

CERVIX CANCER FOURTH MOST COMMON CANCER AMONG WOMEND. K. Awasthi*¹ and Archana Dixit²¹Department of Chemistry Sri J.N.M.PG College Lucknow UP India.²Department of Chemistry Dayanand Girls PG Kanpur UP India.***Corresponding Author: D. K. Awasthi**

Department of Chemistry Sri J.N.M.PG College Lucknow UP India.

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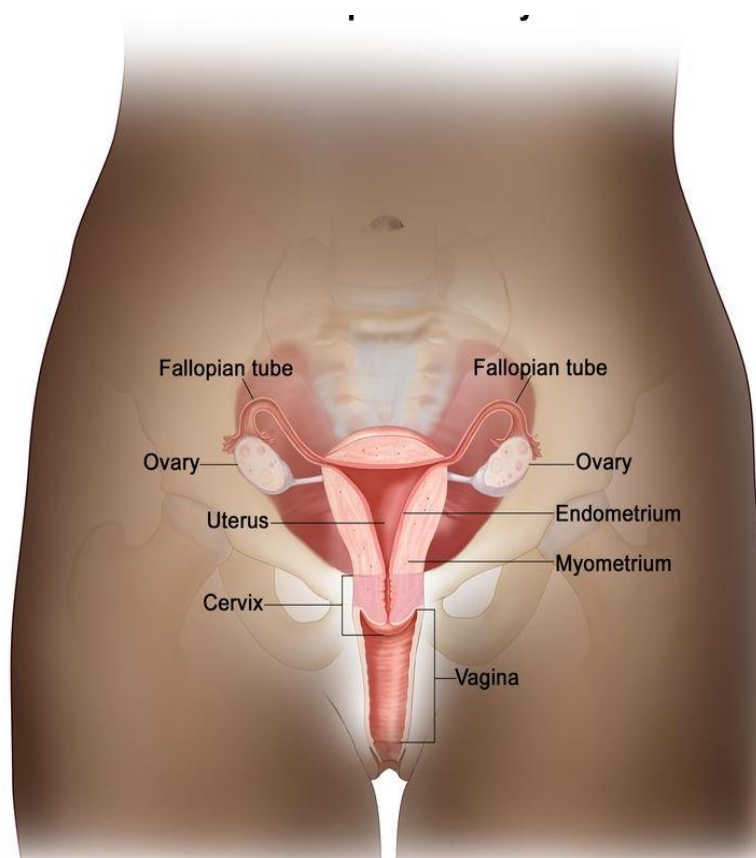
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ABSTRACT

Cervical cancer is cancer that starts in the cells of the cervix. The cervix is the lower, narrow end of the uterus (womb). The cervix connects the uterus to the vagina (birth canal). Cervical cancer usually develops slowly over time. Before cancer appears in the cervix, the cells of the cervix go through changes known as dysplasia, in which abnormal cells begin to appear in the cervical tissues. Over time, if not destroyed or removed, the abnormal cells may become cancer cells and start to grow and spread more deeply into the cervix and to surrounding areas.

KEYWORDS: cancer, cervix, dysplasia, vagina, uterus.

Description: Cervical cancer is cancer that starts in the cells of the cervix. The cervix is the lower, narrow end of the uterus (womb).

ENLARE**Fig-1 Female Reproductive organs**

Anatomy of the female reproductive system. The organs in the female reproductive system include the uterus, ovaries, fallopian tubes, cervix, and vagina. The uterus has a muscular outer layer called the myometrium and an inner lining called the endometrium.

The cervix has two main parts

- The ectocervix (also called exocervix) is the outer part of the cervix that can be seen during a gynaecological examination. The ectocervix is covered with thin, flat cells called squamous cells.
- The endocervix is the inner part of the cervix that forms a canal that connects the vagina to the uterus. The endocervix is covered with column-shaped glandular cells that make mucus.
- The squamocolumnar junction (also called the transformation zone) is the border where the endocervix and ectocervix meet. Most cervical cancers begin in this area.

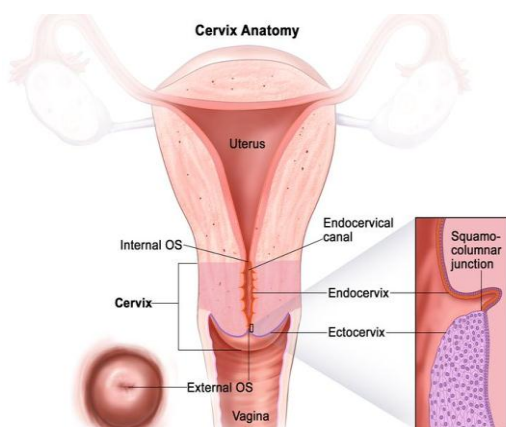


Fig. 2:

Anatomy of the cervix. The cervix is the lower, narrow end of the uterus that connects the uterus to the vagina. It is made up of the internal OS (the opening between the cervix and the upper part of the uterus), the endocervix (the inner part of the cervix that forms the endocervical canal), the ectocervix (the outer part of the cervix that opens into the vagina) and the external OS (the opening between the cervix and vagina). The area where the endocervix and ectocervix meet is called the squamocolumnar junction, which contains both glandular cells (column-shaped cells that make mucus) from the endocervix and squamous cells (thin, flat cells) from the ectocervix. The squamocolumnar junction is sometimes also referred to as the transformation zone.

Types of cervical cancer

Cervical cancers are named after the type of cell where the cancer started. The two main types are:

- Squamous cell carcinoma: Most cervical cancers (up to 90%) are squamous cell carcinomas. These cancers develop from cells in the ectocervix.
- Adenocarcinoma: Cervical adenocarcinomas develop in the glandular cells of the endocervix. Clear cell adenocarcinoma, also called clear cell

carcinoma or mesonephroma, is a rare type of cervical adenocarcinoma.

Sometimes, cervical cancer has features of both squamous cell carcinoma and adenocarcinoma. This is called mixed carcinoma or adenosquamous carcinoma. Very rarely, cancer develops in other cells in the cervix. Most cases of cervical cancer are caused by infection with human papillomavirus (HPV), which is preventable with a vaccine. Women 35 to 44 years old are most likely to get it. More than 20% of new cases are in women over age 65, however, especially those who haven't been getting regular screenings.

You might be at higher risk of cervical cancer if you: Started having sex before age 18 or within a year of starting your period, Have multiple sexual partners, Take birth control pills especially for longer than 5 years, Smoke cigarettes, Have a weakened immune system, Have a sexually transmitted disease (STD).

Symptoms: Pain when you have sex, Unusual vaginal bleeding such as after sex, between periods, after menopause, or after a pelvic exam, Unusual Vaginal discharge.

