Original Article: A Short Review on the Use of Chemotherapy Drugs in Uterine Cancer

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ABSTRACT

Cervical cancer chemotherapy means the use of drugs that destroy cancer cells. Medicines are injected into a vein or taken by mouth as pills. These drugs enter the bloodstream and reach the whole body. For this reason, chemotherapy is used to treat uterine cancer when uterine cancer spreads to parts that are not accessible for surgery. This method can be used to prevent the recurrence of the disease and its spread to other parts of the body. Chemotherapy is not used to treat endometrial cancer in stages I and II. Chemotherapy is often prescribed in a cycle, meaning a period of treatment and a period of rest. Chemotherapy drugs may be administered on one or more days per cycle. Uterine cancer chemotherapy can be administered intravenously, tablets, ointments and injections. Treatment is often done as an outpatient visit in a hospital, clinic, and in very few cases at home. In most cases, you can return home after the treatment, but in some cases, you may need to stay in the hospital for a while. Chemotherapy can be very hard on your veins, so having a venous access device or an indwelling catheter during treatment can be a good option. The catheter is a thin and flexible tube that may be placed in your body so that there is no need to insert the catheter into the body during subsequent treatments. One end of the catheter is placed in a vein near your heart.
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Introduction

They often use surgery to treat uterine cancer, sometimes radiation therapy, and rarely hormone therapy and chemotherapy [1-3]. Early detection of uterine cancer has a 95% chance of recovery. Chemotherapy is usually done cyclically, and each treatment session is done with one or more weeks off to give the patient's body time to rest and recover. The recommended schedule can vary based on the medications prescribed and other factors. Generally, a course of chemotherapy is completed within three to six months and may

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be repeated if necessary. The drugs that are used during chemotherapy for uterine cancer include:

- Paclitaxel (Taxol)
- Carboplatin
- Doxorubicin (Adriamycin) or liposomal doxorubicin (Doxil)
- Cisplatin
- Docetaxel (Taxotere)

Often, 2 or more drugs are combined for treatment. The most common combinations include carboplatin/paclitaxel and cisplatin/doxorubicin (Figure 1). In less cases, carboplatin/docetaxel and cisplatin/ paclitaxel/doxorubicin may be used. For carcinosarcoma, the chemotherapy drug Ifosfamide is often used alone or in combination with cisplatin or paclitaxel [4-6]. A targeted drug called trastuzumab (Herceptin) may be added for carcinosarcomas that are HER2 positive. (HER2) is a protein that helps some cancer cells grow and spread quickly [5-7].

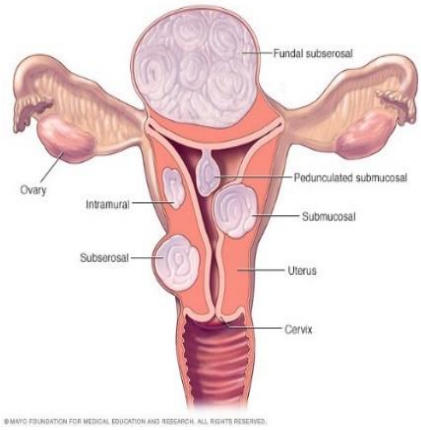

Figure 1. Menorrhagia

In targeted treatment with the help of drugs or other substances, cancer cells are found and attacked without harming the healthy cells of the body. Two types of targeted therapies used to treat uterine cancer are monoclonal antibodies and tyrosine kinase inhibitors. Monoclonal antibody therapy uses antibodies that are either made in the laboratory or naturally produced by the body's immune system. These antibodies identify substances that are on the surface of cancer cells or substances that increase the growth of these cells and neutralize them; As a result, they prevent the growth and development of cancer (Figure 2).

