brachytherapy are used [93]. Conization or radical trachelectomy with pelvic lymphadenectomy is performed in women with a confirmed stage of IA2 negative peritumoral lymphovascular invasion, if they want to preserve fertility. Modified radical hysterectomy with pelvic lymphadenectomy is applied in the case when it is not necessary to preserve fertility [93]. If peritumoral lymphovascular invasion is present in IA2 stage in women who want to preserve fertility, there is a risk of local recurrence, so their therapy must be individualized. A possible approach is radical trachelectomy with pelvic lymphadenectomy [94]. Radical trachectomy has evolved as an alternative to radical hysterectomy in carefully selected patients with early−stage of cervical cancer (IA2 or a small tumor in stage IB1), who want to preserve the reproductive function. After radical resection of cervix, a cerclage is placed and a therapeutic lymphadenectomy is performed [95].

There is insufficient evidence, that would be suggested the conization in these cases. Modified radical hysterectomy with pelvic lymphadenectomy is used in women who have completed the reproductive function. There is no consensus regarding conservative surgical therapy of microinvasive cervical adenocarcinoma. However, there is evidence that conization has the same oncological outcome as radical hysterectomy, so it can be considered as a possibility in cases where fertility is desired [95].

Locally Limited Invasive Cervical Cancer−Stages IB and IIA

It has been proven that both therapeutic modalities are equally effective. The goal of applying a certain type of treatment is achieving of the best success with a minimum complications. The combined application of radical surgery and radiation therapy results in high morbidity and high treatment costs. In order to achieve a reduction of morbidity, the planned application of surgical and radiation therapy should be If cervical cancer is not detected in the microinvasive phase, the invasion continues. The tumor spreads either extensively by infiltrating the endocervix (stage IB). According to the FIGO classification, stage IB is divided into two substages IB1 and IB2 in relation to the size of the local tumor, which is smaller or larger than 4 cm. The invasion can spread to the upper third of the vagina, when the tumor is classified as stage IIA. This stage is divided into two substages IIA1 and IIA2 (in stage IIA1 the tumor is smaller than 4 cm, while in stage IIA2 the tumor is larger than 4 cm). Stages IB and IIA of cervical cancer are considered locally limited disease, which can be primarily treated with surgery or radiation therapy [96]. Avoided in the primary phase of the treatment. In cases when the presence of unfavorable prognostic parameters (large tumor or unfavorable histological type of tumor) requires routine use of postoperative radiation, it is more rational to avoid radical hysterectomy and lymphadenectomy and apply radical radiation therapy or chemo-irradiation as the primary treatment [97]. The standard treatment of locally limited invasive cervical cancer is radical surgery intervention that involves:

- Hysterectomy with resection of parametrium (parametrectomy)− type III according to Piver classification,
- Bilateral salpingectomy with or without ovariectomy,
- Removal of the upper part of the vagina (at least 2 cm from the edge of the tumor),
- Lymphadenectomy of the small pelvic lymph nodes with recording of the anatomical localization of the node,
- In premenopausal women with small planocellular carcinoma (IB1), ovarian transposition and conservation can be performed [98].

Radical hysterectomy enables the excellent local control of the tumor, but on the other hand it is associated with significant morbidity. Most of the morbidity is caused by the removal of parametrium, which contains autonomic nerve fibers connected to the bladder, colon and sexual function. The benefits of parametrial resection in women with early stage of cervical cancer are under discussion [99]. Analysis of a large number of cases of small IA1 to IB1 tumors showed that parametrium involvement in small tumors (less than 2 cm with less than 10 mm depth of stroma invasion and without lymphovascular invasion) was only 0.4% −0.6% with a recurrence rate over 5 years of following between 0.7% and 4%. These data do not justify the radical parametrectomy in all patients with the early stage of the disease, because the number and severity of complications far outweigh risk of reccurence. The modern concept of surgery planning implies adjusting the size of the the surgical resection of the parametrium, which is considered acceptable and safe today. By comparing survival, relapse and morbidity between modified radical and radical hysterectomy (type II and type III according to Piver), it has been proven that both operations have same effects, but the radical hysterectomy is associated with a high rate of late complications [100]. Thus, the previous classification according to Piver was surpassed, so the surgical approach today is reffered to new classifications, from which the most accurate was given by Querle and Morrow [101]. In cases when radical parametrectomy is necessary, the goal is to preserve the innervations of the bladder, in order to avoid serious problems, which are related to the extent of radical hysterectomy. Based on studies conducted during the last ten years, it was concluded that early cervical cancer can be successfully treated with laparoscopically assisted vaginal hysterectomy with similar efficiency and recurrence rate as in abdominal radical hysterectomy [102]. The method of surgical treatment of stages IB and IIA of cervical cancer is radical hysterectomy with bilateral adnexectomy and removal of the pelvic lymph nodes (pelvic lymphadenectomy).

