MINISTRY OF EDUCATION AND SCIENCE OF UKRAINE

UZHHOROD NATIONAL UNIVERSITY

DEPARTMENT OF ONCOLOGY

Cancer of cervix

Methodical instructions for 5, 6-year medical students' individual training

Uzhhorod – 2023

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I.Topic actuality:

Cervical cancer is the second most commonly diagnosed cancer and the third leading cause of cancer death among females in less developed countries. There were an estimated 527 600 new cervical cancer cases and 265 700 deaths worldwide. Nearly 90% of cervical cancer deaths occurred in developing parts of the world. The large geographic variation in cervical cancer rates reflects differences in the availability of screening (which allows for the detection and removal of precancerous lesions) and in human papillomavirus (HPV) infection prevalence. The most significant cause of cervical cancer is persistent papillomavirus infection. HPV is detected in 99% of cervical tumors, particularly the oncogenic subtypes such as HPV 16 and 18.

For many years, the Papanicolaou (Pap) test has been the standard method for cervical cancer screening, reducing the incidence by 60%–90% and the death rate by 90%. However, the limitations of this cytology-based test are the sensitivity (> 50%) and significant proportion of inadequate specimens. More recently, an HPV test has been introduced as a screening tool as HPV deoxyribonucleic acid (DNA) is present in almost all cervical cancers and it has demonstrated higher sensitivity for high grade cervical intraepithelial neoplasia (CIN2þ) than that achieved by cytology in several studies. A pooled analysis of four randomized controlled trials of HPV-based cervical screening versus conventional cytology showed that HPV-based cervical screening provides 60%–70% greater protection against invasive cancer compared with cytology-based screening. Findings support HPV-based screening with triage at prolonged intervals, starting at age 30 year. Therefore, primary prevention of cervical cancer is now possible via immunization with highly efficacious HPV vaccines [II, A] and secondary prevention has gained impetus with the advent of sensitive HPV DNA testing to improve traditional Pap cytology screening programs [II, A].

II. Teaching aim:

2.1. The student must know:

Epidemiology, aetiology and risk factors of cervical cancer' developing, their classification, clinical presentation, modern methods of diagnosis and treatment.

2.2. The student should be able to:

Put clinical diagnosis, stage of disease, make a plan of examination and algorithm of treatment, differential diagnosis of different pathologies of cervix.

Assess prognosis of patient, prescribe follow-up and monitoring of patient.

III. Basic level of knowledge and skills:

- classification and presentation of benign and malignant tumors.
- Structure and function of gynecological organs in normal and pathological cases
- methods of diagnosis and workup of gynecological pathologies.

IV. The program of self-preparation of the students:

№	Task Maintenance	Task maintenance concrete definition
1.	Collecting history	• Risk factors and family history of suspected cancer of cervix. • Epidemiology. • Classification. • Common complains and presentation.
2	Work-up and treatment plan	• Physical examination. • Biopsy, molecular types of cancer of cervix. • Primary methods, modern methods of investigations. • Differential diagnosis of gynecological pathologies, metastatic work-up. • Staging of cancer of cervix • Primary prevention and treatment of different stages of cancer of cervix.

V. Short methodical instructions for practical study work.

The duration of practical classes is 2 academic hours. Classes are held in oncological clinic and consist of four structural parts: learning the theoretical part of the topic; demonstration of thematic patient; students' work on practical skills under the supervision of a teacher; solving of situation tasks and test control learning.

- After introductory teacher's word, control of the level of knowledge and skills of the students.
- The group carried out the individual educational tasks.
- Students conduct curation of patients in the oncogynecology department.

VI. Content of the topic

CANCER OF THE CERVIX

EPIDEMIOLOGY

The American Cancer Society estimated that, in the United States, in 2019, 12,820 new cases of invasive cervical cancer would be diagnosed and there would be 4,210 deaths due to cervical cancer, representing approximately 1.5% of all cancer deaths in women. In the United States and other developed countries, age-adjusted death rates from cervical cancer have declined steadily since the 1930s. This decrease is primarily the result of the adoption of routine screening programs, although the death rates from cervical cancer had begun to decrease before the implementation of Papanicolaou (Pap) screening, suggesting that other, unknown factors may have played some role. However, cervical cancer continues to be a major international public health problem—it is the fourth most common cancer in women worldwide, causing an estimated 260,000 deaths in 2018. International incidences of cervical cancer tend to reflect differences in cultural attitudes toward sexual practices and differences in the penetration of mass screening programs, with the highest incidences occurring in populations that have a high background prevalence of human papillomavirus (HPV) infection combined with low screening rates. These factors, combined with variations in access to effective treatments, result in large regional differences in cervical cancer mortality rates, ranging from less than 2 per 100,000 in western Asia, western Europe, and Australia to more than 20 per 100,000 in central America, Melanesia, and most parts of Africa. Differences in age-specific incidences between developed and medically underserved countries illustrate the probable impact of mass screening on the development of invasive disease. A comparison between data from Brazil and the United Kingdom showed similar rates of cervical cancer in young women, suggesting similar levels of

exposure to HPV, but rapidly diverging rates in older women, probably reflecting differences in the availability of mass screening in the two countries. Although the overall incidence of cervical cancer is low in the United States, the incidence in black Americans is about 30% higher than the incidence in white Americans, and the incidence in Hispanic women is about twice the incidence in white Americans. Barriers to cervical cancer screening, including lack of insurance, low income, and cultural factors, probably contribute to higher incidences and mortality rates in black and Hispanic women. The highest incidences tend to occur in populations that have low screening rates combined with a high background prevalence of human papilloma virus (HPV) infection and relatively liberal attitudes toward sexual behavior. Rates of invasive cervical cancer are particularly high in Latin America, southern and eastern Africa, India, and Polynesia; in many of these developing countries, cervical cancer is the leading cause of cancer deaths among women. Differences in age-specific incidences between developed and medically underserved countries illustrate the probable impact of mass screening on the development of invasive disease. For example, a comparison between data from Brazil and the United Kingdom showed similar rates of cervical cancer in young women, suggesting similar levels of exposure to HPV, but rapidly diverging rates in older women, probably reflecting differences in the availability of mass screening in the two countries. Although the overall incidence of cervical cancer is low in the United States, the incidence in black Americans is about 30% higher than the incidence in white Americans, and the incidence in Hispanic women is about twice the incidence in white Americans. Barriers to cervical cancer screening, including lack of insurance, low income, and cultural factors, probably contribute to higher incidences and mortality rates in black and Hispanic women.

