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Review on uterine cancer

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ABSTRACT

The aim of this work was update current pharmacotherapeutic approaches to practising pharm D students and clinical pharmacists to understand more on risk factors, common signs and symptoms, diagnosis techniques, better management and prevention of uterine cancer. Cancer of the uterus is the most common cancer of female reproductive organs. It's the fourth most common cancer among women overall, behind breast cancer, lung cancer, and colorectal cancer. The most important risk factor for endometrial cancer is the hormone estrogen. Abnormal uterine bleeding can be used as an early detector for uterine cancer. There is no screening test for endometrial cancer. The only reliable diagnostic test for this cancer is a tissue biopsy. Removal of uterus is essential to treat endometrial cancer. By getting better knowledge about this the prevalence of uterine cancer can be reduced. We collected the information from various sources including international journals and databases. Major risk factors, common signs and symptoms, newer diagnostic techniques, and recent developments in management of uterine cancer were analysed and discussed. The aim of this review is to determine the epidemiological data, various signs and symptoms, common risk factors, early detection techniques and newer developments in the managements and preventive methods of uterine cancer. It may be helpful to the people who all are working in the field of healthcare profession.

Keywords: Uterine cancer, Management and prevention of uterine cancer.

1. INTRODUCTION

The uterus, or womb, is part of a woman's reproductive system. It's about the size and shape of a hollow, upside-down pear. The uterus sits low in the abdomen between the bladder and rectum and is held there by muscle. It's joined to the vagina (birth canal) by the cervix, which is the neck of the uterus. The uterus is where a foetus grows.

Cancer that begins from abnormal cells in the lining of the uterus (the endometrium) or the muscle tissue (myometrium).[1] Cancer is a disease in which cells in the body grow out of control. Cancer is always named for the part of the body where it starts, even if it spreads to other body parts later. When cancer starts in the uterus, it is called uterine cancer. The uterus is the pear-shaped organ in a woman's pelvis (the area below your stomach and in between your hip bones). The uterus, also called the womb, is where the baby grows when a woman is pregnant. The most common type of uterine cancer is also called endometrial cancer because it forms in the lining of your uterus, called the endometrium. There are different types of uterine cancer. The most common type starts in the endometrium, the lining of the uterus. This type of cancer is sometimes called endometrial cancer.

All women are at risk for uterine cancer, but the risk increases with age. Most uterine cancers are found in women who are going through or who have gone through menopause (the time of life when your menstrual periods stop). Uterine cancer usually occurs after menopause. [2,3]

Uterine cancer is the fourth most common cancer in women in the United States and the most commonly diagnosed gynecologic cancer. Several risk factors for endometrial cancer have been identified.

Obesity increases the risk threefold for women 21 to 50 pounds overweight; risk is heightened to 10 fold for individuals exceeding ideal body weight by 50 pounds. Risk for nulliparous women is two times higher than primiparas and three times that of multiparous women.Late menopause (age 52 versus age 49)

leads to a 2.4-fold increased incidence of endometrial cancer Hormones significantly alter the risk of endometrial neoplastic disorders. "Unopposed" estrogen replacement therapy in postmenopausal patients increases endometrial cancer risk 4- to 15 fold; risk is related to dose and duration of therapy. Tamoxifen an antiestrogen used in the therapy of breast cancer patients increases the risk of endometrial cancer two- to threefold. Estrogen-secreting tumors (granulosa cell tumors of the ovary) and polycystic ovarian disease increase the risk of endometrial cancer. Hypertension has been reported to increase endometrial cancer risk one fold, and diabetes elevates the risk three fold. Ironically, smoking one pack of cigarettes a day decreases risk by about 30%, presumably due to enhanced estrogen metabolism in smokers.

2. EPIDEMIOLOGY

Uterine cancer is the fourth most common cancer in women in the United States and the most commonly diagnosed gynecologic cancer (Figure 1).

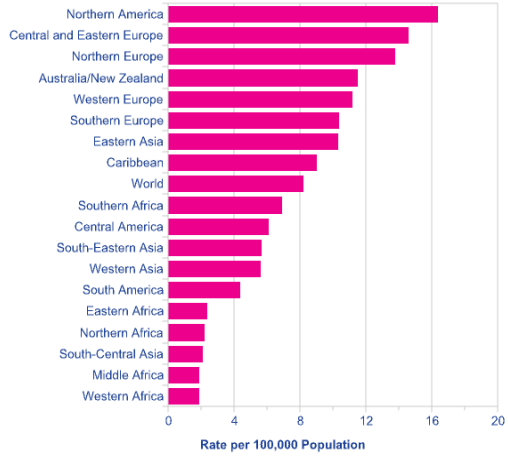

Figure -1: Uterine cancer in world wide

2.1. In india

Endometrial cancer is common in western women, and the rates are very high; however in India, the rates are as low as 4.3 per 100,000 (Delhi).