After it has spread, the cancer can cause: Pelvic Pain, Trouble peeing, Swollen legs, Kidney failure, Bone pain, weight loss and lack of appetite, Fatigue, Bleeding after menopause is never normal, so talk to your doctor as soon as possible if you have it. If you have very heavy periods or often bleed between periods. Some women have bleeding after intercourse, especially after vigorous sex. It's probably nothing to worry about. But you might want to let your doctor know, especially if it happens a lot. Go to the emergency room if you have vaginal bleeding along with weakness or if you feel faint or light-headed, or pass out.

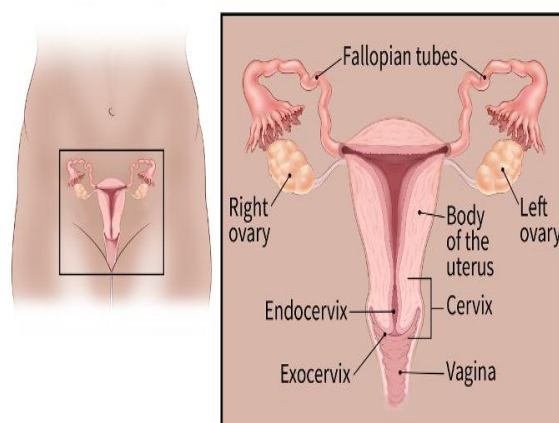


Fig. 3: Pre-cancers of the cervix.

Cells in the transformation zone do not suddenly change into cancer. Instead, the normal cells of the cervix first gradually develop abnormal changes that are called pre-cancerous. Doctors use several terms to describe these pre-cancerous changes, including cervical intraepithelial

neoplasia (CIN), squamous intraepithelial lesion (SIL), and dysplasia.

When the pre-cancers are checked in the lab, they are graded on a scale of 1 to 3 based on how much of the cervical tissue looks abnormal.

- In CIN1 (also called mild dysplasia or low grade SIL), not much of the tissue looks abnormal, and it is considered the least serious cervical pre-cancer.
- In CIN2 or CIN3 (also called moderate/severe dysplasia or high-grade SIL) more of the tissue looks abnormal; high-grade SIL is the most serious pre-cancer.

Although cervical cancers start from cells with pre-cancerous changes (pre-cancers), only some of the women with pre-cancers of the cervix will develop cancer. For most women, pre-cancerous cells will go away without any treatment. But, in some women pre-cancers turn into true (invasive) cancers. Treating cervical pre-cancers can prevent almost all cervical cancers.

The goal of cervical cancer screening is to find pre-cancer or cancer early when it is more treatable and curable. Regular screening can prevent cervical cancers and save lives. The tests for cervical cancer screening are the HPV test and the Pap test. Pre-cancerous changes can be detected by the Pap test and treated to prevent cancer from developing. The HPV looks for infection by high-risk types of HPV that are more likely to cause pre-cancers and cancers of the cervix. HPV infection has no treatment, but a vaccine can help prevent it.

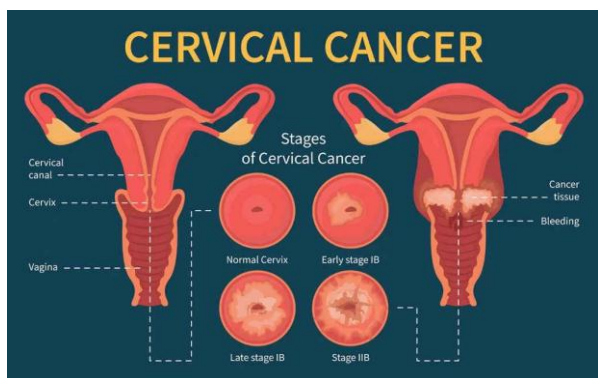


Fig. 5:

Primary prevention of cervical cancer with HPV vaccination

The estimated cross-sectional HPV prevalence worldwide among healthy women aged over 30 years is around 11.7%, with the highest in Sub-Saharan Africa at around 24%, and country-specific prevalence ranging between 2% and 42% globally.^[6] Age-specific cross-sectional HPV prevalence peaks at 25% in women younger than 25 years, which suggests that the infection is predominantly transmitted through the sexual route following sexual debut. Thus, prophylactic HPV vaccination as a preventive strategy should target women

before initiation of sexual activity, focusing on girls aged 10–14 years.

HPV vaccination was launched in 2006. Three prophylactic HPV vaccines are currently available for use in females and males from the age of 9 years for the prevention of premalignant lesions and cancers affecting the cervix, vulva, vagina, and anus caused by hrHPV types: a bivalent vaccine targeting HPV 16 and HPV 18; a quadrivalent vaccine targeting HPV 6 and HPV 11 in addition to HPV 16 and HPV 18; and a nonavalent vaccine targeting HPV types 31, 33, 45, 52, and 58 in addition to HPV 6, 11, 16, and 18. In addition, the last two vaccines target anogenital warts caused by HPV 6 and 11. Recently, a bivalent HPV vaccine (Cecolin; Xiamen Innovax Biotech Co., Ltd) has been licensed in China and is currently undergoing the WHO prequalification process. All the vaccines are recombinant vaccines composed of virus-like particles and are not infectious since they do not contain viral DNA. For girls and boys aged 9–14 years, a two-dose schedule (0.5 mL at 0 and 6–12 months, i.e. the second dose should be given 6–12 months after the first dose) is recommended. Those aged 15 years and older, and immunocompromised patients irrespective of age, must receive three doses (0.5 mL at 0, 1–2, and 6 months, as per the manufacturer's recommendation).^[7] WHO has reviewed the latest data and concluded that there is no safety concern regarding HPV vaccines.

At the population level, there is evidence for the effectiveness of HPV vaccination in terms of reduced prevalence of hrHPV types, anogenital warts, and high-grade cervical abnormalities (CIN2+) caused by the vaccine types among young women; with some evidence of cross-protection against nonvaccine types also.^[9] A recent systematic review and meta-analysis involving 60 million individuals with follow up to 8 years after vaccination indicated that 5–8 years after vaccination, the following outcomes significantly declined: (1) prevalence of HPV 16 and 18 by 83% (RR 0.17; 95% CI, 0.11–0.25) in 13–19-year-old girls, and by 66% (RR 0.34; 95% CI, 0.23–0.49) in women aged 20–24 years; (2) prevalence of HPV 31, 33, and 45 by 54% (RR 0.46; 95% CI, 0.33–0.66) in girls aged 13–19 years; (3) anogenital warts by 67% (RR 0.33; 95% CI, 0.24–0.46) in girls aged 15–19 years, by 54% (RR 0.46; 95% CI, 0.36–0.60) in women aged 20–24 years, and by 31% (RR 0.69; 95% CI, 0.53–0.89) in women aged 25–29 years. CIN2+ decreased significantly by 51% (RR 0.49; 95% CI, 0.42–0.58) among screened girls aged 15–19 years and by 31% (RR 0.69; 95% CI, 0.57–0.84) among women aged 20–24 years. Programs with multicohort vaccination and high vaccination coverage had a greater direct impact and herd effects. The impact of HPV vaccination on significantly reducing the risk of invasive cervical cancer has also been shown recently in a Swedish follow-up evaluation of 1 672 983 girls and women who were 10–30 years of age from 2006 through

2017. Cervical cancer was diagnosed in only 19 vaccinated women and in 538 unvaccinated women.

Recent studies have reported evidence for effectiveness of a single dose in preventing high-risk HPV infections similar to three or two doses. Results from ongoing purpose-designed, prospectively randomized clinical trials assessing the efficacy and immunogenicity of single-dose HPV vaccination compared to currently used schedules are awaited, which will further clarify the role of one dose in preventing cervical neoplasia. There is no evidence of type replacement following vaccination.