ETIOLOGY, RISK FACTORS

Molecular and human epidemiologic studies have demonstrated a strong relationship between HPV, cervical intraepithelial neoplasia (CIN), and invasive carcinoma of the cervix. HPV can be identified in more than 99% of cervical cancers, and infection with HPV is now accepted as a necessary cause of most cervical cancers. It appears that most of the covariables historically associated with an increased risk of cervical cancer are surrogates for sexually transmitted HPV infection. Women who have coitus at a young age, who have multiple sexual partners, who have partners with multiple partners, or who bear children at a young age are at increased risk. A pooled analysis of 26 epidemiologic studies showed a strong inverse association between ever use of intrauterine devices (IUDs) and cervical cancer, perhaps due to a cellular immune response triggered by the device. In addition, circumcised males have a lower incidence of HPV

infection than uncircumcised males and a correspondingly lower incidence of cervical cancer in their female partners.

Risk factors

- HPV
- Use of intrauterine devices (IUDs)
- obesity - the larger the woman, the larger the risk
- high levels of estrogen
- endometrial hyperplasia
- hypertension
- polycystic ovary syndrome
- nulliparity (never having carried a pregnancy)
- infertility (inability to become pregnant)
- early menarche (onset of menstruation)
- late menopause (cessation of menstruation)
- endometrial polyps or other benign growths of the uterine lining
- diabetes
- Tamoxifen
- high intake of animal fat
- pelvic radiation therapy
- breast cancer
- ovarian cancer
- anovulatory cycles
- age over 35
- lack of exercise
- heavy daily alcohol consumption (possibly a risk factor)

Natural History

Most cervical carcinomas arise at the junction between the primarily columnar epithelium of the endocervix and the squamous epithelium of the ectocervix. This junction is a site of continuous metaplastic change, which is greatest in utero, at puberty, and during first pregnancy, and declines after menopause. Long before the relationship between HPV and cervical cancer was known, Richart and Barron 24 demonstrated that invasive squamous cell cancer of the cervix was the end result of progressive intraepithelial dysplastic changes within metaplastic epithelium of the transformation zone. The greatest risk of neoplastic transformation of virally induced atypical squamous metaplasia coincides with periods of greatest metaplastic activity. The

approximately 15-year difference in the mean ages of women with CIN and women with invasive cervical cancer suggests a generally slow progression of CIN to invasive carcinoma. Once tumor has broken through the basement membrane, it may penetrate the cervical stroma directly or through vascular channels. Invasive tumors may develop as exophytic growths protruding from the cervix into the vagina or as endocervical lesions that can cause massive expansion of the cervix despite a relatively normal appearing ectocervix. From the cervix, tumor may infiltrate superiorly to the lower uterine segment, inferiorly to the vagina, laterally to the broad ligaments (where it may cause ureteral obstruction), or posterio-laterally to the uterosacral ligaments. Large tumors may seem fixed on pelvic examination, although true invasion of the pelvic wall musculature is uncommon. Although the cervix is separated from the bladder by only a thin layer of fascia and cellular connective tissue, extensive bladder involvement is uncommon, occurring in fewer than 5% of cases. Tumor may also extend posteriorly to the rectum, although rectal mucosal involvement is a rare finding at initial presentation. The cervix has a rich supply of lymphatics that drain the mucosal, muscularis, and serosal layers. The lymphatics of the cervix anastomose extensively with those of the lower uterine segment. The most important lymphatic collecting trunks exit laterally from the uterine isthmus in three groups. The upper branches, which originate in the anterior and lateral cervix, follow the uterine artery, are sometimes interrupted by a node as they cross the ureter, and terminate in the uppermost hypogastric nodes just distal to the point where the common iliac veins bifurcate to form the external and internal iliac veins. The middle branches drain to deeper hypogastric (obturator) nodes. The lowest branches follow a posterior course to the inferior and superior gluteal, common iliac, presacral, and subaortic nodes, although direct spread to these sites is relatively uncommon. Massive tumors, particularly those that involve the rectovaginal septum or cul-de-sac can metastasize directly to the inguinal lymph nodes.

PATHOLOGY

Cervical Intraepithelial Neoplasia

Several systems have been developed for classifying cervical cytologic findings. Although criteria for the diagnosis of CIN and degree of neoplasia vary somewhat between pathologists, the important features of CIN are cellular immaturity, cellular disorganization, nuclear abnormalities, and increased mitotic activity. If mitoses and immature cells are present only in the lower third of the epithelium, the lesion is usually designated CIN. Lesions involving only the lower and middle thirds are designated CIN2, and those involving the upper third are designated CIN3. The term cervical intraepithelial neoplasia, as proposed by Richart,21 refers only to a lesion that may progress to invasive carcinoma. Although CIN 1 and CIN 2 are

sometimes referred to as mild-to-moderate dysplasia, the term CIN is now preferred over dysplasia.

Adenocarcinoma in Situ

Adenocarcinoma in situ is diagnosed when normal endocervical gland cells are replaced by tall, irregular columnar cells with stratified, hyperchromatic nuclei and increased mitotic activity but the normal branching pattern of the endocervical glands is maintained and there is no obvious stromal invasion. About 20% to 50% of women with cervical adenocarcinoma in situ also have squamous CIN. Because adenocarcinoma in situ is frequently multifocal, cone biopsy margins are unreliable. Although some investigators have described a possible precursor lesion termed endocervical glandular dysplasia, the reproducibility and clinical value of this designation are uncertain.