Radical surgery is suggested for stage IB1 of cervical cancer, unless there is a contraindications to surgery. In cases of small tumors (2 cm) and favorable prognostic parameters, modified

radical hysterectomy with pelvic lymphadenectomy may be considered [103]. In tumors larger than 4 cm (IB2), in order to reduce the morbidity, it is necessary to consider non−surgical treatment, because in these cases, adjuvant irradiation with or without chemotherapy is predicted after surgery. Laparoscopically assisted vaginal hysterectomy should not be performed in patients with a tumor larger than 2 cm [103]. This surgeon, which performs this procedure must be adequately educated. There is not agreement about the number of the lymph nodes, which should be removed during the pelvic lymphadenectomy. Good clinical practice involves removing as many nodes as possible. If the presence of unfavorable prognostic parameters is determined by histopathological examination after surgery, adjuvant radiation therapy or chemo−irradiation is applied. This therapy should be started from 3 to 5 weeks after surgery [104]. Combined modalities of oncological treatment lead to increased levels of complications, especially genitourinary and gastrointestinal [105]. They require a multidisciplinary approach to treatment and a careful assessment of a relative risks and benefits of treatment for each individual patient. If surgery is contraindicated, radical radiation therapy or competitive hemorrhage are used. Concomitant hemorrhage (Cis-platinum based) can be used instead of surgery in cases where preoperative assessment of prognostic parameters indicates that postoperative adjuvant therapy will be necessary [105]. In young patients, who require preservation of fertility, radical trachelectomy with pelvic lymphadenectomy may be considered, if the following conditions are met:

- Tumor type (squamous, adeno, adenosquamous),
- Tumor size <2 cm (IA, IB1),
- Desire to preserve the fertility,
- There was not previous infertility,
- Favorable colposcopic finding (R0, with healthy margins> 5 mm),
- Negative lymph nodes,
- The remaining length of the cervix is more than 1 cm,
- Age < 39 years [91].

Alternative treatment may be neoadjuvant chemotherapy with conization and pelvic lymphadenectomy, but in strictly selected cases and not as standard treatment. Women who require preservation of fertility should be informed about the potential risks of recurrence, as well as about the non−standard nature of trachelectomy. Surgical treatment of cervical cancer requires a good organization. Less complicated surgical techniques can be performed in secondary centers and highly specialized radical operations need to be centralized [106].

Recommendations for Adjuvant Therapy in Surgically Treated Stages IB and IIA

Postoperative radiotherapy should be started from 3 to 5 weeks after surgery. Radiotherapy should be used in patients who have undergone surgery and have negative lymph nodes and any of the following risk factors such as:

- Stromal invasion greater than a third,Lymphovascular invasion,
- Tumor diameter greater than 4 cm [107].

The use of concomitant radio−chemotherapy implies that the patient is in good general condition with neat laboratory analyzes and no serious associated diseases that could contribute to the greater toxicity of combination therapy [107]. If the definitive histopathological findings determine the presence of high risk factors for disease relapse, adjuvant therapy is applied, such as:

A / Postoperative radiation therapy−one of the following factors is sufficient:

- positive lymph nodes (from 1 to 3),
- negative lymph nodes, but high risk for recurrence,
- low-differentiated or undifferentiated tumor (G3),
- invasion of lymph and blood vessels,
- primary tumor larger than 3 cm in diameter,
- endocervical invasion (barrel−shaped cervix),
- if the above operation is incomplete,
- if the histopathological finding of all surgically removed parts is missing [108].