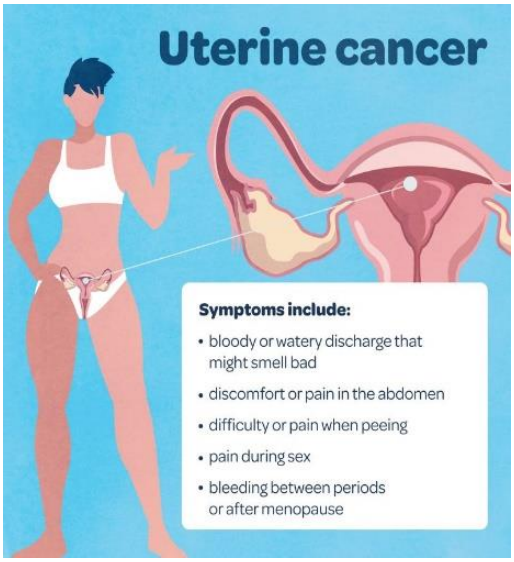

Figure 2. Endometrial Cancer

Anti-metabolites

They are examined in three main groups here:

- Antifolate
- 5-Fluoropyrimidines
- Jamcitabine

Antifolate: The three main drugs in this group include Methotrexate, Pemetrexed, and Pralatrexate.

1) Methotrexate: The most common interpolate used in the clinic. Main applications: Hodgkin's lymphoma, breast, bladder, osteogenic sarcoma, head and neck cancers.

The main route of excretion of the drug is renal. If GFR is reduced, the dose should be adjusted. Renal excretion of all three classes of anti-folate drugs is inhibited by the following drugs. Therefore, they increase the risk of drug toxicity: probenecid, penicillins, cephalosporins, aspirin and NSAIDs

Toxicity: The most important of these are myelosuppression and GI toxicity, which usually resolve within 14 days. Nephrotoxicity - Severe hydration and alkalinization of urine is recommended in cases of high dose of the drug.

Transient increase in hepatic enzyme and bilirubin, which is more common in high doses and returns to normal after 10 days.

Mucositis, diarrhea, pneumonitis and neurotoxicity are other side effects of the drug. Methotrexate enters the fluids accumulated in third body spaces such as ascites, pleural effusion, and then is slowly released. Therefore, due to the increase in half-life, its probability of toxicity increases. These effusions should be drained before methotrexate is administered.

2) Pemetrexed: The main uses of the drug are mesothelioma and NSCLC. Standard dose: 500 mg/m^2 intravenously every three weeks. Metabolism and side effects are similar to methotrexate. Hand Foot Syn How to reduce drug toxicity: Supplementation (350 micrograms oral folic acid + 1000 Bg subcutaneous vitamin B12) should be started at least one week before treatment and repeated every three cycles.

3) Pralatrexate: This drug is stronger than methotrexate and has been approved for the treatment of Peripheral Tcell Lymphoma. Metabolism and side effects are similar to methotrexate. Dosage: 30 mg/m^2 weekly intravenously for 6 weeks - cycles are repeated every 7 weeks.

Methotrexate

Drug classification: Anti-cancer, anti-metabolite.

Dosage: 2.5 and 5 mg tablets, 50 and 100 mg ampoules.

Indication: Methotrexate is used in the treatment of rheumatoid arthritis, psoriasis, as well as in the treatment of carcinomas of the breast, head and neck, lung, trophoblastic tumor, acute lymphocytic leukemia, meningeal leukemia, non-Hodgkin's lymphomas, mycosphonoid, osteosarcoma. It has also been used to treat cancers of the cervix, ovaries, bladder, kidneys, prostate and testes, acute myelocytic leukemia, multiple myeloma, psoriatic arthritis and dermatomycoses.

Pharmacodynamics: Methotrexate is an anti-metabolite and folic acid analogue that binds to dihydrofolate reductase to prevent the reduction of dihydrofolate to tetrahydrofolate, thereby inhibiting the production of DNA and RNA, thymidylate and protein.

Pharmacokinetics: Drug uptake is highly variable. It crosses the blood-brain barrier in small amounts. While after injection through the spinal cord sheath, it easily enters the bloodstream of the brain. Drug metabolism is hepatic. The final half-life with low consumption values is 3-10 hours and high values are 8-15 hours. The time required to reach the maximum serum concentration after oral administration is 1-2 hours and after intramuscular injection is 30-60 minutes. Excretion of the drug is mainly renal.