The present study showed that endometrial cancer patients with localized disease at diagnosis have a good outcome in India. [4-9]

2.2. Diagnosis

2.2.1. Pelvic examination

A speculum - a device that opens the vagina - is inserted so that the doctor may look carefully at the vagina and cervix. The doctor will be looking out for any lumps or changes in shape or size. [10-13]

2.2.2. Imaging tests for endometrial cancer

2.2.2.1. Transvaginal ultrasound or sonography

Ultrasound tests use sound waves to take pictures of parts of the body. For a *transvaginal ultrasound* a probe that gives off sound waves is inserted into the vagina. The sound waves create images of the uterus and other pelvic organs. These images often help show whether the endometrium is thicker than usual, which can be a sign of endometrial cancer. It may also help see if a cancer is growing into the muscle layer of the uterus (myometrium).

2.2.2.2. Cystoscopy and proctoscopy

In cystoscopy the tube is placed into the bladder through the urethra. In proctoscopy the tube is placed in the rectum. These exams allow the doctor to look for possible cancers. Small tissue samples can also be removed during these procedures for pathologic (microscopic) testing.

2.2.3. Blood tests

2.2.3.1. Complete blood count

Many times women with a lot of blood loss from the uterus will have low red blood cell counts (anemia).

2.2.3.2. CA 125 blood test

CA 125 is a substance released into the bloodstream by many, but not all, endometrial and ovarian cancers. In endometrial cancer, a very high blood CA 125 level suggests that the cancer has probably spread beyond the uterus. If CA 125 levels are high before surgery. [14]

2.2.4. Biopsy

A biopsy is the removal of a sample of tissue or cells so that a pathologist can examine them, usually under a microscope for the presence of cancerous cells.

2.2.5. Hysteroscopy

The doctor uses a hysteroscope, a thin kind of telescope which is inserted through the vagina and into the uterus. For this technique doctors insert a tiny telescope (about $^{1}/_{6}$ inch in diameter) into the uterus through the cervix. To get a better view of the inside of the uterus, the uterus is filled with salt water (saline). This lets the doctor see and biopsy anything abnormal, such as a cancer or a polyp.

2.2.6. Dilation and curettage (D&C)

If the endometrial biopsy sample doesn't provide enough tissue, or if the biopsy suggests cancer but the results are uncertain, a D&C must be done. In this outpatient procedure, the opening of the cervix is enlarged (dilated) and a special instrument is used to scrape tissue from inside the

uterus. This may be done with or without a hysteroscopy.

2.2.7. Computed tomography (CT)

CT scans are not used to diagnose endometrial cancer. CT scans can also be used to precisely guide a biopsy needle into a suspected area of cancer spread. For this procedure, called a CT-guided needle biopsy, you remain on the CT scanning table while a doctor moves a biopsy needle toward the mass. CT scans are repeated until the doctor is sure that the needle is inside the mass. A fine needle biopsy sample (tiny fragment of tissue) or a core needle biopsy sample (a thin cylinder of tissue about ½ inch long and less than $^1/_8$ inch in diameter) is removed and looked at under a microscope.

2.2.8. Magnetic resonance imaging (MRI)

MRI is a good way to tell whether, and how far, the endometrial cancer has grown into the body of the uterus.

2.2.9. Positron emission tomography (PET)

In this test radioactive glucose (sugar) is given to look for cancer cells. Because cancers use glucose (sugar) at a higher rate than normal tissues, the radioactivity will tend to concentrate in the cancer. [15-20]

2.3. Treatment

2.3.1. Surgery

Most doctors will recommend that women with endometrial cancer have their uterus surgically removed (hysterectomy). The fallopian tubes and ovaries will usually be removed as well (salpingo-oophorectomy).