In the presence of several unfavorable prognostic factors, decisions are made by careful consideration of each individual case and therapy usually implies concomitant hemoradiation.

B / postoperative concomitant hemorrhage-sufficient one of the following factors:

- ✓ positive three or more lymph nodes,
- ✓ parametrium involvement,
- ✓ positive resection edges (positive surgical margin),
- ✓ rest tumors [105].

In cases not covered by the above conditions, and the finding in the lymph nodes is negative, adjuvant therapy should be applied according to the GOG scoring system to assess the clinical and pathological risk of recurrence. If the score is above 120 (relative risk of recurrence is 40% in the first three years for a score greater than 120), adjuvant radiotherapy should be used [109].

Recommendations for the Treatment of Stage IIB−IV of Cervical Cancer

Any patient with cervical cancer at whom radical radiotherapy is planned (locally advanced disease, stage IB2, high−risk early−stage disease or positive lymph nodes should have competitive chemoirradiation with platinum−based chemotherapy, if her general condition allows. The balance between benefits and risks must be weighed, before chemoirradiation is offered as a treatment for cervical cancer. Previous studies have not directly compared different cisplatin regimens [98]. Based on data about the toxicity from randomized controlled trials, cisplatin should be administered weekly at 40 mg / m^2. Patients who cannot receive chemotherapy due to their general condition or associated diseases (comorbidities) can only be treated with radiotherapy. Treatment at stage IIB may be combined radical radiation therapy, radical radiochemotherapy concomitantly, in the case of bilateral parametrium infiltration, CT verified enlarged lymph nodes of the pelvis (pelvic lymphadenopathy) and the size of the tumor on the cervix ≥ 5

cm. Treatment for stage IIIA and IIIB may be radical combined radiation therapy, radical radiochemotherapy concomitantly if it is bilateral parametrium infiltration, CT verified magnification of pelvic lymph nodes (pelvic lymphadenopathy) and the size of the tumor on the cervix ≥ 5 cm [98].

The therapy used in stage IVA is radical combined radiation therapy, radical radiochemotherapy concomitantly. The primary surgical therapy is applied at advanced cervical cancer in IVA stage. In cases of centrally localized tumor that led to vesicovaginal fistula, pelvic exenteration can be done according to strict indications and provided that the imaging of the pelvis, abdomen and chest excludes distant metastases. If there is a rectovaginal or vesicovaginal fistula, a colostomy or percutaneous nephrostomy can be placed with the continuation of specific oncological treatment. Therapy which is applied in IVB stage of cervical cancer is cisplatin as the most effective mono chemotherapy with a therapeutic response from 20% to 30% [98]. Chemotherapy can also be applied as a combined mode, whereby it used most often in combination with cisplatin and paclitaxel as systemic in the primary approach at metastases in viscelar and distant organs. Concomitant radiochemotherapy is used for isolated metastases in juxtaregional paraaortic lymph nodes. As therapy in stage IVB are used palliative radiation therapy (pelvic regions, bones, CNS, lymphadenopathy at unresectable solitary metastases due to antidolorous and hemostatic effects), palliative surgery and supportive or symptomatic therapy [98].

Recommendations for the Treatment of Recurrence/Relapse of Cervical Cancer

All relapses / recurrences must be discussed in detail by the Multidisciplinary Team (Council) for Gynecological Tumors. MR or CT examination of the abdomen, pelvis and chest must initially be performed in all patients with symptoms in order to determine exactly whether and where there is a recurrence / relapse of the disease. A PET scan or PET−CT should be performed in all patients with recurrent disease in whom the disease has been confirmed by MR or CT and salvage therapy is

planned, either pelvic exenteration or radiotherapy [110]. If the patient has not previously received radiotherapy, it can be used concomitant chemoradiotherapy or surgical treatment. Surgical resection or hemoirradiation may be considered in patients with limited value of local locoregional pelvic recurrence who do not perform the invasion of surrounding structures who have not previously received pelvic radiotherapy as part of initial treatment [110].