Contra indication: This drug is strictly forbidden during pregnancy. It is a group X drug. May cause death or organ failure. In immunodeficiency, it should not be used as an anti-neoplasm drug, as an anti-neoplasm drug, except in special cases. In the treatment of non-neoplastic cases, it should not be used in the presence of severe immune deficiency, renal and hepatic impairment, and decreased bone marrow function.

Side effects: Gastrointestinal ulcers and bleeding, diarrhea, gastrointestinal perforation (may be fatal), decreased white blood cells, bacterial or septic infections, decreased platelets, stomatitis, ulcers, gingivitis, pharyngitis, loss of appetite, nausea and vomiting an important and relatively common side effect is methotrexate.

Fluorouracil

Drug classification: Anti-cancer, anti-metabolite

Dosage: 500 and 1000 mg ampoules

Consumption in pregnancy: Group X

Indication: Fluorouracil is used to treat colorectal, breast, stomach and pancreatic carcinomas. It has also been used in the treatment of carcinoma of the bladder, prostate, ovary, cervix, uterus, lungs and liver, neck, discharge from malignant tumors in the pleura, peritoneum and pericardium. Fluorouracil is used to treat multiple keratosis from sunlight and skin carcinomas. It has also been used to treat inflammation of the lips caused by sunlight, mucosal leukopenia, dermatitis caused by radiation therapy, Bowen's disease and Query erythroplasia.

Pharmacodynamics: Fluorouracil is an analogue of pyrimidine. In the cell cycle, it is specifically involved in the S phase of cell division and inhibits the production of DNA and RNA by becoming active metabolites in tissues.

Pharmacokinetics: Fluorouracil crosses the blood-brain barrier. Drug metabolism is hepatic and rapid. The half-life of intravenous injection is 10-20 minutes in alpha phase and 20 hours in beta phase. Excretion is mainly through the lungs (60-80%) and kidneys (7-20%).

Contra indication: This drug is strictly forbidden during pregnancy and is classified as a group X drug and may cause fetal death or organ failure (Figure 3).

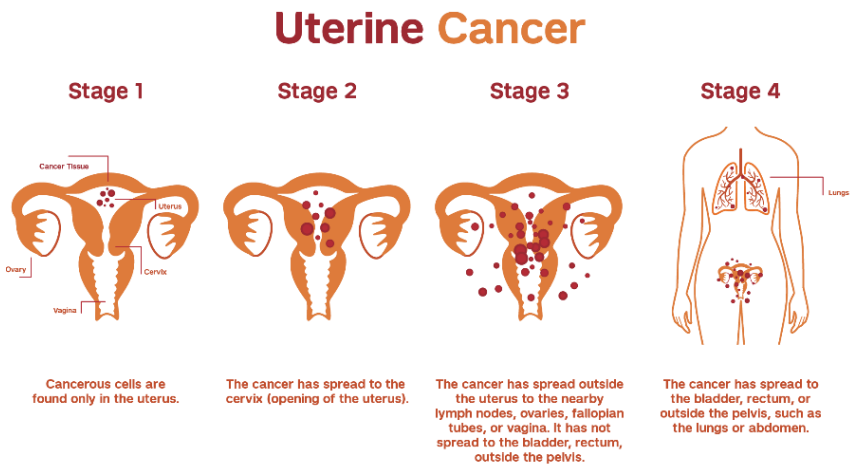

Figure 3. Endometrial and Uterine Cancers

Side effects: Diarrhea, esophagopharyngitis, decreased white blood cells or infection, ulcerative stomatitis, dermatitis and peptic ulcer are important and relatively common side effects of fluorouracil. Inflammatory or allergic reactions, irritation, contact dermatitis, increased skin sensitivity to light, itching, discharge, pain or tenderness of the site are important and relatively common side effects after taking the drug form of the cream.