Microinvasive Carcinoma

Microinvasive carcinoma is defined by International Federation of Gynecology and Obstetrics (FIGO) as invasive carcinoma which can be diagnosed only by microscopy, with deepest invasion $\leq$5 mm and largest extension $\geq$7 mm. Thus, this diagnosis can be made only after examination of a specimen that includes the entire neoplastic lesion and cervical transformation zone. This requires a cervical cone biopsy. Following the advent of cytologic screening, the proportion of invasive carcinomas that invade less than 5 mm increased more than tenfold to about 20% in the United States.

The earliest invasion appears as a blurring of the stromo-epithelial junction with a protrusion of cells into the stroma; these cells are less well differentiated than the adjacent noninvasive cells; have abundant pink-staining cytoplasm, hyperchromatic nuclei, and prominent nucleoli; they also exhibit a loss of polarity at the stromo-epithelial junction. Early microinvasion is usually characterized by a desmoplastic response in adjacent stroma with scalloping or duplication of the neoplastic epithelium or formation of pseudo glands (nests of invasive carcinoma that can mimic crypt involvement). In a study of cone specimens, Reich et al. reported that 12% of microinvasive carcinomas were multifocal. The depth of invasion should be measured with a micrometer from the base of the epithelium to the deepest point of invasion. Lesions that have invaded less than 3 mm (FIGO stage IA1) are rarely associated with metastases; 5% to 10% of tumors that have invaded 3 to 5 mm (FIGO stage IA2) are associated with positive pelvic lymph nodes.

Until FIGO refined its definition of microinvasive carcinoma, most clinicians in the United States used a different definition of microinvasive carcinoma formulated by the Society of Gynecologic Oncologists: cancers that invaded less than 3 mm with no evidence of LVSI. The importance of LVSI remains somewhat controversial; the risk of metastatic regional disease appears to be exceedingly low for any tumor that invades less than 3 mm, even in the presence of LVSI. Although most clinicians have adopted the FIGO definitions, many think that the risk of regional spread from tumors that have invaded 3 to 5 mm is sufficiently high to warrant treatment of the parametria and regional nodes.

Invasive Squamous Cell Carcinoma

Between 80% and 90% of cervical carcinomas are squamous cell carcinomas. Although squamous neoplasms are often subclassified as large cell keratinizing, large cell nonkeratinizing, or small cell carcinomas, these designations do not correlate well with prognosis. Small cell squamous carcinomas have small to medium-sized nuclei, open chromatin, small or large nucleoli, and abundant cytoplasm and are believed by most authorities to have a somewhat poorer prognosis than large cell neoplasms with or without keratin.

Papillary variants of squamous carcinoma may be well differentiated (occasionally confused with immature condyloma) or very poorly differentiated (resembling high-grade transitional carcinoma). Verrucous carcinoma is a very rare warty-appearing variant of squamous carcinoma that may be difficult to differentiate from benign condyloma without multiple biopsies or hysterectomy. Sarcomatous squamous carcinoma is another very rare variant, demonstrating areas of spindle-cell carcinomatous tumor confluent with poorly differentiated squamous cell carcinoma; immunohistochemistry demonstrates expression of cytokeratin as well as vimentin. The natural history of this uncommon tumor is not well understood.

Adenocarcinoma

Invasive adenocarcinoma may be pure or mixed with squamous cell carcinoma (adenosquamous carcinoma). About 80% of cervical adenocarcinomas are endocervical-type adenocarcinomas, which are composed predominantly of cells with eosinophilic cytoplasm, brisk mitotic activity, and frequent apoptotic bodies, although many other patterns and cell types have also been observed. Endocervical type adenocarcinomas are frequently referred to as mucinous; however, although some have abundant intracytoplasmic mucin, most have little or none.

Minimal-deviation adenocarcinoma (adenoma malignum) is a rare, extremely well-differentiated adenocarcinoma that is sometimes associated with Peutz-Jeghers syndrome.38 Because the branching glandular pattern strongly resembles normal

endocervical glands and the mucin-rich cells can be deceptively benign-appearing, minimal-deviation adenocarcinoma may not be recognized as malignant in small biopsy specimens. Earlier studies reported a poor outcome for women with this tumor, but more recently, patients have been reported to have a favorable prognosis if the disease is detected early. Glassy cell carcinoma is a variant of poorly differentiated adenosquamous carcinoma characterized by cells with abundant eosinophilic, granular, ground-glass cytoplasm with large round to oval nuclei and prominent nucleoli. Adenoid basal carcinoma is a well-differentiated tumor that histologically resembles basal cell carcinoma of the skin and tends to have a favorable prognosis. Adenoid cystic carcinoma consists of basaloid cells in a cribriform or cylindroma to us pattern; metastases are frequent, although the natural history of these tumors may be long.

Rarely, primary carcinomas of the cervix are composed of endometrioid, serous, or clear cells; mixtures of these cell types may be seen, and histologically, some of these tumors are indistinguishable from those arising elsewhere in the endometrium or ovary. In a study of 17 cases, Zhou et al. found that serous carcinomas of the cervix have an aggressive course, similar to that of high-grade serous tumors originating in the other miillerian sites.

Anaplastic Small Cell/Neuroendocrine Carcinoma

Anaplastic small cell carcinomas resemble small cell carcinomas of the lung and are made up of small tumor cells that have scanty cytoplasm, small round to oval nuclei, and high mitotic activity; they frequently display neuroendocrine features. Anaplastic small cell carcinomas behave more aggressively than poorly differentiated small cell squamous carcinomas; most investigators report survival rates of less than 50% even for patients with early stage I disease, although recent studies of aggressive multimodality treatments have been somewhat more encouraging. Widespread hematogenous metastases are frequent, but brain metastases are rare unless preceded by pulmonary involvement.