If the patient has previously received radiotherapy, surgery (hysterectomy with bilateral adnexectomy when the central recurrence is up to 2 cm or exenteration according to indications), re-irradiation and chemotherapy may be performed. Selection of patients for surgery is performed on the basis of PET or PET / CT scan with MR and CT, which confirms recurrent or persistent disease [111]. If there is an extrapelvic relapse, it can be used chemotherapy, palliative chemotherapy palliative surgery (isolated secondary deposits) ansd supportive or symptomatic therapy of the disease. Palliative chemotherapy is used in women with FIGO stage IVb or recurrent cervical cancer that are not candidates for curative hemorrhage, after discussing the possible benefits and risks. Recommended chemotherapy regimens are Cisplatin 50-100 mg / m^2 per day, every 3 weeks. When it is estimated that, due to the achievement of rapid control, it is symptomatic diseases, it is necessary to apply a combined regimen, the following combination are considered, such as Cisplatin 50 mg / m^2 per day Paclitaxel 135 mg / m^2 every three weeks [111].

Recommendations for the Treatment of Invasive Cervical Cancer in Pregnancy

Treatment of invasive cervical cancer during pregnancy as carried out, as well as the patient is not pregnant. Planning of treatment must be performed in collaboration with a perinatologist / obstetrician. The stage of the disease, the gestational age and the patient s desire to keep the pregnancy determine the type and time of treatment [112]. When cervical cancer is diagnosed in the first trimester of pregnancy, IA treatment must be done immediately. At microinvasive cancer

which diagnosed in pregnancy by conization, pregnancy can be extended until the term of vaginal delivery [113]. After giving birth is applied the definitive procedure according to the protocol. Cesarean section should not carry out, in the case when obstetric indications have not exist especially if the change is completely eliminated by conization.

Treatment in **I trimester** of pregnancy:

A) Surgical treatment: radical hysterectomy with pelvic lymphadenectomy along with pregnancy. Curettage abortion before surgery is not indicated. Adjuvant treatment is determined as well as outside pregnancy according to histopathological finding after surgery.
B) Inoperable stages (IIB, III, IV, in this category may be included large IB2 and IIA tumors), radical radiotherapy (radiation starts transcutaneously). Unless a miscarriage occurs within 2−5 weeks of starting radiation, the pregnancy is terminated surgically. After the end of the pregnancy, either by a miscarriage or by evacuation, the brachytherapy part of the radiation can be continued in the standard way [114].

II Trimester
Early II trimester of pregnancy (<20 weeks)

A) Operating stages (Ib and IIa)

- surgical treatment as in the first trimester
- adjuvant treatment as in the first trimester

B) Inoperable stages; (Ib2, II, III and IV)

- Radical air treatment as in the first trimester

Late II Trimester (> 20 weeks)

If there are conditions to wait for the maturity of the fetus (tumor less than 2cm, disease stage less than IIb and pregnancy older than 20 weeks) therapy may delay for 2 to 10 weeks without increasing the risk to the mother. Further procedure is same as in

the third trimester. In these cases, the application of neoadjuvant chemotherapy is considered [115].

III Trimester

A) Operating stages (IA and IIA)

Waiting for fetal maturity or inducing lung maturation in cooperation with perinatologist and then a classic (corporal) caesaren section is performed and the surgical approach is continued as in the first trimester. If it is necessary, adjuvant therapy is applied after the operation, according to the same standards as outside of pregnancy.

B) Inoperable stage: (IIb, III and IV, in this category may be included large Ib2 and IIa2 tumors) [116].

After the established maturity of the fetus, a classic (corporal) caesarean section is performed, followed by a radical radiation treatment 10 days to 2 weeks after the operation.

Postpartum period: The treatment is carried out as well as outside of pregnancy. If you have cervical cancer diagnosed at or after childbirth, regular colposcopy of the episiotomy site with or without biopsy is necessary during the first 2 years of childbirth [117].