Drug interactions

Nursing Care

- ❖ This drug is very toxic and should be discontinued as soon as the first symptoms of poisoning such as diarrhea, decreased blood cells, ulcers and gastrointestinal bleeding, esophagopharyngitis, bleeding in any organ, stomatitis and vomiting.
- ❖ However, the drug can be resumed at a lower dose after these symptoms have resolved.
- ❖ Due to the possibility of neurotoxicity, injection of the drug into the spinal sheath should be avoided.
- ❖ The pharmaceutical form of the cream should be used with caution in tissues with

bleeding wounds due to systemic absorption and intoxication, as well as in chloasma.

❖ In case of widespread inflammatory reactions on normal skin after using the cream, stop treatment. Topical corticosteroids after completing drug treatment can accelerate the healing of lesions.

❖ The patient should be hospitalized at the beginning, treatment, hospital.

❖ The dose of drug maintenance should be adjusted according to the individual needs of each patient and based on the patient's hematological responses in proportion to the previous dose. The next dose should be prescribed only after the toxic effects have improved.

❖ It is necessary to measure hematocrit or hemoglobin and count leukocytes and platelets at the beginning and duration of treatment.

❖ Slow intravenous infusion (2-24 hours) reduces the toxicity of the drug, although rapid intravenous injection (1-2 minutes) is more effective.

❖ Before using fluorouracil cream, biopsy is recommended at the beginning and duration of treatment to confirm the improvement of superficial basal cell carcinoma.

❖ In case of pink and soft spots on the cream, the drug should be stopped.

❖ There is a possibility of photosensitivity reaction during treatment with fluorouracil cream and 1-2 months after the end of treatment, so avoid exposure to sunlight.

Jamcitabine

Drug classification: Anti-cancer, anti-metabolite

Dosage: Vials of 200 and 1000 mg

Consumption in pregnancy: Group X

Indication: Gemcitabine is one of the analogues of Cytarabine, which is metabolized inside the cell to active diphosphate and triphosphate nucleosides, which inhibit DNA synthesis and stimulate apoptosis, and are mainly active against S-phase cells in the treatment of hard tumors. Used as tumors of the bladder, breast, lung and pancreas. It is also used in cervical and ovarian cancers.

It is administered intravenously and in the form of hydrochloride. Prescription doses are calculated on a base basis. 1.14 grams of hydrochloride form of the drug is approximately equivalent to one gram of Gemcitabine. The concentration of the infusion solution should not exceed 40 mg/ml of Gemcitabine. The recommended starting dose is 1 g/m Gemcitabine given by infusion over 30 minutes, followed by adjusted doses based on therapeutic response and intoxication. In the treatment of pancreatic cancer, the initial course of treatment is given up to 7 times this dose at one-week intervals, and one week after recovery with the infusion regimen once a week for 3 consecutive weeks of 4 weeks. In the treatment of non-small cell lung cancer and bladder cancer, this drug is usually given in combination with cisplatin.

The recommended doses of gemcitabine are high once a week for 3 weeks, followed by a week of rest or alternatively 1.25 g/m of this drug on days 1 and 8 of a 21-day period. Patients are given and adjusted doses according to the occurrence of poisoning. In breast cancer, the drug is given in combination with a taxan such as paclitaxel and the prescribed dose of gemcitabine is 1.25 g on days 1 and 8 of a 21-day period, adjusted according to the toxicity.

Pharmacodynamics

Citabine kills cells that cause DNA synthesis and blocks cell progression across the G1/S phase boundary. Citabine is metabolized by nucleoside kinase to diphosphate (dFdCDP) and nucleoside triphosphate (dFdCTP). Citabine diphosphate inhibits ribonucleotide reductase. The enzyme responsible for catalyzing the reactions that deoxynucleotide phosphate promotes for DNA

synthesis, thereby reducing the concentration of deoxynucleotide containing dCTP. Citabine triphosphate competes with dCTP for DNA binding. Decrease in intracellular concentration of dCTP by diphosphate action increases triphosphate binding to DNA (self-amplification).