It is estimated that, without vaccination, the global burden of cervical cancer among young girls born between 2005–2014 birth cohorts will be 11.6 million cases by 2094. Four-fifths of this burden will be in 25 countries in Africa (5.6 million cases) and Asia (4.5 million cases), with 51.3% of the overall expected burden of 5.9 million cervical cancer cases over a lifetime affecting birth cohorts in India, Nigeria, China, Tanzania, Indonesia, Uganda, the Democratic Republic of the Congo, Ethiopia, and Kenya. Another 2.8 million cases, corresponding to 24.2% of the total burden, would be in 17 countries, mostly in Sub-Saharan Africa (South Africa, Malawi, Zambia, Mozambique, Angola, Zimbabwe, Madagascar, Mali, Ghana, and Burkina Faso); Asia (Pakistan, Bangladesh, and the Philippines); the Americas (Brazil, Mexico, and the USA); and Russia. The remaining 24.5% (2.8 million cases) in unvaccinated birth cohorts is expected to occur in the remaining 159 countries. It has been estimated that worldwide HPV vaccination with high coverage could prevent about 8.7 million cases by 2094.

Secondary prevention of cervical cancer by early detection and treatment of precancerous lesions.

Screening is an important strategy in the global elimination of cervical cancer. While HPV vaccination aims to prevent cervical neoplasia by preventing HPV infection, screening aims to detect prevalent cervical precancerous lesions such as high-grade CIN and adenocarcinoma in-situ early, and effectively treat them to prevent invasive cancer and decrease cervical cancer mortality rates. It will therefore remain a priority for cervical cancer prevention for several decades.

Several cervical screening strategies have been used effectively in varied settings: conventional cytology (Pap smear); in recent years, liquid-based cytology (LBC) and HPV testing; and, in LMICs, visual inspection with acetic acid (VIA). While screening with Pap smear at regular intervals has resulted in substantial decline in cervical cancer risk in high-income countries, it is resource-intensive, needs repeated rounds to compensate for poor sensitivity, and is not feasible in low-resource settings where poor organization, coverage, and lack of

quality assurance result in suboptimal outcomes. HPV-based screening has higher sensitivity and accuracy, lower variability and better reproducibility compared with conventional or LBC. In the context of declining HPV infections in vaccinated populations, many healthcare systems are switching to primary HPV screening, whose higher negative predictive value allows extended screening intervals or even a single lifetime screening in low-resource settings. Recent European guidelines strongly recommend primary HPV-based screening over standard cytology-based screening. Currently The Netherlands, Turkey, Finland, Italy, Sweden, and the UK are implementing HPV screening nationally or regionally. Countries such as Australia, Argentina, Chile, and Mexico are implementing HPV-based screening programs. This has increased the colposcopy referral rates, but also resulted in higher detection rates of CIN3+ lesions and cervical cancers.

VIA screening involves detection of acetowhite lesions on the cervix 1 minute after the application of 3%–5% freshly prepared acetic acid. In view of its feasibility, it has been widely implemented in opportunistic settings in many low-income countries in Sub-Saharan Africa. A single-visit approach (SVA) for screening with rapid diagnosis and treatment improves coverage, eliminates follow-up visits, and improves cost-efficiency in low-resource settings. VIA screening is particularly suitable for SVA and WHO has issued guidelines for implementing SVA in public health settings.

Introducing a cervical cancer screening program in a country should be preceded by policy and managerial guidelines that clearly indicate the target age group, screening test and screening intervals, methods to reach target women, management of screen-positive women (triaging and treating or SVA), treatment methods (cryotherapy, thermal ablation, loop electrosurgical excisions procedure [LEEP]) for CIN lesions, and criteria for type of treatment for prevalent cervical cancers detected by screening. Availability of adequate infrastructure and trained human resources is critical for initiating and sustaining the various inputs of the program. A program information system supported by a database and linkage with other information systems such as cancer registration, mortality registers, and health insurance databases is important for monitoring and evaluation. The screening strategy chosen must be feasible, simple, safe, accurate, acceptable, and easily accessible to the highest-risk women. In studies from Bangladesh and India it has been observed that following the right approach to organize several components and meticulous attention to quality is crucial for the success of a screening program and not merely the choice of a good screening test. A judicious combination of HPV vaccination and screening has enormous TABLE 1. FIGO staging of cancer of the cervix uteri (2018).

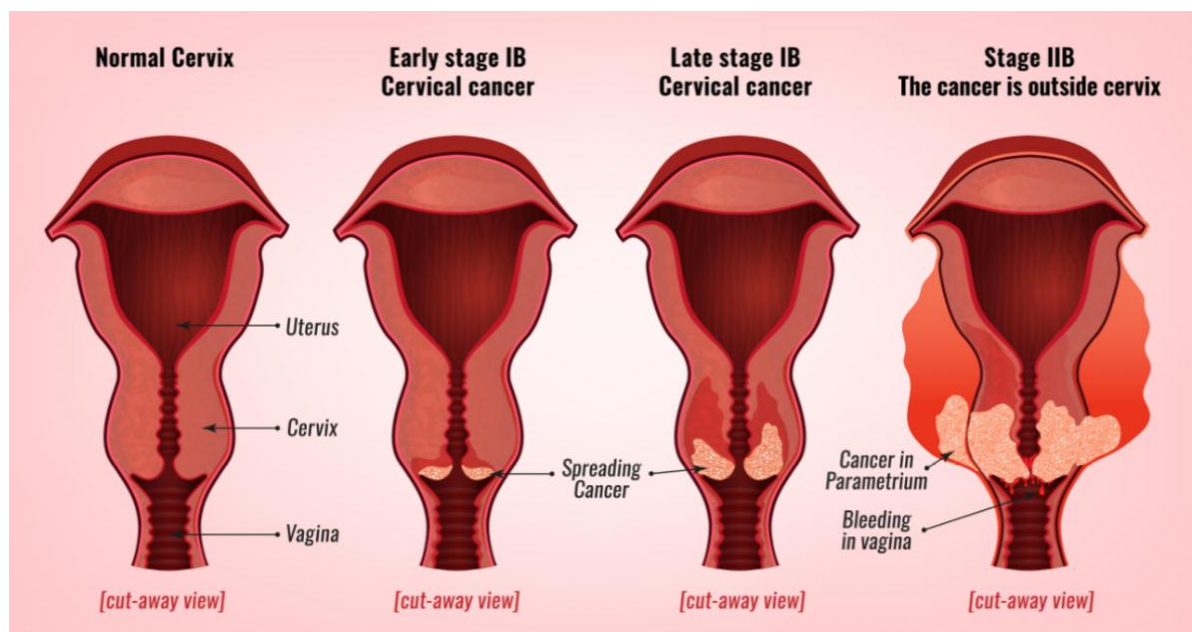


Fig. 6: Stages of cervix cancer.