Lymph nodes may also be removed and sent to the laboratory for testing. Removing lymph nodes helps in the staging of the cancer.If the patient is premenopausal, she will stop having periods after the operation and will not be able to get pregnant. There may be symptoms of menopause, such as hot flashes, night sweats and vaginal dryness.oophorectomy, and node sampling followed by postoperative irradiation .Preoperative intracavitary and external-beam radiation

2.3.2. Stage I disease

For disease confined to the uterus, patients are placed in low-, intermediate-, and high-risk categories, and adjuvant therapies are based on pathologic features. In general, stage I tumors that are higher grade and more deeply invasive into the myometrium have a greater risk for recurrence and benefit from adjuvant therapy postoperatively.

Whole-pelvis radiotherapy, with or without vaginal cuff brachytherapy, is the most commonly used adjuvant postoperative treatment modality. Patients with the histologic variant papillary serous carcinoma, an aggressive endometrial lesion with a high risk for extrapelvic recurrence, are generally offered chemotherapy to reduce postoperative recurrence risk.

2.3.3. Stage II disease

For disease involving the uterine cervix, there are several treatment options. When unsuspected cervical stromal involvement is found during surgery, postoperative external-beam radiotherapy with vaginal cuff brachytherapy is indicated. If cervical involvement is known preoperatively, various combinations of surgery and radiotherapy have been used:

- Hysterectomy, bilateral salpingo-oophorectomy, and node sampling followed by postoperative irradiation
- Preoperative intracavitary and external-beam radiation therapy followed by hysterectomy and bilateral salpingo-oophorectomy
- Radical hysterectomy and pelvic lymphadenectomy

2.3.4. Stage III disease

In general, postoperative whole-pelvis radiotherapy (vaginal cuff brachytherapy) is indicated when disease involves adnexal structures or retroperitoneal nodes. Patients with para-aortic involvement might benefit from extended-field radiotherapy.

2.3.5. Stage IV disease

The site of metastatic disease and associated symptoms dictate the appropriate treatment of stage IV endometrial cancer. For bulky pelvic disease, radiation therapy consisting of a combination of intracavitary and external beam irradiation is used. When distant metastases are present, systemic therapy is indicated. Satisfactory tumor responses to hormonal treatment with progestational agents can often be achieved in well-differentiated (grades 1 and 2) tumors. Useful chemotherapeutic agents include doxorubicin and paclitaxel.

2.4. Pharmacological treatment

2.4.1. Medication choices

Medicine treatment for endometrial cancer may include hormone therapy or chemotherapy.

Progestin hormone therapy. Examples include:

- Hydroxyprogesterone (Delalutin).
- Megestrol (Megace).

- Medroxyprogesterone (Provera).
- Chemotherapy, used alone or in combination. Examples include:
- Doxorubicin.
- Cisplatin.
- Paclitaxel.
- Carboplatin.
- Topotecan.

Side effects

The common side effects of progesterone hormones include:

- Breast tenderness
- Tiredness
- Nausea
- Fluid retention

2.4.2. Progestin hormonal therapy

Hormone therapy works by blocking the action of hormones and stopping cancer cells from growing. Progestin hormone therapy may be used to slow the growth of endometrial cancer. This may be done when the cancer has spread to other parts of the body. Or it may be done for a young woman with early-stage cancer so she can become pregnant in the future. Progestin hormone therapy may be given to women who are unable to have surgery or radiation therapy.

Side Effects

- Dizziness.
- Mild shortness of breath
- Hot flashes or sweating.
- Decreased sex drive.
- Insomnia.
- Changes in eyesight.

Dose

Progesterone Injection USP, 50 mg/mL is available in 10 mL multiple dose vials, individually boxed.

2.4.3. Chemotherapy

Chemotherapy (often called “chemo”) is the use of cancer-fighting drugs given into a vein or by mouth. These drugs enter the bloodstream and reach throughout the body, making this treatment potentially useful for cancer that has spread beyond the endometrium. The ability of chemotherapy to kill cancer cells depends on its ability to halt cell division. Usually, the drugs work by damaging the RNA or DNA that tells the cell how to copy itself in division. Chemotherapy will kill the cells, causing the tumor to shrink. They also induce cell suicide (self-death or apoptosis).

Chemo is often given in cycles, in which a period of treatment is followed by a rest period. The chemo drugs may be given on one or more days in each cycle.

Drugs used in treating endometrial cancer may include:

- Paclitaxel
- Carboplatin
- Doxorubicin or liposomal doxorubicin
- Cisplatin

Most often two or more drugs are combined for treatment. Sometimes chemo is given for a few cycles, followed by radiation. Then chemo is given again. This is called sandwich therapy and is sometimes used for endometrial papillary serous cancer and uterine carcinosarcoma.