Recommendations for Monitoring Patients with Treated Cervical Cancer

Anamnesis and clinical examination must be carried out during following of patients with cervical cancer to detect symptoms and asymptomatic recurrence. Patients should be educated about the symptoms and signs of relapse, because many of them get discomfort between scheduled controls. Follow−up after primary treatment should be done and coordinated by a doctor with experienced in the supervision of cancer patients [118]. Continuity of care and conversation can contribute to early recognition and detection of relapse. An acceptable strategy of control examination is every 3 months during the first 2 years and then every 6 months to 5 years from the end of therapy.

After 5 years, patients without signs of recurrence can be examined once a year with a anamnesis, general physical and pelvic examination with cervical / vaginal cytology [119]. The minimum examination includes anamnesis, complete physical examination, gynecological examination including Papanicolaou test. Symptoms to pay attention to are general status, lower back pain, part of the back, especially if it spreads to the leg, vaginal bleeding or unexplained weight loss. The physical examination should aim to detect abnormal findings associated with optimal health and / or those that indicate recurrence of the vagina, pelvic wall or distant recurrence. Central relapses are common curable and examination must include examination by speculum as well bimanual and pelvic / rectal examination [119].

MR or CT must initially be done in all cases, where exist symptoms to detect potential recurrence. Caring for quality of life presents a necessary part of the treatment of every patient with uterine cancer. In case of lower lymphedema extremities, it is necessary to provide specialized physical treatment. Doctors inevitably provide patients treated from cervical cancer psychologically supportive treatment as early as possible after treatment which include personalized information about the disease and treatment, assistance in psychosexual functioning, relaxation techniques and emotional support and care. Every patient treated from cervical cancer should be introduced in the National Registry for Cervical Cancer, which provides precise data about the method of previous treatment and monitoring the course of the disease [120].

The Prognosis of Cervical Cancer

The prognosis of the cervical cancer depends on the numerous factors that have the potential to indicate its outcome. Prognostic factors may be useful in selecting the appropriate choice of therapy. In everyday practice, their synergistic impact is evaluated and assessed individually. Prognostic factors depend on the individual characteristics of the patient, the parameters related to the tumor and stage of the disease, the applied therapeutic modalities and the presence or absence of certain biomarkers [105]. Numerous studies have examined the

importance of HPV status of patients in the domain of disease prognosis. In most cases, it has been proven that presence of HPV infection indicates a better prognosis. In a metaanalysis, Lee and coworkers established that the presence of HPV DNA in cervical cancer cell indicates a better prognosis with longer survival to disease progression and longer overall survival [121]. It is considered that HPV−negative cancers possess more aggressive mutations in the p53 tumor suppressor gene and higher metastatic potential. The prognosis of cervical cancer also depends on the type of HPV infection [122]. Thus, patients infected with the HPV−18 have a poorer prognosis and a higher recurrence rate as opposed to HPV−16 positives. Infection with HPV−16 or multiple HPV types is an indication of a poorer response to radiotherapy [63]. The immunogenicity of this tumor stems from persistent infection with high−risk HPV viral oncotypes. The local immune response to persistent HPV infection is a key determinant of carcinogenesis [123]. The role of the immune system in the development of cervical cancer is supported by the fact that the incidence of cervical dysplasia associated with HPV infection is significantly higher in immunosuppressed patients [124]. It has been confirmed that in healthy women, a strong response to E2 and E6 is associated with increased production of interferon □ and interleukin−5 in CD4+ T lymphocytes and regression of low−risk HPV infection has been attributed to CD4+ T lymphocyte activity in genital lesions [18]. However, in patients with cervical cancer, an inadequate response of T lymphocytes is observed, which is caused by reduced expression of the major histocompatibility complex (MHC) of class I molecules on tumor cells, which is necessary to trigger an immune response to malignantly transformed cells. Lymphocytes, present in the tumor milieu (tumor infiltrating lymphocytes) reflect the image of the body□s immune response. Namely the presence of cytotoxic (CD8+ T) and helper T (CD4+) lymphocytes correlates with longer survival, while the increased presence of T regulatory cells (Tregs) in the tumor epithelium creates immunosuppressive environment suitable for tumor development [18]. The formation of neoantigens, as a consequence of somatic mutations in tumor cells, induces the activation of cytotoxic T lymphocytes, but at the same time stimulates an immune system involving