Pharmacokinetics

Following intravenous administration, the drug is rapidly cleared from the blood and is metabolized by cytidine deaminase in the liver, kidney, blood, and other tissues of the body. Its clearance is approximately 25% lower in women than in men, and almost all of the prescribed dose is excreted in the urine in the form of doxy-difluorouridine (dFdU), with only about 1% found in the feces. Its intracellular metabolism produces the metabolites mono, di and triphosphate, the latter two of which are active. Its half-life varies from 42 to 94 minutes, depending on age and sex. The intracellular half-life of the triphosphate form varies between 0.7 and 1.2 hours.

Contra indication: Allergy to gemcitabine, pregnancy, lactation.

Drug interactions: No case reported.

Side effects: Like cytarabine, flu-like symptoms and skin rashes are relatively common. Edema, shortness of breath and alopecia are also common. Pulmonary edema has been reported uncommonly, and rare cases of hypotension have been reported. It can cause insomnia, and patients who have been severely affected should not drive or use machines. Severe poisoning in the form of life-threatening esophagitis and pneumonia has been reported in patients receiving chest radiotherapy while taking the drug. Kidney and liver disorders should be used with caution. In some cases, uremic-hemolytic syndrome has been reported to lead to irreversible renal failure, and medication should be discontinued in the early stages of the symptoms of hemolytic microangiopathy.

Aminoglutethimide

Drug classification: Anti-cancer, anti-androgen

Dosage: 250 mg tablets

Consumption in pregnancy: Group X

Indication: Metastatic breast cancer, Cushing's syndrome, symptomatic treatment of advanced prostate cancer in men, prostate cancer. For the treatment of cancer, 250 mg up to 4 times a day is prescribed. For complementary treatment with a corticosteroid, hydrocortisone is usually given at a dose of 20-30 mg per day in divided doses. Used to treat Cushing's syndrome up to 2 grams per day. Complementary corticosteroid therapy may not be required in these patients.

Pharmacodynamics

Antineoplastic effect: Aminogluttemide interferes with the action of the cholesterol-converting enzyme delta-5-pregnenolone and inhibits the synthesis of corticosteroids, androgens, and estrogens, so by suppressing the adrenal glands, they also inhibit the growth of tumors that need growth.

Pharmacokinetics

Half-life: 13 hours (in long-term use 7 hours), method of use: oral, onset of action: 3-5 days, peak effect: unknown, duration of action: unknown, excretion: This drug is metabolized in the liver and its metabolites through The kidneys are excreted.

Contra indication: Hypersensitivity to the drug.

Side effects: Drowsiness, headache, dizziness, hypertension, tachycardia, rash of morbilliforms, pruritus, urticarial, nausea, anorexia, vomiting, transient leukopenia, agranulocytosis, thrombocytopenia, fever, myalgia, adrenal insufficiency, hirsutism, hypothyroidism.

Drug interactions: Concomitant use of this drug with dexamethasone reduces the half-life and therapeutic effects of dexamethasone. Concomitant use of this drug with warfarin

reduces the half-life and therapeutic effects of warfarin.

Tamoxifen

Drug classification: Anti-cancer, anti-metabolite

Therapeutic dose: 10 and 20 mg tablets

Consumption in pregnancy: Group X

Indication: Tamoxifen is used to treat breast cancer and infertility associated with oligomenorrhea or secondary amenorrhea.

Pharmacodynamics: Tamoxifen is a non-steroidal anti-estrogen that also has weak estrogenic effects. Tamoxifen inhibits estradiol receptors. Induction of ovulation occurs by occupying estrogen receptors and eliminating the inhibitory effect of the hormone, thereby stimulating the secretion of gonadotropin-releasing hormone from the hypothalamus.

Pharmacokinetics

The metabolism of tamoxifen is hepatic and has an intestinal-hepatic cycle. The desired therapeutic effect is achieved 4-10 weeks after the start of treatment. The antagonistic effects of the drug may continue for several weeks after a single dose. The drug is often excreted as a metabolite in the bile and feces.

Contra indication: Pregnancy and lactation

Side effects: Flushing, vaginal bleeding, menstrual cramps, vulvar itching, gastrointestinal disorders, tumor inflammation, platelet depletion, fluid retention, baldness, uterine fibroids, visual disturbances (corneal changes, cataracts and retinopathy) and decreased platelets or white blood cells They are side effects of the drug.