2.4.3.1. PACLITAXEL

Paclitaxel is an anti-cancer ("antineoplastic" or "cytotoxic") chemotherapy drug.Paclitaxel is classified as a "plant alkaloid," a "taxane" and an "antimicrotubule agent."

Side effects

- Low blood counts. Your white and red blood cells and platelets may temporarily decrease.
- Hair loss
- Arthralgias and myalgias
- Peripheral neuropathy (numbness and tingling of the hands and feet)
- Diarrhea
- Mouth sores
- Hypersensitivity reaction.Fever, facial flushing, chills, shortness of breath, or hives.

Mechanism

- Antimicrotubule agents (such as Paclitaxel), inhibit the microtubule structures within the cell. Microtubules are part of the cell's apparatus for dividing and replicating itself. Inhibition of these structures ultimately results in cell death.

Dose

- TAXOL (paclitaxel) Injection is a clear, colorless to slightly yellow viscous solution. It is supplied as a nonaqueous solution intended for dilution with a

suitable parenteral fluid prior to intravenous infusion.

- TAXOL is available in 30 mg (5 mL), 100 mg (16.7 mL), and 300 mg (50 mL) multidose vials.
- Each mL of sterile nonpyrogenic solution contains 6 mg paclitaxel, 527 mg of purified Cremophor® EL (polyoxyethylated castor oil) and 49.7% (v/v) dehydrated alcohol.

2.4.3.2. CARBOPLATIN

Carboplatin is an anticancer drug ("antineoplastic" or "cytotoxic") chemotherapy drug. Carboplatin is classified as an "alkylating agent."

Side effects

- Low blood counts (including red blood cells, white blood cells and platelets)
- Taste changes
- Hair loss
- Blood test abnormalities: Abnormal magnesium level
- Burning sensation at the injection site
- Peripheral neuropathy
- Central neurotoxicity: Infrequent but patients over age 65 are at increased risk.
- Nephrotoxicity
- Hearing loss (ototoxicity) - loss of high pitched sounds.

Dose

Carboplatin Injection is supplied as a sterile, aqueous solution available in 50 mg/5 mL, 150 mg/15 mL, 450 mg/45 mL or 600 mg/60 mL multi-dose vials containing 10 mg/mL of carboplatin for administration by intravenous infusion.

Mechanism

The drugs work by damaging the RNA or DNA that tells the cell how to copy itself in division. If the cells are unable to divide, they die. The faster the cells are dividing, the more likely it is that chemotherapy will kill the cells, causing the tumor to shrink. They also induce cell suicide (self-death or apoptosis).

2.4.3.3. Doxorubicin

Mechanism

Doxorubicin interacts with DNA by intercalation and inhibition of macromolecular biosynthesis. This inhibits the progression of the enzymetopoisomerase II, which relaxes supercoils in DNA for transcription. Doxorubicin stabilizes the topoisomerase II complex after it has broken the DNA chain for replication, preventing the DNA double helix from being resealed and thereby stopping the process of replication.

Side effects

- sores in the mouth and throat
- loss of appetite (and weight loss)
- weight gain
- stomach pain
- diarrhea
- increased thirst
- unusual tiredness or weakness
- dizziness
- hair loss

Dose

- Doxorubicin is an intravenous (IV) medicine. The exact dose that you receive and how often you are treated depend on your body size, the type of cancer you have, and how much of your body is affected by the cancer.
- When used in combination with other chemotherapy drugs, the most commonly used dosage of doxorubicin is 40 to 60 mg/m2 IV every 21 to 28 days
- Alternatively, 60 to 75 mg/m2 IV once every 21 days.
- The lower doses are recommended for patients with inadequate marrow reserves due to old age, prior therapy, or neoplastic marrow infiltration. [21-38]

2.4.3.4. Preoperative evaluation

Patients with endometrial cancer often have comorbidities such as obesity, hypertension, diabetes, and cardiac and pulmonary dysfunction that make them high-risk or poor surgical candidates.

A physical examination and chest radiography are required for preoperative staging of the usual histology (i.e., type I endometrioid grade 1), clinical stage I patient. Directing all other preoperative testing toward optimizing the surgical outcome is recommended.