StageI	Description: The carcinoma is strictly confined to the cervix (extension to the uterine corpus should be disregarded)
IA	Invasive carcinoma that can be diagnosed only by microscopy, with maximum depth of invasion ≤ 5 mm ^a
IA1	Measured stromal invasion ≤ 3 mm in depth
IA2	Measured stromal invasion >3 and ≤ 5 mm in depth
IB	Invasive carcinoma with measured deepest invasion >5 mm (greater than Stage IA); lesion limited to the cervix uteri with size measured by maximum tumor diameter ^b
IB1	Invasive carcinoma >5 mm depth of stromal invasion and ≤ 2 cm in greatest dimension
IB2	Invasive carcinoma >2 and ≤ 4 cm in greatest dimension
IB3	Invasive carcinoma >4 cm in greatest dimension
II	The carcinoma invades beyond the uterus, but has not extended onto the lower third of the vagina or to the pelvic wall
IIA	Involvement limited to the upper two-thirds of the vagina without parametrial involvement
IIA1	Invasive carcinoma ≤ 4 cm in greatest dimension
IIA2	Invasive carcinoma >4 cm in greatest dimension
IIB	With parametrial involvement but not up to the pelvic wall
III	The carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or nonfunctioning kidney and/or involves pelvic and/or para-aortic lymph nodes
IIIA	The carcinoma involves the lower third of the vagina, with no extension to the pelvic wall
IIIB	Extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney (unless known to be due to another cause)
IIIC	Involvement of pelvic and/or para-aortic lymph nodes (including micrometastases) ^c , irrespective of tumor size and extent (with r and p notations) ^d
IIIC1	Pelvic lymph node metastasis only
IIIC2	Para-aortic lymph node metastasis
IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. A bullous edema, as such, does not permit a case to be allotted to Stage IV
IVA	Spread of the growth to adjacent pelvic organs
IVB	Spread to distant organs

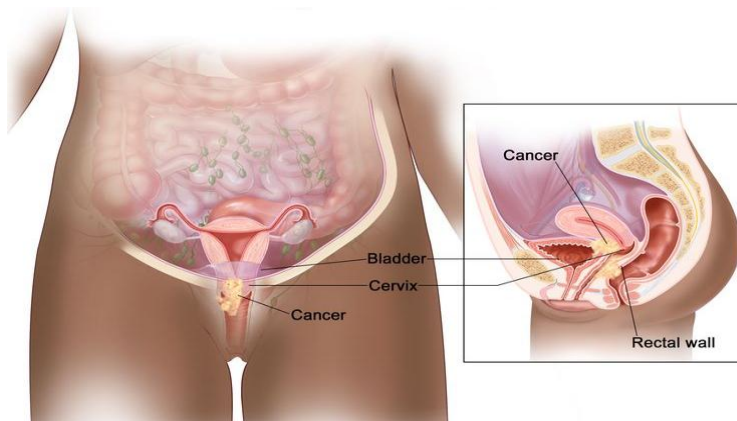


Fig. 7: Stage-4 cervix cancer.



Fig. 8.

Table 2 shows the types of radical hysterectomy. In Stage IVA, selected cases may be suitable for pelvic exenteration.

Table 2: Types of radical hysterectomy.

Simple extrafascial hysterectomy	Modified radical hysterectomy	Radical hysterectomy	Type III
Querleu and Morrow classification	Type A	Type B	Type C
Indication	Stage IA1	Type IA1 with LVSI. IA2	Stage IB1 and IB2, selected Stage IIA
Uterus and cervix	Removed	Removed	Removed
Ovaries	Optional removal	Optional removal	Optional removal
Vaginal margin	None	1–2 cm	Upper one-quarter to one-third
Ureters	Not mobilized	Tunnel through broad ligament	Tunnel through broad ligament
Cardinal ligaments	Divided at uterine and cervical border	Divided where ureter transits broad ligaments	Divided at pelvic side wall
Uterosacral ligaments	Divided at cervical border	Partially removed	Divided near sacral origin
Urinary bladder	Mobilized to base of bladder	Mobilized to upper vagina	Mobilized to middle vagina
Rectum	Not mobilized	Mobilized below cervix	Mobilized below cervix
Surgical approach	Laparotomy or laparoscopy or robotic surgery	Laparotomy or laparoscopy or robotic surgery	Laparotomy or laparoscopy or robotic surgery

Staging

The International Federation of Gynecology and Obstetrics (FIGO) staging system was recently updated in 2018 and remains the dominant staging methodology. The AJCC 8 addition also has a TNM classification system where the T stages correspond to the FIGO stage however it is not regularly used. Classically, the FIGO staging would rely on clinical examination as well as cystoscopy, proctoscopy, hysteroscopy, urography, and plain film X-ray. These relatively basic tests were allowed so that developing countries with fewer healthcare resources could adequately stage patients. More recently, advanced imaging techniques such as MRI and PET became part of the staging workup. MRI is preferred for establishing the T stage given superior tissue delineation compared to CT with contrast. FIGO stage I disease is strictly confined to the cervix with the A/B designation indicating the depth of invasion ≤ 5 mm or >5 mm. FIGO stage II represents disease that invades beyond the uterus but has not extended into the lower vagina. This stage also has an A/B designation based on the involvement of the parametria. FIGO stage III indicates disease that has extended to the lower third of the vagina (IIIA) or extension to the pelvic side wall and/or hydronephrosis (IIIB). Classically, nodal disease did not influence the FIGO staging system, however, it has been shown that nodal disease is one of the most important prognostic indicators for reduced 5-year overall survival. As a result, new stages IIIC1 and IIIC2 were added to reflect the involvement of pelvic nodes or para-aortic nodes respectively. FIGO Stage IVA disease indicates locally aggressive disease with the involvement of adjacent organs such as the bladder, rectum, or tumor extension beyond the true pelvis. FIGO stage IVB disease indicates spread to other solid organs or non-regional nodal disease.