Other Rare Neoplasms

A variety of neoplasms may infiltrate the cervix from adjacent sites, and this makes differential diagnosis difficult. In particular, it may be difficult or impossible to determine the origin of adenocarcinomas involving the endocervix and uterine isthmus. Although endometrioid histology suggests endometrial origin and mucinous tumors in young patients are most often of endocervical origin, both histologic types can arise in either site. Metastatic tumors from the colon, breast, or other sites may involve the cervix secondarily. Malignant mixed miillerian tumors, adenosarcomas, and leiomyosarcomas occasionally arise in the cervix but more often involve it secondarily. Primary lymphomas and melanomas of the cervix are extremely rare

CLINICAL PRESENTATION

Preinvasive disease is usually detected during routine cervical cytologic screening. Early invasive disease may not be associated with any symptoms and is also usually detected during screening examinations. The earliest symptom of invasive cervical cancer is usually abnormal vaginal bleeding, often following coitus or vaginal douching. This may be associated with a clear or foul-smelling vaginal discharge. Pelvic pain may result from locoregionally invasive disease or from coexistent pelvic inflammatory disease. Flank pain may be a symptom of hydronephrosis, often complicated by pyelonephritis. Patients with very advanced tumors may have hematuria or incontinence from a vesicovaginal fistula caused by direct extension of tumor to the bladder. External compression of the rectum by a massive primary tumor may cause constipation, but the rectal mucosa is rarely involved at initial diagnosis.

DIAGNOSTICS AND SCREENING

The long preinvasive stage of cervical cancer, the relatively high prevalence of the disease in unscreened populations, and the sensitivity of cytologic screening make cervical carcinoma an ideal target for cancer screening.

In the United States, screening with cervical cytologic examination and pelvic examination has led to a decrease of more than 50% in the incidence of cervical cancer since 1975. Only nations with well-developed screening programs have experienced substantial decreases in cervical cancer incidence.

Citing a large body of data on screening effectiveness, the American College of Obstetrics and Gynecology recently updated their guidelines for cervical cancer screening. The guidelines are as follows

- Screening is recommended to begin at age 21 years; screening should be avoided before this age because it may lead to unnecessary and harmful evaluation and treatment in women at very low risk of cancer. For patients in this young age group, the emphasis should be on HPV vaccination.
- Between ages 21 and 29 years, Pap tests are recommended every 3 years; because of the high prevalence of transient, benign HPV infections in women aged younger than 30 years, HPV testing is not recommended for this group.
- Because for women between ages 30 and 65 years, a single negative test for HPV has been demonstrated to be sufficient to reassure against cervical cancer for 5 years, women in this age group are recommended to have both Pap and HPV testing every 5 years. If a Pap test has been performed without HPV testing, the patient should be rescreened in 3

years. Women with a normal Pap test result who test positive for oncogenic HPV should be rescreened annually.

- Epidemiologic studies indicate that the 5-year screening interval may also be recommended for HIV-infected women who have a negative Pap and HPV test; these patients do not appear to have a higher cumulative incidence of HSIL and CIN 2 than HIV-negative women with negative screening studies.
- Women who have had a total hysterectomy for benign conditions and who have no history of high-grade CIN may discontinue routine screening. It is also reasonable to discontinue screening for women older than ages 65 to 70 years who have three or more consecutive negative studies and have had no abnormal test results in the past 10 years. Women previously treated for high-grade CIN or for cancer should continue to have annual screening for at least 20 years and periodic screening indefinitely. Annual gynecologic examination may still be appropriate even if cytologic screening is not performed.

Accurate calculation of false-negative rates for the Pap test is difficult; estimates range from less than 5% to 20% or more. The sensitivity of individual tests may be improved by ensuring adequate sampling of the squamocolumnar junction and the endocervical canal; smears without endocervical or metaplastic cells are inadequate, and in such cases the test must be repeated.

The sensitivity of a screening program is increased by repeated testing; studies of the test frequency required to optimize the sensitivity of screening formed the basis of the American College of Obstetrics and Gynecology recommendations.

Most United States gynecologists currently prefer newer liquid-based screening methods to conventional Pap tests. However, the authors of a recent meta-analysis of available data concluded that "liquid-based cervical cytology is neither more sensitive nor more specific for detection of high-grade CIN compared with the conventional Pap. Liquid-based tests are more costly but have the potential advantage that additional studies, such as HPV typing, can be performed on the fluid remaining after cytologic examination. HPV testing of ASC-US smears followed by colposcopy in patients with HPV-positive lesions has been shown to be a highly accurate and cost-effective means of detecting HSIL in cases of equivocal smears and may also be used to triage postmenopausal women with LSIL.

Patients with abnormal findings on cytologic examination who do not have a gross cervical lesion must be evaluated with colposcopy and directed biopsies.

Following application of a 3% acetic-acid solution, the cervix is examined under 10- to 15-fold magnification with a bright, filtered light that enhances the aceto-whitening and vascular patterns characteristic of dysplasia or carcinoma. The skilled colposcopist can accurately distinguish

between low- and high-grade dysplasia, but microinvasive disease cannot consistently be distinguished from intraepithelial lesions on colposcopy. In patients with a high-grade Pap smear finding, if no abnormalities are found on colposcopy examination or if the entire squamocolumnar junction cannot be visualized, an additional endocervical sample should be collected. Although some authorities advocate the routine addition of endocervical curettage to colposcopy examination, it is probably reasonable to omit this step i n previously untreated women if the entire squamocolumnar junction is visible with a complete ring of unaltered columnar epithelium in the lower canal. The rate of detection of endocervical lesions may be higher when specimens are collected using a cytobrush rather than by curettage. Cervical cone biopsy is used to diagnose occult endocervical lesions and is an essential step in the diagnosis and management of microinvasive carcinoma of the cervix. Cervical cone biopsy yields an accurate diagnosis and decreases the incidence of inappropriate therapy when

(1) the squamocolumnar junction is poorly visualized on colposcopy and a high-grade lesion is suspected,

(2) high-grade dysplastic epithelium extends into the endocervical canal,

(3) the cytologic findings suggest high-grade dysplasia or carcinoma in situ,

(4) a microinvasive carcinoma is found on directed biopsy,

(5) the endocervical curettage specimens show high-grade CIN, or

(6) the cytologic findings are suggestive of adenocarcinoma in situ.