suppressive mechanisms, which resultsin a reduced ability of the immune system to eliminate tumor cells [125]. Often, there is a predominance of Th2 subpopulation of lymphocytes in conjuction with a reduced Th1 cytokine, proinflammatory profile. Tumor cells cause Th2 polarization by IL−4 production and inhibition of IFN− production in effector T lymphocytes [126]. In the serum and tumor tissue of patients with cervical cancer, an increased concentration of IL-10 and transforming growth factor-β1 (transforming growth factor - TGF-β1) is detected, which increases with the evolution of the lesion, showing that the defective immune microenvironment may be induced by these immunosuppressive cytokines, or favor the persistence of HVP and the progression of cervical cancer [127]. An important factor in the adequate immune response and an important predictive indicator is the vascular system, which, in addition to delivering nutrients, also delivers cells of the immune system to the tumor microenvironment. Neoangiogenesis, stimulated by vascular endothelial growth factor-A (VEGF), angiopoietin-2 (ANGPT2) and fibroblast growth factor is associated with poorer survival [128]. Hypoxia−inducible factor−1α (HIF−1α) regulates growth, metastasis and angiogenesis via vascular endothelial growth factor−A. It also plays a role in increasing the tolerance of tumor tissue to hypoxia, which complicates access to immune cells, chemotherapeutics and affects on the poorer response of tumors to applied radiotherapy [129]. It has been observed that aberrant micro ribonucleic acid (miRNA) expression correlates with tumor aggressiveness, while decreased miR−877 expression is associated with higher FIGO stage of disease and nodal metastases. DNA methylation regulates miRNA, miR−375 and miR−196a−1 and the methylation status of promoters of various genes can affect on the disease prognosis. Poor regulation causes the pathophysiological progression of cervical cancer [130]. Also, poor regulation potentiates the pathophysiological progression of cervical cancer. A study by Xie et al indicates that hypermethylation of the CCDC136, ABCG2, CYP26A1, and TNNI3 genes is associated with longer overall survival (OS) [131]. The findings of standard laboratory analyzes may indicate a disease prognosis. It is known that anemia has an extremely bad effect on the long−term prognosis and reduces the five−year

progression−free survival (PFS) to 33.2%, if the hemoglobin level is below 12.5 g / dL. Pre-therapeutic lymphocyte counts and the presence of lymphopenia in the second week of treatment, as well as their relationship, may affect disease prognosis and survival [132]. Data from the literature show that pre-therapeutic neutrophil levels above 7 × 103 / mL are associated with a poorer prognosis, while elevated neutrophil levels in the initial week of chemotherapy and radiotherapy result in poorer locoregional disease control and decreased OS and RFS [133]. Elevated platelet pre-treatment levels have the same effect. High pre-therapeutic and post-therapeutic levels of C-reactive protein and lactic dehydrogenase (LDH) may be associated with poor OS. The prognosis of the cervical cancer is mostly related to the initially assessed stage of the disease. In addition, the prognosis of the disease is influenced by the pathohistological type and size of the tumor, histological and nuclear grade, involvement of parametrium and lymph nodes [134]. An independent predictor of poor outcome is a higher FIGO stage of the disease, especially IIIB, which correlates with poor general condition of the patient and a higher percentage of complications during treatment. The five−year survival of patients in II FIGO stage of the disease is 50 to 70% , while in stage III it ranges from 30 to 50%. Unlike previous, a recent study by Tian et al [135] indicates that there is no significant difference in survival of patients in adenocarcinoma or squamous cell carcinoma, but that survival depends on the FIGO stage, race, application of chemotherapy and external beam radiation therapy (EBRT) with brachytherapy [136]. Persistent lymphadenopathy stands out as an independent predictor of overall survival. Metastases in pelvic lymph nodes are present in 40% of patients. In the absence of pelvic lymphadenopathy, good regional control of thedisease is achieved in about 80% of cases. In the early stages of the disease without the presence of lymphadenopathy, the five−year survival of patients is over 90%, unlike patients with lymphadenopathy in whom it ranges from 25 to 50%. In a study by the Gynecologic Oncology Group has been proven that paraaortic and pelvic lymphadenopathy, tumor size and age of patients affect on the progression−free survival and overall survival in patients with locally advanced cervical cancer [137]. The identification of the influence of pelvic and