Diagnosis

The most important advance in cervical cancer screening is broader use of the Papanicolaou test (Pap smear) and high-risk HPV testing. A Pap smear is part of a woman's regular pelvic exam. Your doctor collects cells from the surface of your cervix, and a technician looks at them under a microscope. If they spot anything unusual, your doctor will take out a bit of cervical tissue in a procedure called a biopsy.

Other tools can find changes in your cervix. They include: A colposcopy is like a pelvic exam. Your doctor may use it if a Pap smear finds unusual cells. They stain your cervix with a harmless dye or acetic acid so the cells are easier to see. Then, they use a microscope called a colposcope, which magnifies your cervix by eight to 15 times, to look for unusual cells for biopsy. You can usually have this procedure in your gynecologist's office. You might need another biopsy later if the colposcopy shows signs of invasive cancer. In the **loop electrosurgical excision procedure (LEEP)**, your doctor uses an electrified loop of wire to take a sample of tissue from your cervix. You might have this in your

gynecologist's office. Your doctor can do conization (removal of part of your cervix) in the operating room while you're under anesthesia. They might use a LEEP, a scalpel (cold knife conization), or a laser. These are usually outpatient procedures, so you can go home the same day.

Precancerous changes

Unusual changes in cells on the surface of your cervix are usually called squamous intraepithelial lesions (SIL). "Lesion" means an area of unusual tissue; "intraepithelial" means these cells are only in the surface layer. These are precancerous cells. They might not become cancerous or invade deeper layers of tissue for months or years.

Invasive cancer

If a biopsy shows cancer that's further along, your doctor will probably do more tests to see whether it's spread and how far. They include:

- A chest X-ray to check your lungs
- Blood tests to see whether it's spread to your liver; you might have a CT scan to refine the results
- An intravenous pyelogram (IVP) or CT scan to look at your urinary tract; a cystoscopy can check your bladder and urethra
- A colposcopy to look at your vagina
- A proctosigmoidoscopy and barium enema to check your rectum
- CT, MRI, or PET scans of your LYMPH NODES.

Surgery and radiation therapy are the most common treatments for invasive cervical cancer. Others are chemotherapy and biological therapy.

If the cancer is only on the surface of your cervix, your doctor can remove or destroy the cancerous cells with procedures like LEEP or cold knife conization.

If cancerous cells have passed through a layer called the basement membrane, which separates the surface of your cervix from underlying layers, you'll probably need surgery. If the disease has invaded deeper layers of your cervix but hasn't spread to other parts of your body, you might have an operation to take out the tumor.

If it's spread into your uterus, your doctor will probably recommend a hysterectomy. Talk with them about the pros and cons.

Radiation therapy (or radiotherapy) uses high-energy rays to damage cancer cells and stop their growth. As with surgery, the radiation affects cancer cells only in the treated area.

Your treatments might be external, internal, or both.

External radiation comes from a large machine that aims a beam of radiation at your pelvis. You'll probably get treatments, which take only a few minutes, 5 days a

week for 5 to 6 weeks. Finally, you may have an extra dose of radiation called a "boost."

Internal radiation (also called implant radiation or brachytherapy) comes from a capsule containing radioactive material, which your doctor puts into your cervix. The implant puts cancer-killing rays close to the tumor while sparing most of the healthy tissue around it.

Chemotherapy uses powerful drugs to kill cancer cells. Doctors often use it for cervical cancer that's locally advanced or has spread to other parts of the body.

Chemotherapy happens in cycles of intensive treatment followed by recovery periods. Most people have it as an outpatient (in an outpatient clinic at the hospital, at the doctor's office, or at home).

Biological therapy or immunotherapy targets "checkpoints" in your immune cells that are turned on or off to set off an immune response. Pembrolizumab (keytruda) or nivolumab (opdivo) can be used to help block a protein on the cells to shrink tumors or slow their growth.

Doctors use it if chemo isn't working or if the cancer has spread. You'll get it through a vein (called intravenous, or IV) every 3 weeks.

Caring for Cervical Cancer at Home

Certain things can ease the physical and mental stresses of cervical cancer and treatment.

One of the best things you can do is get the right nutrition. You may lose your appetite or have trouble eating during treatment. But if you get enough calories and protein, you'll have more strength and energy, and you'll be able to handle treatment better. You might want to work with a nutritionist to keep up your calorie and protein intake. They may suggest you eat smaller portions more often.

Other lifestyle changes may help keep you stronger and more comfortable during treatment

- Get mild Physical activity to keep up your energy level. Make sure it doesn't wear you out.
- Get enough rest at night, and take naps if you need.
- Quit smoking
- Don't drink alcohol. You may not be able to drink alcohol while taking some medications.

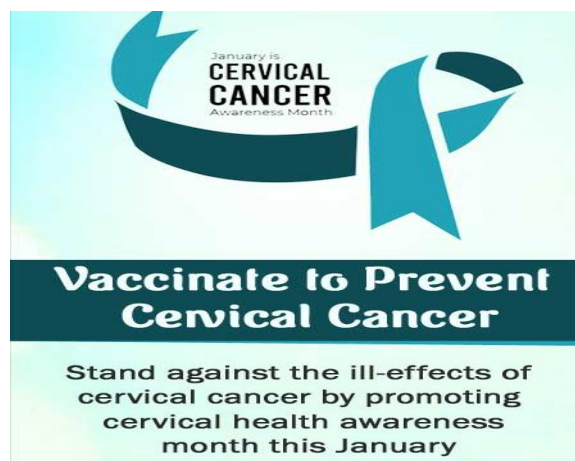
Regular pelvic exams and Pap tests are the best way to do this. Experts recommend this schedule

- If you're 25 to 65, you should get a human papillomavirus (HPV) test every 5 years. Beyond that age, you may be able to stop testing if your doctor says you're at low risk.
- If HPV alone isn't available, you can get a combined HPV and Pap test every 5 years or a Pap test alone every 3 years.

- Women of any age don't need screening if they've had their cervix removed and have no history of cervical cancer or precancerous lesions.
- If you're sexually active and have a higher risk for STDs

Avoiding HPV is also important. Steps to prevent infection include

- Use a barrier, like a condom, if you have sex.
- Get the HPV Vaccine. The FDA has approved Gardasil-9 for males and females ages 9 to 45. It protects against numerous strains of HPV that cause the great majority of both genital warts, as well as cervical and other HPV-caused cancers.
- Because cigarette smoking also raises your odds of having cervical cancer, quitting can lower your risk.
- The survival rate is close to 100% when you find and treat precancerous or early cancerous changes. The prognosis for invasive cervical cancer depends on the stage.
- More than 90% of women with stage 0 survive at least 5 years after diagnosis.
- Stage I cervical cancer patients have a 5-year survival rate of 80% to 93%.
- Women with stage II cervical cancer have a 5-year survival rate of 58% to 63%.
- The survival rate for women with stage III cervical cancer is 32% to 35%.
- Sixteen percent or fewer women with stage IV cervical cancer survive 5 years.