Histopathological evaluation

- Dimensions of the tumor.
- Stromal invasion/depth of the wall involved.
- Tumor differentiation.
- Lymphovascular space invasion.
- Status of resection margins.
- Status of parametria and vaginal cuff.
- Number and status of lymph nodes.

TNM-CLASSIFICATION

Endometrial carcinoma is surgically staged using the FIGO cancer staging system.
Following are presented two stage systems in comparing.

T – Primary Tumor

Table 1: TNM vs FIGO staging.

TNM Categories	FIGO Stages	
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
Tis	1	Carcinoma in situ (preinvasive carcinoma)
T1	I	Tumor confined to the cervix (extension to corpus should be disregarded)
T1a2	IA	Invasive carcinoma diagnosed only by microscopy. Stromal invasion with a maximal depth of 5.0 mm measured from the base of the epithelium and a horizontal spread of 7.0 mm or less3
T1a1	IA1	Measured stromal invasion 3.0 mm or less in depth and 7.0 mm or less in horizontal spread
T1a2	IA2	Measured stromal invasion more than 3.0 mm and not more than 5.0 mm with a horizontal spread of 7.0 mm or less
T1b	IB	Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a/IA2
T1b1	IB1	Clinically visible lesion 4.0 cm or less in greatest dimension
T1b2	IB2	Clinically visible lesion more than 4.0 cm in greatest dimension
T2	II	Tumor invades beyond uterus but not to pelvic wall or to lower third of vagina
T2a	IIA	Tumor without parametrial invasion
T2a1	IIA1	Clinically visible lesion 4.0 cm or less in greatest dimension
T2a2	IIA2	Clinically visible lesion more than 4.0 cm in greatest dimension
T2b	IIB	Tumor with parametrial invasion
T3	III	Tumor extends to pelvic wall, involves lower third of vagina, causes hydronephrosis or non-functioning kidney
T3a	IIIA	Tumor involves lower third of vagina
T3b	IIIB	Tumor extends to pelvic wall, causes hydronephrosis or nonfunctioning kidney
T4	IVA	Tumor invades mucosa of the bladder or rectum, or extends beyond true pelvis 4,5

Note: The depth of invasion should be taken from the base of the epithelium, either surface or glandular, from which it originates. The depth of invasion is defined as the measurement of the tumor from the epithelial-stromal junction of the adjacent most superficial papillae to the deepest point of invasion. Vascular space involvement, venous or lymphatic, does not affect classification.

Notes:

1 FIGO no longer includes Stage 0 (Tis).

2 All macroscopically visible lesions even with superficial invasion are T1b/IB.

3 Vascular space involvement, venous or lymphatic, does not affect classification.

4 Bullous edemas are not sufficient to classify a tumor as T4.

5 Invasion of bladder or rectal mucosa should be biopsy proven according to FIGO.

N – Regional lymph nodes

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Regional lymph node metastasis

M – Distant Metastasis

M0 No distant metastasis

M1 Distant metastasis (includes inguinal lymph nodes and intraperitoneal disease except metastasis to pelvic serosa).

It excludes metastasis to vagina, pelvic serosa, and adnexa.

Staging

Table 2: staging

Stage	T	N	M
0*	Tis	N0	M0
I	T1	N0	M0
IA	T1a	N0	M0
IA1	T1a1	N0	M0
IA2	T1a2	N0	M0

IB	T1b	N0	M0
IB1	T1b1	N0	M0
IB2	T1b2	N0	M0
II	T2	N0	M0
IIA	T2a	N0	M0
IIA1	T2a1	N0	M0
IIA2	T2a2	N0	M0
IIB	T2b	N0	M0
III	T3	N0	M0
IIIA	T3a	N0	M0
IIIB	T3b	Any N	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
IVA	T4	Any N	M0
IVB	Any T	Any N	M1

TREATMENT

A number of factors may influence the choice of local treatment for cervical cancer, including tumor size, stage, histologic features, evidence of lymph node metastasis, risk factors for complications of surgery or radiotherapy, and patient preference. However, as a rule, HSILs are managed with a loop electro excision procedure (LEEP); microinvasive cancers invading less than 3 mm (stage IA1) are managed with conservative surgery (excisional conization or extra fascial hysterectomy) ; early invasive cancers (stage IA2 and IB1 and some small stage IIA tumors) are managed with radical or modified radical hysterectomy, radical trachelectomy (if fertility preservation is desired), or radiotherapy; and locally advanced cancers (stages IB2 through IVA) are managed with combined chemotherapy and radiotherapy.

Selected patients with centrally recurrent disease after maximum radiotherapy may be treated with radical exenterative surgery; isolated pelvic recurrence after hysterectomy is treated with irradiation.

<u>Preinvasive Disease</u>

LEEP is the preferred treatment for HSIL. With this technique, a charged electrode is used to excise the entire transformation zone and distal canal. Although control rates are similar to those achieved with cryotherapy or laser ablation, LEEP is more easily learned, is less expensive than laser ablation, and preserves the excised lesion and transformation zone for histologic evaluation. LEEP is an outpatient procedure that preserves fertility. LEEP conization or excisional conization with a scalpel should be performed when microinvasive or invasive cancer is suspected and in patients with adenocarcinoma in situ. Although recurrence rates are low (1% to 5%) and progression to invasion rare (less than 1% in most series), patients treated with LEEP require careful post-LEEP surveillance.

Treatment with total hysterectomy currently is reserved for women who have other gynecologic conditions that justify the procedure; invasive cancer still must be excluded before surgery to rule out the need for a more extensive operative procedure.

Microinvasive Carcinoma (Stage lA)

The standard treatment for patients with stage IA1 disease is cervical conization or total (type I) hysterectomy. Because the risk of pelvic lymph node metastases from these minimally invasive tumors is less than 1%, pelvic lymphadenectomy is not usually recommended. Patients who have FIGO stage IA1 disease without LVSI and who wish to maintain fertility may be adequately treated with a therapeutic cervical conization if the margins of the cone are negative.