If the cervix appears to be enlarged which suggests possible tumor involvement the differential diagnosis of cervical adenocarcinoma should be considered. If cervical involvement is confirmed, treatment options include radical hysterectomy or preoperative radiation therapy.

The finding of vaginal, parametrial, or adnexal extension of disease can complicate treatment planning, and a subspecialist may be required for complete surgical resection.

2.4.3.5. Surgical staging

Most women with endometrial cancer benefit from systematic surgical staging, which includes pelvic washings, bilateral pelvic and para-aortic lymphadenectomy, and complete resection of all disease. Exceptions include young or perimenopausal women with grade 1 endometrioid adenocarcinoma associated with atypical endometrial hyperplasia, and women at increased risk of mortality secondary to comorbidities.

Retroperitoneal lymph node assessment is a critical component of surgical staging and is associated with improved survival rates. Palpation of the retroperitoneum is not recommended because it cannot substitute for surgical dissection of nodal tissue for histopathology. Women who test negative for disease of the pelvic and para-aortic lymph nodes and for abnormal pelvic cytology have better survival rates compared with women who have matched uterine histologic factors and positive results on testing of nodes or cytology.

2.4.3.6. Postoperative therapy

Women who do not receive postoperative radiation with surgical stage I endometrial cancer may have isolated recurrent disease in the vagina. Treatment of these recurrences demonstrates a 60 to 75 percent survival rate; these recurrences can be managed subsequently, avoiding the unnecessary exposure of radiation toxicity. Therefore, postoperative radiation therapy can reduce the risk of local recurrence in patients with surgical stage I disease. When radiation therapy is being considered, the cost and toxicity should be balanced with the evidence that therapy neither improves survival nor reduces distant metastasis.

2.4.3.7. Radiation therapy

Typically, the primary treatment of endometrial cancer involves hysterectomy. However, in patients who are exceptionally poor surgical candidates (less than 3.5 percent), primary therapeutic radiation may be considered.

Radiation therapy alone does not allow for directed therapy, and it fails to eradicate the uterine cancer in 10 to 15 percent of patients. The cancer-specific five-year survival rates in stage I inoperable patients (80 percent) are less than the rates in stage I operable patients (98 percent) and are related to tumor grade. Therefore, a careful preoperative evaluation and appropriate consultation are recommended before denying any woman the benefits of hysterectomy.

2.4.3.8. Progestin therapy in atypical endometrial hyperplasia and endometrial cancer

Atypical endometrial hyperplasia and endometrial cancer should be considered as part of a continuum. For women who do not desire fertility, hysterectomy should be recommended for treatment of atypical endometrial hyperplasia because of the high risk of an underlying cancer. However, women who wish to maintain fertility, whether they have a diagnosis of atypical endometrial hyperplasia or grade 1 endometrioid adenocarcinoma, may be treated with progestins to try to reverse the lesion.

Progestational agents have been evaluated as a primary treatment modality of early grade 1 disease in women who want to maintain their fertility or in women who are extremely poor operative candidates. Oral, parenteral, or intrauterine device delivery of progestin has been successful, with response rates ranging from 58 to 100 percent. Long-term outcomes are uncertain, but the disease will likely recur in most patients.

Continued histologic monitoring is vital to ensure the response of medication and exclude recurrence. It is recommended that, after therapy, patients undergo serial complete intrauterine evaluation every three months to document response.

3. FOLLOW UP

When the disease is confined to the uterus, the types of recurrence depend on histologic cell type, lymph- vascular invasion, depth of invasion, and the use of radiation therapy.

Recurrent disease in the pelvis, particularly in the vaginal cuff, can be treated successfully with radio-therapy in the nonirradiated patient. Vaginal or pelvic recurrence can be detected and treated successfully in 68 to 88 percent of women who have not received radiation therapy. Monitoring patients with a speculum and rectovaginal examination is recommended every three to four months for two to three years, then twice a year.

4. REVIEW

Patients treated for endometrial cancer should be followed up for both recurrence and late toxicity. Although there is lack of evidence for clear benefit and follow-up schedules vary between centres, the following schedule could be advised. For the first 3 years patients can be seen

3- to 4-monthly. History, physical and vaginal examination should be performed.

Further investigations (CT, MRI, blood tests, examination under anaesthesia) can be requested if clinically indicated. For the next 2 years and until the completion of 5 years in total, 6-monthly appointments are recommended. During this surveillance the increased risk of cancers of the breast, ovary and colon in patients with endometrial cancer should be taken into account. [39]

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