CONCLUSION

Cervical cancer is the fourth most common cancer among women worldwide. Primary prevention and screening are by far the most effective modalities for decreasing the healthcare burden and mortality attributable to cervical cancer. In the United States and other developing countries, most screening and diagnostic efforts are directed towards early identification of high-risk human papillomavirus (HPV) lesions through HPV testing and pap smears. Interprofessional team members must recognize that cervical cancer is a preventable disease. It is largely

preventable even in women who are sexually active if they receive early human papillomavirus (HPV) vaccination. The potential opportunity for prevention of cervical cancer via early HPV vaccination is one that interprofessional team members and their patients cannot afford to miss. Since 2006, HPV vaccination has been available for the prevention of cervical cancer. Interprofessional team members have a moral obligation to educate their young female patients about this the opportunity to prevent cervical cancer. The potential opportunity for prevention of cervical cancer via early HPV vaccination is one that interprofessional team members and their patients cannot afford to miss. This activity reviews the evaluation and management of cervical cancer and highlights the role of the interprofessional team in providing HPV vaccination to women of childbearing age so that these women will not develop what currently stands as the 4th most common cancer in females worldwide.

REFERENCES

1. Brisson M, Drolet M. Global elimination of cervical cancer as a public health problem. *Lancet Oncol*, 2019 Mar; 20(3): 319-321. [PubMed]
2. Pimple SA, Mishra GA. Global strategies for cervical cancer prevention and screening. *Minerva Ginecol*, 2019 Aug; 71(4): 313-320. [PubMed]
3. Cervical Cancer Screening Every 5 Years OK. *Cancer Discov.*, 2018 Oct; 8(10): 1204. [PubMed]
4. Farghaly H, Bourgeois D, Houser PM, Padmanabhan V, Lage JM, Hoda RS. Routine vaginal Pap test is not useful in women status-post hysterectomy for benign disease. *Diagn Cytopathol*, 2006 Sep; 34(9): 640-3. [PubMed]
5. Foran C, Brennan A. Prevention and early detection of cervical cancer in the UK., 2015 May 28-Jun 10 *Br J Nurs*. 24(10): S22-4, S26, S28-9. [PubMed]
6. Pierre-Victor D, Stephens DP, Omondi A, Clarke R, Jean-Baptiste N, Madhivanan P. Barriers to HPV Vaccination Among Unvaccinated, Haitian American College Women. *Health Equity*, 2018; 2(1): 90-97. [PMC free article] [PubMed]
7. Manini I, Montomoli E. Epidemiology and prevention of Human Papillomavirus. *Ann Ig.*, 2018 Jul-Aug; 30(4 Suppl 1): 28-32. [PubMed]
8. Ghosh I, Mandal R, Kundu P, Biswas J. Association of Genital Infections Other Than Human Papillomavirus with Pre-Invasive and Invasive Cervical Neoplasia. *J Clin Diagn Res.*, 2016 Feb; 10(2): XE01-XE06. [PMC free article] [PubMed]
9. Kuhn L, Denny L. The time is now to implement HPV testing for primary screening in low resource settings. *Prev Med*, 2017 May; 98: 42-44. [PMC free article] [PubMed]
10. Rauh-Hain JA, Melamed A, Schaps D, Bregar AJ, Spencer R, Schorge JO, Rice LW, Del Carmen MG. Racial and ethnic disparities over time in the treatment and mortality of women with gynecological malignancies. *Gynecol Oncol*, 2018 Apr; 149(1): 4-11. [PubMed]
11. Wang X, Huang X, Zhang Y. Involvement of Human Papillomaviruses in Cervical Cancer. *Front Microbiol*, 2018; 9: 2896. [PMC free article] [PubMed]
12. Senol T, Polat M, Ozkaya E, Karateke A. Comparison of Two Step LEEP and Cold Conisation For Cervical Intraepithelial Lesions to Decrease Positive Surgical Margins. *Asian Pac J Cancer Prev*, 2016; 17(7): 3317-20. [PubMed]
13. Pötter R, Tanderup K, Schmid MP, Jürgenliemk-Schulz I, Haie-Meder C, Fokdal LU, Sturdza AE, Hoskin P, Mahantshetty U, Segedin B, Bruheim K, Huang F, Rai B, Cooper R, van der Steen-Banasik E, Van Limbergen E, Pieters BR, Tan LT, Nout RA, De Leeuw AAC, Ristl R, Petric P, Nesvacil N, Kirchheiner K, Kirisits C, Lindegaard JC., EMBRACE Collaborative Group. MRI-guided adaptive brachytherapy in locally advanced cervical cancer (EMBRACE-I): a multicentre prospective cohort study. *Lancet Oncol*, 2021 Apr; 22(4): 538-547. [PubMed]
14. Dimopoulos JC, Petrow P, Tanderup K, Petric P, Berger D, Kirisits C, Pedersen EM, van Limbergen E, Haie-Meder C, Pötter R. Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group (IV): Basic principles and parameters for MR imaging within the frame of image based adaptive cervix cancer brachytherapy. *Radiother Oncol*, 2012 Apr; 103(1): 113-22. [PMC free article] [PubMed]. Report 89. *J ICRU*. 2013 Apr; 13(1-2): NP. [PubMed].
15. Mazon R, Fokdal LU, Kirchheiner K, Georg P, Jastaniyah N, Šegedin B, Mahantshetty U, Hoskin P, Jürgenliemk-Schulz I, Kirisits C, Lindegaard JC, Dörr W, Haie-Meder C, Tanderup K, Pötter R., EMBRACE collaborative group. Dose-volume effect relationships for late rectal morbidity in patients treated with chemoradiation and MRI-guided adaptive brachytherapy for locally advanced cervical cancer: Results from the prospective multicenter EMBRACE study. *Radiother Oncol*, 2016 Sep; 120(3): 412-419. [PubMed].
16. Lucidarme D, Marteau P, Foucault M, Vautrin B, Filoche B. Efficacy and tolerance of mesalazine suppositories vs. hydrocortisone foam in proctitis. *Aliment Pharmacol Ther*, 1997 Apr; 11(2): 335-40. [PubMed].
17. Rigaud J, Hetet JF, Bouchot O. [Management of radiation cystitis]. *Prog Urol*, 2004 Sep; 14(4): 568-72. [PubMed].
18. Pereira D, Ferreira C, Catarino R, Correia T, Cardoso A, Reis F, Cerqueira M, Prisco R, Camacho O. Hyperbaric oxygen for radiation-induced cystitis: A long-term follow-up. *Actas Urol Esp (Engl Ed)*, 2020 Oct; 44(8): 561-567. [PubMed].
19. Boice JD, Day NE, Andersen A, Brinton LA, Brown R, Choi NW, Clarke EA, Coleman MP, Curtis RE, Flannery JT. Second cancers following radiation