Drug interactions: Estrogens may interfere with the therapeutic effects of tamoxifen. Compounds such as cimetidine, famotidine, ranitidine, and other antacids increase the pH of the stomach, causing the drug to dissolve prematurely, resulting in abnormal opening of the intestinal coated tablets.

Dactinomycin

Therapeutic classification: DNA transcription inhibitor, anti-cancer

Dosage: 0.5 mg vial

Consumption in pregnancy: X Group

Indication: Dactinomycin is used to treat Owing sarcoma, thyroid and trophoblastic tumors. It has also been used in the treatment of carcinoma of the uterus, testis, Wilms' tumor, tumorrophoblastic tumor and rhabdomyosarcoma, malignant melanoma and Kaposi's sarcoma.

Pharmacodynamics: Dactinomycin acts non-specifically in the cell cycle, by binding to DNA and substituting between its bases, inhibiting the production of DNA-dependent RNA.

Pharmacokinetics: The drug does not cross the blood-brain barrier. It is poorly metabolized and has a half-life of 36 hours. Excretion of the drug is mainly through bile and 30% of the drug can be recovered in the feces and urine after a week.

Contra indication: Hypersensitivity to this drug, active shingles or chickenpox.

Side effects: Anemia that may lead to aplastic anemia, difficulty swallowing and heartburn, gastrointestinal ulcers or inflammation of the rectum, decreased white blood cells and platelets, ulcerative stomatitis, anaphylaxis and thrombophlebitis are important and relatively common side effects of the drug.

Drug interactions: Interferes with allopurinol, colchicine, doxorubicin and vitamin K.

Eribulin

Drug classification: Anti-cancer and mitosis inhibitor

Therapeutic dose: 1 mg ampoule

Consumption in pregnancy: X Group

Indication: Aribulin is a mitotic inhibitor that is prescribed for some cancers, including metastatic breast cancer and liposarcoma. This drug is produced as an injection ampoule with different doses and is available under the brand name Halaven in Iran at a dose of 0.44 mg in 1 ml and 2 ml.

Pharmacodynamics: It is an inhibitor of mitosis that leads to cell death by inhibiting the growth phase of microtubules.

Pharmacokinetics: The metabolism of this drug is brief and unknown, and most of it is excreted in the feces, and about 9% of it is excreted in the urine. Aribulin has a half-life of about 40 hours.

Contra indication

Contraindications: Allergy to this drug or similar drugs, electrolyte disturbance congenital long QT syndrome. Caution: People with QT prolongation or family history. If a person has torsade's depointes. In people with ventricular arrhythmias, bradycardia, congestive heart failure, people with liver and kidney defects.

Side effects: Neutropenia, anemia, alopecia, peripheral neuropathy, nausea/vomiting, constipation, arthralgia/ myalgia, fever, weight loss, loss of appetite, headache, increased liver enzymes, diarrhea, pain, dyspnea, cough, urinary tract infection, mucositis, increased tears eye, dyspepsia, abdominal pain, dry mouth, peripheral edema, lung infection, hypokalemia, muscle spasm, muscle weakness, change in mouth taste, dizziness, insomnia, depression, rash. Serious complications: pancytopenia, fibril neutropenia, allergic reactions, peripheral neuropathy, increased QT on ECG, pancreatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis.

Drug Interactions: Aribulin interacts with immunosuppressive drugs, bone marrow suppressants, and drugs that prolong QT in the patient's ECG.

Discussion

Advanced endometrial cancer (FIGO stage III and IV) is uterine cancer that has spread from the uterus to the ovaries, vagina, other nearby tissues, draining lymph nodes, or other organs. Women are usually treated with surgery to remove as much of the tumor as possible. They are then given adjuvant (meaning "added") radiotherapy (high-energy X-rays and other radiation that destroy cancer cells), or chemotherapy (anti-cancer drugs), or both. There is uncertainty about which treatment (radiotherapy or chemotherapy or both) has the greatest impact on patient survival after surgery, and which anticancer drugs work best. Cervical cancer begins in the cells of the lining of the cervix and the lower part of the uterus. For many patients with cervical cancer, some type of surgery is used to diagnose cervical cancer, determine how far the cancer has spread, and treat cervical cancer (if the cancer is detected at an early stage).