Although reports suggest that recurrences are infrequent, patients who have this conservative treatment must be followed very closely with periodic cytologic evaluation, colposcopy, and endocervical curettage.

The likelihood of residual invasive disease after cone biopsy is correlated with the status of the internal cone margin and the results of an endocervical curettage performed after cone biopsy. Roman et al. reported the surgical findings in 87 patients who underwent a conization that showed microinvasive squamous carcinoma, followed by either a repeat conization or hysterectomy. Residual invasive disease was present in only 4% of patients whose cone margins were free of CIN and who had no disease detected on endocervical curettage.

However, residual invasive disease was present in 13% of women who had either CIN in cone margins or positive endocervical curettage findings and 33% of women who had both of these features ($P<.015$), suggesting the need for a second procedure in any patient who has one of these findings.

The authors did not find any correlation between the depth of invasion or the number of invasive foci and residual invasive disease.

Therapeutic conization for microinvasive disease is usually performed with a scalpel while the patient is under general or spinal anesthesia. Because an accurate assessment of the maximum depth of invasion is critical, the entire specimen must be sectioned and carefully handled to maintain its original orientation for microscopic assessment. Complications occur in 2% to 12% of patients, are related to the depth of the cone, and include hemorrhage, sepsis, infertility, stenosis, and cervical incompetence. The width and depth of the cone should be tailored to produce the least amount of injury while providing clear surgical margins.

For patients whose tumors invade 3 to 5 mm into the stroma (FIGO stage IA2), the risk of nodal metastases is approximately 5%. Therefore, in such patients, bilateral pelvic lymphadenectomy should be performed in conjunction with modified radical (type II) hysterectomy. Modified radical hysterectomy is a less extensive procedure than classic radical (type III) hysterectomy. The uterus, cervix, upper vagina, and paracervical tissues are removed after careful dissection of the ureters to the point of their entry to the bladder.

The medial halves of the cardinal ligament and the uterosacral ligaments are also removed. With this treatment, significant urinary tract complications are rare, and cure rates exceed 95%.

Although surgical treatment is standard for in situ and microinvasive cancer, patients with severe medical problems or other contraindications to surgical treatment can be successfully treated with radiotherapy. Depending on the depth of invasion, these early lesions are treated with brachytherapy alone or brachytherapy combined with external-beam irradiation, and cure rates exceed 95%.

Stage IB and IIA Disease

Early-stage IB cervical carcinomas can be treated effectively with combined external-beam irradiation and brachytherapy or with radical hysterectomy and bilateral pelvic lymphadenectomy. The goal of both treatments is to destroy malignant cells in the cervix, paracervical tissues, and regional lymph nodes. Patients who are treated with radical hysterectomy whose tumors are found to have high-risk

disease features may benefit from postoperative radiotherapy or chemoradiation.

Disease-specific survival rates for patients with stage IB cervical cancer treated with surgery or radiation usually range between 80% and 90%, suggesting that the two treatments are equally effective. However, biases introduced by patient selection, variations in the definition of stage IA disease, and variable indications for postoperative radiotherapy, concurrent chemotherapy, or adjuvant hysterectomy confound comparisons of efficacy between radiotherapy and surgery. Because young women with small, clinically node negative tumors tend to be favored candidates for surgery and because tumor diameter and nodal status are inconsistently described in

published series, it is difficult to compare the results reported for patients treated with surgery and those treated with radiotherapy.

Radical Trachelectomy.

In 1994, Dargent et al.l pioneered the use of radical trachelectomy and laparoscopic pelvic lymphadenectomy as a means of sparing fertility in young women with early cervical cancer.

Since then, it has been demonstrated that when these procedures are performed by experienced surgeons, the cure rates are high and many women are able to carry subsequent pregnancies to viability. Successful pregnancies have also been reported after radical abdominal trachelectomy.

In order to keep the residual uterine segment intact, a nonabsorbable cervical cerclage is placed around the uterine isthmus at the time of the trachelectomy.

Alexander-Sefre et al. reported that radical trachelectomy was associated with shorter operative times and hospital stays, less blood loss, and a lower incidence of bladder hypotony than radical hysterectomy.

However, patients who had radical trachelectomy had more problems with dysmenorrhea, irregular menstruation, and vaginal discharge; in addition, 14% had

cervical suture problems, 10% had isthmic stenosis, and 7% had prolonged amenorrhea. The use of radical vaginal or abdominal trachelectomy and laparoscopic

lymphadenectomy may be indicated in carefully selected women with small IB1 ($\leq$ 2 cm) lesions who are eager to preserve fertility. Patients with extensive endocervical extension are poor candidates for fertility-sparing surgery.

Preoperative MRI is a relatively sensitive and specific method to evaluate the possibility of tumor extension beyond the internal os. A recent review of 504 women who underwent radical trachelectomy summarized the outcome of 200 pregnancies.

Although 84 of 200 pregnancies (42%) produced full-term viable infants, 37% of third-trimester deliveries were preterm, indicating that these women are at high risk for complicated pregnancies.

Stage IIB, III, and IVA Disease

Radiotherapy is the primary local treatment for most patients with locoregionally advanced cervical carcinoma. The success of radiotherapy depends on a careful balance between external-beam radiotherapy and brachytherapy, optimizing the dose to tumor and normal tissues and the overall duration of treatment.

For patients treated with radiotherapy alone for stage IIB, IIIB, and IV disease, 5-year survival rates of 65% to 75%, 35% to 50%, and 15% to 20%, respectively, have been reported.

Results of major clinical trials reported at the end of the 1990s indicate that, barring medical contraindications, most patients with locally advanced tumors should also receive concurrent chemotherapy along with radiotherapy. With appropriate chemoradiotherapy, even patients with massive locoregional disease have a significant chance for cure.