paraaortic lymphadenopathy on the prognosis of the disease and survival conditioned the changes in the FIGO classification from 2018. A recent study conducted in China indicates that survival is also affected by the number of positive lymph nodes, their volume and diameter [138]. Kim and co−workers are determined that a poor prognosis was associated with positive lymph node counts and squamous cell carcinoma antigen (SCC−Ag) pretherapy [139]. On the prognosis of the disease, in addition to the individual characteristics and general condition of the patient is significantly influenced by comorbidities. It has been established that the presence of diabetes mellitus and hyperinsulinemia may be correlated with a worse prognosis and shorter survival [140]. Age can be an extremely important prognostic factor. It has been shown that in elderly patients, the diagnosis is usually made, when the disease is already in an advanced stage and that due to age, poor general condition and the presence of comorbidities, patients are usually treated with less aggressive therapeutic modalities [4] Treatment is usually accompanied by a higher rate of complications. Older patients more often refuse the use of brachytherapy, which significantly affects on the outcome of treatment and overall survival [141]. By detailed analysis of prognostic factors, it is possible to single out patients who have an increased risk of complications during and after treatment, early disease progression and shorter survival. Separation of risk group requires a well−organized system of monitoring and control of patients. In order to more easily anticipate the prognosis and length of survival, within the Surveillance, Epidemiology, and End Results Program (SEER), nomogram systems have been developed that are based on socio-demographic, clinical, and parameters associated with tumor features and spreading of the disease can predict the length of three-year and five- year survival [142].

Conclusion

Cervical cancer is one of the most common malignancies. In patients with cervical cancer, the diagnosis shouldbegin with a anamnesis, gynecological and rectal bimanual examination, cytological examination of the cervical smear according to Papanicolaou, colposcopy, targeted biopsy and endocervical

curettage if necessary. Risk factors for the development of cervical cancer with their oncogenic potential act in the area of the transformation zone of the cervix, leading to a whole series of cellular and molecular events, which are the result of certain pathohistological changes, which pass through different degrees of dysplasia over time. In the normal squamous epithelium, mitosis takes place continuously in the parabasal layer, while in dysplastic cervical lesions the same mitotic activity takes place in the superficial layers with signs of cellular atypia. Dysplastic changes in the cervix represent the stages that precede the development of invasive cervical cancer, histologically they can be classified as follows:

- mild−grade cervical intraepithelial neoplasia (CIN1) - changes are diagnosed most often in the younger female population with a high incidence of spontaneous clinical regression of 60-70%, while about 10% may progress to CIN2 or CIN3,
- moderate−grade cervical intraepithelial neoplasia (CIN2) - can regress spontaneously, but there is a risk of progression to severe dysplasia or cancer. Approximately 22% of the changes may progress to CIN3,
- high−grade cervical intraepithelial neoplasia (CIN3) - may persist to a greater extent or progress to cancer- 12%.

The Bethesda cytological classification offers new terminology when it comes to dysplastic changes of the cervix.

- ❖ Low−grade squamous intraepithelial lesions that include planar condylomata and CIN1,High−grade squamous intraepithelial lesions including CIN2 and CIN3.