Radical hysterectomy for the treatment of cervical cancer

For this operation, the surgeon removes the uterus along with the tissues near the uterus (parametric and uterine and sacral ligaments), the cervix and the upper part about [2-3 cm]. The ovaries are not removed unless there is another medical reason to do so. In a radical hysterectomy, more than one simple tissue is removed. Therefore, the hospital stay can be longer. At this time, some lymph nodes are also removed and checked for cancer (Figure 4). This surgery is usually done through a large incision in the abdomen (also called open surgery).

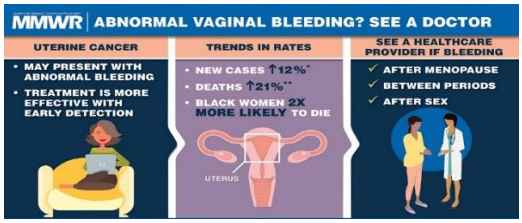

Figure 4. Uterine Cancer Incidence and Mortality

This surgery is usually done through a large incision in the abdomen (also called open surgery). Often, some pelvic lymph nodes are also removed. (This procedure, known as lymph node dissection, is discussed later in this section.) Radical hysterectomy can also be performed laparoscopically or robotically. Also, these methods are referred to as minimally invasive surgery. Compared to open surgery, laparoscopic (or robotic) surgery can result in less pain, less blood loss during the procedure, and less hospital stay.

However, it is important to note that recent studies have shown that women who have a minimally invasive radical hysterectomy for cervical cancer have a higher risk of cancer recurrence and higher risk of death from cancer than those who have surgery through an abdominal incision. do Laparoscopic surgery may still be an option for a small group of women with early-stage cancer, but you should discuss your options carefully with your doctor.

A modified radical hysterectomy is similar to a radical hysterectomy, but it does not remove as much of the vagina and the tissues around the uterus (the parametrium and uterine and sacral ligaments), and the lymph nodes are usually not removed.

A radical tracheectomy allows women to be treated without losing the ability to have children. The procedure is performed either through the vagina or abdomen, and is sometimes performed using a laparoscope. This method removes the cervix and the upper part of the vagina, but not the body of the uterus. The surgeon then places a permanent "string" suture inside the uterine cavity to keep the cervix closed, as is done naturally in the cervix. Nearby lymph nodes are also removed using laparoscopy, which may require another incision. This operation is performed either through the vagina or the abdomen. After a trachectomy, some women can carry their pregnancy to term and give birth to a healthy baby by caesarean section. Although there is a possibility of miscarriage in women who have done this surgery.

Conclusion

In radiation therapy, X-rays or high-energy particles are used to destroy cancer cells. Aggressive chemotherapy is usually more effective, so radiation therapy is rarely used as the main treatment for ovarian cancer. However, it can be useful in treating areas where the cancer has spread, either near the original tumor or in a distant organ, such as the brain or spinal cord. Cryotherapy is a type of ablation in which a very cold metal probe is placed directly on the cervix and destroys abnormal cells by freezing them. This method is used to treat (CIN). This treatment method can be done in a doctor's office or clinic. In this method, a focused laser beam is directed through the vagina to burn the abnormal cells. This may be done in the doctor's office under local anesthesia or in the operating room under general anesthesia because it can be more uncomfortable than cryotherapy. It is also used to treat (CIN). Another method for treating cervical intraepithelial neoplasia (CIN) is called conization surgery. In this method, the doctor removes a piece of cone-shaped tissue from the cervix. This removed tissue includes the transformation area, which is most likely where

cervical pre-cancers and cancers start from this area. Cone biopsy is not only used to detect pre-cancers and cancers, but it can also be used as a treatment because it can sometimes remove pre-cancers and some early-stage cancers.

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