External-beam irradiation is used to deliver a homogeneous dose to the primary cervical tumor and to potential sites of regional spread and may also improve the efficacy of subsequent intracavitary brachytherapy by shrinking bulky tumor and bringing it within the range of the high-dose portion of the brachytherapy dose distribution. To facilitate brachytherapy, patients with locally advanced disease usually begin with a course of external-beam treatment with concurrent chemotherapy.

Subsequent brachytherapy exploits the inverse square law to deliver a high dose to the cervix and paracervical tissues while minimizing the dose to adjacent normal tissues.

Although intracavitary treatment may be delayed until pelvic irradiation has caused some initial tumor regression, breaks during or between external-beam and intracavitary therapy should be discouraged, and every effort should be made to complete the entire radiation treatment in less than 7 to 8 weeks. Several studies have suggested that treatment courses longer than 8 weeks are associated with decreased pelvic disease control and survival rates.

External-Beam Radiotherapy Technique. High-energy photons (15 to 18MV) are usually preferred for pelvic treatment because they spare superficial tissues that are unlikely to be involved with tumor. At these energies, the pelvis can be treated either with four fields (anterior, posterior, and lateral fields) or with anterior and posterior fields alone.

When high-energy beams are not available, four fields are usually used because less-penetrating 4- to 6-m V photons often deliver an unacceptably high dose to superficial tissues when only two fields are used.

CT simulation is recommended to confirm adequate coverage of the iliac lymph nodes. Information gained from radiologic studies such as MRI, CT, and positron emission tomography can improve estimates of disease extent and assist in localization of regional nodes and paracervical tissues that may contain microscopic disease. The caudad extent of disease can be determined by inserting radiopaque markers in the cervix or at the lowest extent of vaginal disease. Potential internal organ motion must be taken into account; prospective studies have revealed that the positions of the uterus and cervix can vary by as much as 4 cm from day to day.

For this reason, it is usually wise to cover the entire presacrococcygeal region when locally advanced cancers are treated. Tumor response should be evaluated with periodic pelvic examinations. Some practitioners prefer to maximize the brachytherapy component of treatment and begin it as soon as the tumor has responded enough to permit a good placement of the

brachytherapy applicators, delivering subsequent pelvic irradiation with a central shield. This technique may reduce the volume of normal tissue treated to a high dose but can also result in overdoses to medial structures such as the ureters or underdosage of posterior uterosacral disease.

For these reasons, many clinicians prefer to give an initial dose of 40 to 45 Gy to the whole pelvis, believing that the ability to deliver a homogeneous distribution to the entire region at risk for microscopic disease outweighs other considerations. External beam doses of more than 40 to 45 Gy to the central pelvis tend to compromise the dose deliverable to paracentral tissues and increase the risk of late complications.

A total dose (external-beam and intracavitary) of 45 to 55 Gy appears to be sufficient to sterilize microscopic disease in the pelvic nodes in most patients. It is customary to treat lymph nodes known to contain gross disease and heavily involved parametria to a total dose of 60 to 65Gy (including the contribution from brachytherapy treatments).

Intensity-Modulated Radiotherapy.

There has been a recent surge of interest in possible applications of intensity-modulated radiotherapy (IMRT) and other forms of highly conformal radiotherapy in patients with gynecologic tumors. Unlike standard two-field and four-field techniques, IMRT makes it possible to deliver a lower daily dose to the intrapelvic contents than to surrounding pelvic lymph nodes. Some of the most intriguing uses of IMRT involve treatment of gross regional disease. With standard techniques, the close proximity of bowel has made it difficult to sterilize disease in nodes larger than 2 cm; IMRT allows delivery of doses exceeding 60Gy to regional nodes with relative sparing of adjacent critical structures.

However, the highly conformal dose distributions achievable with IMRT also increase the potential for error and require considerable experience and attention to detail on the part of the radiation oncologist. In particular, great attention must be paid to the influence of internal organ motion and intratreatment tumor response on the doses to tumor and critical structures. Although some investigators have begun to explore the use of IMRT to treat patients with intact cervical cancers, large inter and intratreatment variations in the position and size of the target volume raise serious concerns about the risk of missing tumor with these highly conforming treatments; if very ample margins are used to account for variability in the target, the gain relative to simpler treatments may not j justify such complex treatment.

There is no evidence that IMRT can safely be used as an alternative to brachytherapy for routine treatment of intact cervical cancer. Although IMRT achieves very conformal dose distributions, it cannot accurately reproduce the high dose gradients produced with intracavitary brachytherapy.

More importantly, the large, unpredictable variations that occur in the positions of the bladder, rectum, and target mandate the use of large treatment margins that inevitably encompass adjacent critical structures and reduce the dose deliverable to tumor.

Stage IVB Disease

Patients who present with disease in distant organs are almost always incurable. The care of these patients must emphasize palliation of symptoms with use of appropriate pain medications and localized radiotherapy. Tumors may respond to chemotherapy, but responses are usually brief.

Single-Agent Chemotherapy.

Cisplatin has been studied in a variety of doses and schedules in the management of recurrent or metastatic cervical cancer and is considered the most active agent against this malignancy. Although a number of other agents (e.g., Ifosfamide, carboplatin, irinotecan, and paclitaxel) have exhibited a modest level of biologic activity in cervical cancer (producing response rates of 10% to 15%), the clinical utility of these drugs in patients who have not responded to cisplatin or who have experienced recurrence or progression after chemoradiation is uncertain. Further, it is well recognized that the objective rate of response to chemotherapy is lower in previously irradiated areas (e.g., pelvis) than in nonirradiated sites (e.g., lung).

Combination Chemotherapy.

Most reports of combination chemotherapy for carcinoma of the cervix have described small, uncontrolled phase 2 trials of drug combinations.