Given the significant degree of regression in mild dysplasia, ie CIN1, especially in younger women, this degree of dysplastic changes is usually only monitored. Moderate and severe degree of dysplasia are classified in the group of more severe squamous intraepithelial lesions, depending on the age of women, who are treated with ablative or excisional therapeutic techniques in order to remove the changes in the cervix. In the unfortunate sequence

of events, a high-grade squamous intraepithelial lesion develops into invasive cervical cancer. The mildest degree of invasion that can be identified only by microscopic examination is microinvasive cancer in which the depth of stromal invasion does not exceed 5 mm and is not wider than 7 mm. It is needed 8 to 10 years to progress severe dysplasias and in situ carcinoma to invasive cervical cancer. The symptoms associated with cervical cancer depend primarily on the stage of the disease. In the early stages when the disease is least widespread, the symptoms are very scarce or almost non-existent, so they do not warn of the presence of cervical cancer. The present symptomatology largely depends on the clinical form of cervical cancer. There are three forms:

- ✓ Exophytic form of the cervical cancer−most common, its starting point is the exocervix, so the cervix isenlarged with a visible change that is vulnerable and contact bleeds,
- ✓ Ulcerative shape of cervical cancer− cervix is altered in the form of a crater. It occurs the abundantsero−purulent hemorrhagic discharge with an unpleasant odor.
- ✓ Infiltrative shape of cervical cancer−cervix of the uterus is enlarged and firm, while the external uterinecervix is ulceratively altered, sometimes with an exophytic mass.

The first symptom that should arouse suspicion that it is cervical cancer is scanty, disturbing bloody discharge in combination with increased vaginal secretion of unpleasant odor. A typical anamnestic data obtained in a conversation with patients suffering from cervical cancer is painless bleeding, most often during and after sexual intercourse. This symptom is characteristic for exophytic tumors. With further tumor growth, bleeding episodes are more frequent and abundant, either in the form of intermenstrual bleeding or prolonged menstrual bleeding. If bleeding occurs during menopause, a large number of patients willcontact to their gynecologist and thus prevent further spread of the disease. Pain is a significant symptom, but it very rarely occurs in the initial stages of the disease. As the disease progresses and spreads to the iliac and paraaortic lymph glands, pain occurs in the lumbosacral and gluteal regions. Propagation of the disease towards the pelvic wall and

lumbosacral nerve endings leads to intense pain that transfers to the lower extremities. In advanced cases, hydronephrosis, malignant infiltration of the bladder and rectum can occur−when dysuric problems, hematuria, rectal bleeding and constipation.

In the terminal stage of cervical cancer, when the disease has affected the entire organism, some of the symptoms that occur are massive bleeding, severe anemia, uremia and cachexia. Cervical cancer can progress through direct spread to surrounding structures, lymphogenic spread and most rarely through hematogenous dissemination. The most common way of propagating cervical cancer is by direct spread−invasion into the lateral parametrium, which is favored by the unhindered penetration of the malignant tumor through the loose connective tissue. Lymph glands can also be affected, along the cervix itself or glands near the pelvic wall. From the area of lateral parametrium, the cancer can spread to the pelvic wall to the upper third of the vagina and fornix and it is also possible for the malignant process to propagate towards the body of the uterus. Infiltration of the bladder, rectum and sigmoid colon occurs in advanced stages of the disease and often results in the development of vesicovaginal or rectovaginal fistula. Lymphogenic metastasis usually first appear in the lymph glands of the parametrium, obturator pit, internal and external iliac lymph glands, as well as the sacral group of glands. With further progression of the disease, the lymph glands around the common iliac artery and paraaortic lymph gland are affected. In the final stage of the disease, metastasis can occur in the mediastinal and supraclavicular lymph glands. The risk from appearing of metastasis and spread of the disease is directly correlated with the size of the tumor, but it is not completely predictable, as evidenced by the fact that the lymph glands in the parametrial tissue and parauterine glands can be skipped, so the first metastasis can occur in the pelvic lymph glands. Hematogenous dissemination of cervical cancer occurs later and it is the rarest way of metastasis, and on that occasion the malignant process carries out the invasion on the venous pool or spreads by establishing anastomoses between the lymphatic and venous systems, giving metastasis to the liver, bones, lungs and brain.

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