- treatment for cervical cancer. An international collaboration among cancer registries. *J Natl Cancer Inst.*, 1985 May; 74(5): 955-75. [PubMed].
20. Wright JD, St Clair CM, Deutsch I, Burke WM, Gorrochurn P, Sun X, Herzog TJ. Pelvic radiotherapy and the risk of secondary leukemia and multiple myeloma. *Cancer*, 2010 May 15; 116(10): 2486-92. [PubMed].
 21. Wallace WH, Thomson AB, Saran F, Kelsey TW. Predicting age of ovarian failure after radiation to a field that includes the ovaries. *Int J Radiat Oncol Biol Phys*, 2005 Jul 01; 62(3): 738-44. [PubMed].
 22. Small W, Kim YS, Joyce C, Surucu M, Leshyk M, Harkenrider MM, Potkul RK, Liotta M, Winder A, Altoos B. Uterine perforation during brachytherapy for cervical cancer: Complications, outcomes, and best practices for forward treatment planning and management. *Brachytherapy*, 2021 May-Jun; 20(3): 557-564. [PubMed].
 23. Van Dyk S, Schneider M, Kondalsamy-Chennakesavan S, Bernshaw D, Narayan K. Ultrasound use in gynecologic brachytherapy: Time to focus the beam. *Brachytherapy*, 2015 May-Jun; 14(3): 390-400. [PubMed].
 24. Rowlands S, Oloto E, Horwell DH. Intrauterine devices and risk of uterine perforation: current perspectives. *Open Access J Contracept*, 2016; 7: 19-32. [PMC free article] [PubMed].
 25. Rose PG, Bundy BN, Watkins EB, Thigpen JT, Deppe G, Maiman MA, Clarke-Pearson DL, Insalaco S. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. *N Engl J Med*, 1999 Apr 15; 340(15): 1144-53. [PubMed].
 26. Dueñas-González A, Zarbá JJ, Patel F, Alcedo JC, Beslija S, Casanova L, Pattaranutaporn P, Hameed S, Blair JM, Barraclough H, Orlando M. Phase III, open-label, randomized study comparing concurrent gemcitabine plus cisplatin and radiation followed by adjuvant gemcitabine and cisplatin versus concurrent cisplatin and radiation in patients with stage IIB to IVA carcinoma of the cervix. *J Clin Oncol*, 2011 May 01; 29(13): 1678-85. [PubMed].
 27. Moore DH, Blessing JA, McQuellon RP, Thaler HT, Cella D, Benda J, Miller DS, Olt G, King S, Boggess JF, Rocereto TF. Phase III study of cisplatin with or without paclitaxel in stage IVB, recurrent, or persistent squamous cell carcinoma of the cervix: a gynecologic oncology group study. *J Clin Oncol*, 2004 Aug 01; 22(15): 3113-9. [PubMed].
 28. Monk BJ, Sill MW, McMeekin DS, Cohn DE, Ramondetta LM, Boardman CH, Benda J, Cella D. Phase III trial of four cisplatin-containing doublet combinations in stage IVB, recurrent, or persistent cervical carcinoma: a Gynecologic Oncology Group study. *J Clin Oncol*, 2009 Oct 01; 27(28): 4649-55. [PMC free article] [PubMed].
 29. Tewari KS, Sill MW, Penson RT, Huang H, Ramondetta LM, Landrum LM, Oaknin A, Reid TJ, Leitao MM, Michael HE, DiSaia PJ, Copeland LJ, Creasman WT, Stehman FB, Brady MF, Burger RA, Thigpen JT, Birrer MJ, Waggoner SE, Moore DH, Look KY, Koh WJ, Monk BJ. Bevacizumab for advanced cervical cancer: final overall survival and adverse event analysis of a randomised, controlled, open-label, phase 3 trial (Gynecologic Oncology Group 240). *Lancet*, 2017 Oct 07; 390(10103): 1654-1663. [PMC free article] [PubMed].
 30. Marabelle A, Le DT, Ascierto PA, Di Giacomo AM, De Jesus-Acosta A, Delord JP, Geva R, Gottfried M, Penel N, Hansen AR, Piha-Paul SA, Doi T, Gao B, Chung HC, Lopez-Martin J, Bang YJ, Frommer RS, Shah M, Ghorri R, Joe AK, Pruitt SK, Diaz LA. Efficacy of Pembrolizumab in Patients With Noncolorectal High Microsatellite Instability/Mismatch Repair-Deficient Cancer: Results From the Phase II KEYNOTE-158 Study. *J Clin Oncol*, 2020 Jan 01; 38(1): 1-10. [PMC free article] [PubMed].
 31. Colombo N, Dubot C, Lorusso D, Caceres MV, Hasegawa K, Shapira-Frommer R, Tewari KS, Salman P, Hoyos Usta E, Yañez E, Gümüş M, Olivera Hurtado de Mendoza M, Samouëlian V, Castonguay V, Arkhipov A, Toker S, Li K, Keefe SM, Monk BJ., KEYNOTE-826 Investigators. Pembrolizumab for Persistent, Recurrent, or Metastatic Cervical Cancer. *N Engl J Med*, 2021 Nov 11; 385(20): 1856-1867. [PubMed].
 32. Kitagawa R, Katsumata N, Shibata T, Kamura T, Kasamatsu T, Nakanishi T, Nishimura S, Ushijima K, Takano M, Satoh T, Yoshikawa H. Paclitaxel Plus Carboplatin Versus Paclitaxel Plus Cisplatin in Metastatic or Recurrent Cervical Cancer: The Open-Label Randomized Phase III Trial JCOG0505. *J Clin Oncol*, 2015 Jul 01; 33(19): 2129-35. [PubMed].
 33. Salib MY, Russell JHB, Stewart VR, Sudderuddin SA, Barwick TD, Rockall AG, Bharwani N. 2018 FIGO Staging Classification for Cervical Cancer: Added Benefits of Imaging. *Radiographics*, 2020 Oct; 40(6): 1807-1822. [PubMed] 66.
 34. Spinner C, Ding L, Bernstein DI, Brown DR, Franco EL, Covert C, Kahn JA. Human Papillomavirus Vaccine Effectiveness and Herd Protection in Young Women. *Pediatrics*, 2019 Feb; 143(2) [PMC free article] [PubMed].
 35. Castellano T, Ding K, Moore KN, Landrum LM. Simple Hysterectomy for Cervical Cancer: Risk Factors for Failed Screening and Deviation From Screening Guidelines. *J Low Genit Tract Dis.*, 2019 Apr; 23(2): 124-128. [PubMed].
 36. Rauh-Hain JA, Clemmer JT, Bradford LS, Clark RM, Growdon WB, Goodman A, Boruta DM, Schorge JO, del Carmen MG. Racial disparities in cervical cancer survival over time. *Cancer*, 2013 Oct 15; 119(20): 3644-52. [PubMed].
 37. Pergialiotis V, Bellos I, Thomakos N, Haidopoulos D, Perrea DN, Kontzoglou K, Daskalakis G, Rodolakis A. Survival outcomes of patients with cervical cancer and accompanying hydronephrosis:

- A systematic review of the literature. *Oncol Rev.*, 2019 Jan 14; 13(1): 387. [PMC free article] [PubMed].
38. Mendu S, Boukhechba M, Gordon JR, Datta D, Molina E, Arroyo G, Proctor SK, Wells KJ, Barnes LE. Design of a Culturally-Informed Virtual Human for Educating Hispanic Women about Cervical Cancer. *Int Conf Pervasive Comput Technol Healthc*, 2018 May; 2018: 360-366. [PMC free article] [PubMed].
39. Nasser S, Berek J, Ullrich A, Giordano L, Sehouli J. A report on the Marrakech International Women's Cancer Days: dialogs and implications. *Int J Gynecol Cancer*, 2019 Feb; 29(2): 417-421. [PubMed].
40. Cunningham-Erves J, Forbes L, Ivankova N, Mayo-Gamble T, Kelly-Taylor K, Deakings J. Black mother's intention to vaccinate daughters against HPV: A mixed methods approach to identify opportunities for targeted communication. *Gynecol Oncol*, 2018 Jun; 149(3): 506-512. [PMC free article] [PubMed].
41. Mabelele MM, Materu J, Ng'ida FD, Mahande MJ. Knowledge towards cervical cancer prevention and screening practices among women who attended reproductive and child health clinic at Magu district hospital, Lake Zone Tanzania: a cross-sectional study. *BMC Cancer*, 2018 May 16; 18(1): 565. [PMC free article] [PubMed].
42. Lai D, Bodson J, Davis FA, Lee D, Tavake-Pasi F, Napia E, Villalta J, Mukundente V, Mooney R, Coulter H, Stark LA, Sanchez-Birkhead AC, Kepka D. Diverse Families' Experiences with HPV Vaccine Information Sources: A Community-Based Participatory Approach. *J Community Health*, 2017 Apr; 42(2): 400-412. [PMC free article] [PubMed].
43. Bayu H, Berhe Y, Mulat A, Alemu A. Cervical Cancer Screening Service Uptake and Associated Factors among Age Eligible Women in Mekelle Zone, Northern Ethiopia, 2015: A Community Based Study Using Health Belief Model. *PLoS One*, 2016; 11(3): e0149908. [PMC free article] [PubMed].
44. Shachner TR, Van Meter SE. Metastatic melanoma of the uterine cervix diagnosed on cervical Pap smear: Case report and literature review. *Diagn Cytopathol*, 2018 Dec; 46(12): 1045-1049. [PubMed].
45. Brun JL, Youbi A, Hocké C. [Complications, sequelae and outcome of cervical conizations: evaluation of three surgical techniques]. *J Gynecol Obstet Biol Reprod (Paris)*, 2002 Oct; 31(6): 558-64. [PubMed].
46. Smith ES, Moon AS, O'Hanlon R, Leitao MM, Sonoda Y, Abu-Rustum NR, Mueller JJ. Radical Trachelectomy for the Treatment of Early-Stage Cervical Cancer: A Systematic Review. *Obstet Gynecol*, 2020 Sep; 136(3): 533-542. [PMC free article] [PubMed], 33-46. [PubMed].
47. Charra-Brunaud C, Harter V, Delannes M, Haie-Meder C, Quetin P, Kerr C, Castelain B, Thomas L, Peiffert D. Impact of 3D image-based PDR brachytherapy on outcome of patients treated for cervix carcinoma in France: results of the French STIC prospective study. *Radiother Oncol*, 2012 Jun; 103(3): 305-13. [PubMed].
48. Monk BJ, Sill MW, McMeekin DS, Cohn DE, Ramondetta LM, Boardman CH, Benda J, Cella D. Phase III trial of four cisplatin-containing doublet combinations in stage IVB, recurrent, or persistent cervical carcinoma: a Gynecologic Oncology Group study. *J Clin Oncol*, 2009 Oct 01; 27(28): 4649-55. [PMC free article] [PubMed].
49. Tewari KS, Sill MW, Penson RT, Huang H, Ramondetta LM, Landrum LM, Oaknin A, Reid TJ, Leitao MM, Michael HE, DiSaia PJ, Copeland LJ, Creasman WT, Stehman FB, Brady MF, Burger RA, Thigpen JT, Birrer MJ, Waggoner SE, Moore DH, Look KY, Koh WJ, Monk BJ. Bevacizumab for advanced cervical cancer: final overall survival and adverse event analysis of a randomised, controlled, open-label, phase 3 trial (Gynecologic Oncology Group 240). *Lancet*, 2017 Oct 07; 390(10103): 1654-1663. [PMC free article] [PubMed].
50. Marabelle A, Le DT, Ascierio PA, Di Giacomo AM, De Jesus-Acosta A, Delord JP, Geva R, Gottfried M, Penel N, Hansen AR, Piha-Paul SA, Doi T, Gao B, Chung HC, Lopez-Martin J, Bang YJ, Frommer RS, Shah M, Ghorri R, Joe AK, Pruitt SK, Diaz LA. Efficacy of Pembrolizumab in Patients With Noncolorectal High Microsatellite Instability/Mismatch Repair-Deficient Cancer: Results From the Phase II KEYNOTE-158 Study. *J Clin Oncol*, 2020 Jan 01; 38(1): 1-10. [PMC free article] [PubMed].
51. Colombo N, Dubot C, Lorusso D, Caceres MV, Hasegawa K, Shapira-Frommer R, Tewari KS, Salman P, Hoyos Usta E, Yañez E, Gümüş M, Olivera Hurtado de Mendoza M, Samouëlian V, Castonguay V, Arkhipov A, Toker S, Li K, Keefe SM, Monk BJ., KEYNOTE-826 Investigators. Pembrolizumab for Persistent, Recurrent, or Metastatic Cervical Cancer. *N Engl J Med*, 2021 Nov 11; 385(20): 1856-1867. [PubMed].
52. Kitagawa R, Katsumata N, Shibata T, Kamura T, Kasamatsu T, Nakanishi T, Nishimura S, Ushijima K, Takano M, Satoh T, Yoshikawa H. Paclitaxel Plus Carboplatin Versus Paclitaxel Plus Cisplatin in Metastatic or Recurrent Cervical Cancer: The Open-Label Randomized Phase III Trial JCOG0505. *J Clin Oncol*, 2015 Jul 01; 33(19): 2129-35. [PubMed].