The results of two phase 3 randomized trials, published in 2004 and 2005, have provided the first solid evidence that combination chemotherapy can improve both progression-free survival (cisplatin plus paclitaxel vs. single-agent cisplatin, cisplatin plus topotecan vs. single-agent cisplatin) and overall survival (cisplatin plus topotecan vs. single-agent cisplatin) when it is administered for recurrent or metastatic carcinoma of the cervix. However, a recently reported phase 3 trial comparing combinations of cisplatin with either topotecan, paclitaxel, gemcitabine, or vinorelbine revealed no significant differences in outcome between patients treated with the four cisplatin-based regimens.

Palliative Radiotherapy.

Localized radiotherapy can provide effective relief of pain caused by metastases in bone, brain, lymph nodes, or other sites. A rapid course of pelvic radiotherapy can also provide excellent relief of pain and bleeding for patients who present with incurable disseminated disease.

Fertility sparing

More than 40% of women with early cervical cancer are affected during reproductive age and wish to remain fertile. Thus, many patients demand a more conservative policy for managing these lesions in order to increase the chance of having an uneventful pregnancy in the future.

Sentinel lymph node dissection in cervical cancer.

SLN dissection (SLND) is standard in the treatment of breast cancer as well as vulvar cancer and increasing evidence also suggests an important role for SLND in cervical cancer. While the evidence is still evolving and guideline recommendations are not yet clearly defined, it should be considered in FIGO stage I.

patients with tumors of 4 cm. Some evidence suggests that the detection rate is highest if the tumor is < 2 cm. Tracer is injected directly into the cervix, and blue dye, technetium radiocolloid or fluorescent indocyanine green is used. SLND should be done only in centers with enough expertise and training. Sentinel nodes should be detected on both sides [II, B]

Follow up and monitoring

No definitive agreement exists on the best post-treatment surveillance of cervical cancer. At a minimum, follow-up visits with a complete physical examination, including a pelvic–rectal exam and a patient history, should be conducted by a physician experienced in the surveillance of cancer patients. There is little evidence to suggest that vaginal vault cytology adds significantly to the clinical exam in detecting early disease recurrence. Routine use of various other radiological or biological follow-up investigations in asymptomatic patients is not advocated, because the role of those investigations has yet to be evaluated in a definitive manner. CT or PET/CT scan should be carried out as clinically indicated. A reasonable follow-up schedule involves follow-up visits every 3–6 months in the first 2 years and every 6–12 months in years 3–5. Patients should return to annual population-based general physical and pelvic examinations after 5 years of recurrence-free follow-up [III, C].

VII. QUESTIONS FOR SELF-CONTROL:

1. What place does cervical cancer take in the structure of oncological diseases?
Give a characteristic of it.
2. What is the incidence of cervical cancer in the industrial countries?
3. At what age is the cancer of the cervix diagnosed more frequently?
4. Name two main morphological forms of lung cancer.
5. What is the pathogenesis of cervical cancer?
6. Give a characteristic of the early stage cancer of the cervix.
7. Give a characteristic of the locally spread cancer of the cervix.
8. What method of treatment is the main at the cancer of the cervix?

9. How does cervical cancer spread?

10. What is the main colposcopy signs of cervical cancer?

VIII. Tasks for verification of concrete teaching aims achievement:

1. Most typical histologic type of cervical cancer:

a. Adenocarcinoma

b. Myoma

c. Squamous cell carcinoma

d. Mesonephroid cancer

2. The leading colposcopy sign of cervical cancer:

a. Lesion color

b. Lesion borders

c. Capillary structure

d. Lesion surface

3. The most important method for detecting precancer cervical lesions?

a. Cytological examination

b. Cervical biopsy

c. MRI d. Colposcopy

4. What sign determinates the indication for organ-saving operation:

a. Age of the woman

b. Stage of disease

c. Wish of the patient

d. Anatomical status of the cervix

5. What are common method of material collection for cytological examination of the endometrium:

a. Aspiration

b. Contact

c. Puncture

d. Biopsy

6. All are service delivery components of cervical cancer screening program, except:

a. Community mobilization and education.

b. HPV vaccination

c. Screening services

d. Diagnosis and/or treatment services

7. All the following statements are true for cervical cancer, except:

a. Second most common cancer among Asian women

b. More common in women who never had sexual relations.

c. Has a curable premalignant stage

d. Mortality can be significantly reduced by systematic screening of women

8. The FIGO (Federation of Gynecology and Obstetrics) staging of cervical cancer, which is the internationally accepted classification, is based on which of the following?

a. Clinical examination with cystoscopy and proctoscopy

b. Radiological examination with computed tomography (CT) and magnetic resonance imaging (MRI)

c. Surgical examination

9. What are kinds of special treatment stage IA cervical cancer you will choose?

a. radical hysterectomy

b. radiation therapy

c. cisplatin chemotherapy

d. LEEP

10. Which is the most common type of cervical cancer?

a. Adenocarcinoma

b. Squamous cell carcinoma

c. Adenosquamous carcinoma

d. Sarcoma

Correct answers: 1-c, 2-c, 3-d, 4-b, 5-a,6-b,7-b,8-a,9-d,10-b.

IX. Suggested Literature:

IX 1. Basic:

1. NCCN clinical practice Guidelines of cervical cancer, December 2022.

2. Cancer principles and practice of oncology – DeVita, Hellman and Rosenberg's ,10th edition.

3. ANNALS OF ONCOLOGY, ESMO Clinical Practice Guidelines of cervical cancer treatment, 2020.

4. Surgical oncology, theory and multidisciplinary practice 2nd edition,2020.

5.Clinical gynecological oncology, 9th edition.

IX 2. Additional:

1. Textbook of complex general surgical oncology -SHYNE Y. MORITA, CHARLES M. BALCH, V. SUZANNE KLIMBERG, TIMOTHY M. PAWLIK, MITCHELL C. POSNER, KENNETH K. TANABE, 2018.

2. Clinical oncology, basic principles and practice – Anthony J. Neal and Peter J. Hoskin ,4th edition.

3. manual of clinical oncology (Lippincott manual), 8th edition.

4.Practical radiation oncology, 1st edition,2020.

5.Gynecological oncology handbook: an evidence based clinical guide, 2nd edition.

X. CONTENT