Treatment Strategies of Cancers in Female Reproductive System

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Abstract
This review aims to sketch current scenario of cancers in female reproductive system such as cancer in uterus, ovary, cervix, vagina, vulva, fallopian tube along with hydatidiform and their treatment strategies.

Keywords: Cancer; Female Reproductive System; Treatment Strategy

Introduction
Cancers can take part in any portion of the reproductive tracts. Moreover, linking between each other and metastasize are the major facts in cancer in female reproductive system (FRDC) as well as the development of other cancers. Among a numerous causes, genetic mutation and structural malformations are two major concerns in mutogenic therapy-induced reproductive cancers [1]. A general FRDCs linking is shown in Figure 1.

Figure 1: Linking between cancers in female reproductive system. [UTC: upper part of uterus → cervix → nearby tissues, vagina, lymph nodes → bladder, intestine. distant organs; OVC: ovary(s) → uterus, fallopian tubes, pelvis → outside of pelvis, lymph nodes, liver, small intestine, abdomen → abdomen, liver; CRC: cervix → vagina → vagina, pelvis, ureters, kidney → bladder, rectum, distant organs; VLC: vulva → lower part of urethra or vagina → lymph nodes → bladder, vagina, urethra, rectum, distant lymph nodes; VGC: vagina → pelvis → pelvis (spread) → bladder, rectum, pelvis; FLTC: fallopian tubes → pelvis → intestine, liver; lymph nodes → distant organs (Stage I → Stage II → Stage III → Stage IV)].
Aim of this review is to tell about current circumstances on FRDCs.

Cancers and treatment strategies of FRDCs

Uterus cancer (UTC)

Uterus (UTC) or endometrial cancer develops in the lining of the endometrium. It is an elderly (50 to 60 years) occurring cancer and is the most common gynecologic cancer (fourth most common) in women. Adenocarcinomas (Type I: non-aggressive, respond to estrogen; Type II: aggressive) account > 80%, while sarcomas by < 5%. High fatty diet, obesity, diabetes, hypertension and high level of estrogen are the most frequent causes of UTC. Early menstruation (menarche), menstrual problems (related to ovulation), not having any children, tumors that may produce estrogen, drugs (estrogen and/or estrogen like activity, or without a progestin) along with family history with other reproductive cancers and using tamoxifen for more than 5 years are also linked to UTC. Abnormal bleeding after menopause and between menstrual periods, irregular, heavy, or longer periods, vaginal bleeding and blood-tinged discharge are the symptoms in UTC. PAP test, endometrial biopsy, blood tests (especially for estrogen levels), kidney and liver function tests, chest x-ray, electrocardiography and CT are done to detect the UTC.

Treatment strategy

Surgery: salpingo-oophorectomy, laparoscopic surgery, robotic-assisted laparoscopic surgery, subtotal (supracervical) hysterectomy, total hysterectomy, radical hysterectomy, chemo and/or radiation therapy, or a progestin (synthetic drugs similar to the hormone progesterone) are commonly used in UTC. Radiotherapy can be given after surgery. Carboplatin, cisplatin, doxorubicin, and paclitaxel are the commonly used chemotherapeutic drugs in this context.

Generally, estrogen promotes the growth of tissue and rapid cell division in the endometrium. Progesterone counterbalances it. Although, tamoxifen blocks the effects of estrogen but it has the same effects as estrogen in the uterus, thus increases the risk of UTC.

Ovarian cancer (OVC)

Ovarian cancer (OVC) or ovarian carcinoma occurs in the elderly women (50 to 70 years). It is the second most common gynecologic cancer and fifth most common cause of cancer deaths in women. Older age, having any children and/or a first late child, early menstruation, late menopause, cancers in uterus, breast, or large intestine (colon) or family history are the common causes of OVC. In the latter case, about 5 to 10% are related to the BRCA1 and BRCA2 genes (most common among Ashkenazi Jewish women). Epithelial carcinomas (surface of the ovaries) account for at least 80%. Others concern with germ cell (more common in younger age: < 30 years) and stromal cell (connective tissue) tumors. Metastasize of other cancers are also a cause on OVC. Moreover, it may metastasize to other parts of the body, even to the liver and lung. Enlarged ovary, noncancerous fluid-filled sac (cyst), vague discomfort in the lower abdomen, similar to indigestion, bloating, loss of appetite, gas pains, backache, vaginal bleeding in the pelvic area, anemia, weight loss, high production of estrogens (responsible for uterine lining to grow excessively and breasts to enlarge), production of male hormones (androgens, responsible: body hair to grow excessively) and hyperthyroidism are the symptoms of OVC. Ultrasonography, CT, MRI, and tumor markers such as cancer antigen 125 (CA-125) are used in detection of OVC. Laparoscopy and open surgery are the two most common ways of doctoral detection of OVC.

Treatment strategy

Surgery and targeted therapy are very much effective in OVC. Radiotherapy is rarely used in OVC, while chemotherapy consists of paclitaxel combined with carboplatin (given 6 times), bleomycin, cisplatin, etoposide, bevacizumab, docetaxel, liposomal doxorubicin, gemcitabine and topotecan.

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Cervical cancer (CRC)

CRC develops in the cervix (lower part of the uterus). It is the third most common gynecologic cancer in all types of women. HVP is the major cause of CRC. In addition, sexual intercourse at a young age, having more than one sex partner, intercourse with CRC contaminated partners, smoking cigarettes and history with AIDS, cancers and some drugs such as chemotherapy or corticosteroids are the other potential sources of CRC. Squamous cell carcinomas account for 80 to 85% in CRC. Adenocarcinomas (gland cells) are also to be seen in CRC. CRC begins on the surface of the cervix and can penetrate deep beneath the surface, finally causes dysplasia or cervical intraepithelial neoplasia (CIN) (precancerous). It is spread through the bloodstream and can cause VGC. Abnormal bleeding from the vagina (most often after sexual intercourse) with a foul-smelling and pain in the pelvic area are the symptoms of CRC. It can cause lower back pain and swelling of the legs. Blocking of urinary tract (if remain untreated) may causes kidney failure and even death. Routine PAP tests (colposcopy: punch biopsy and endocervical curettage) and laser detection is done to detect up to 90% of CRC. Physical examination of the pelvis and a chest x-ray, CT, MRI, or a combination of CT and positron emission tomography (PET), cystoscopy (bladder), sigmoidoscopy (colon), or IV urography (urinary tract) are also done in CRC.

Treatment strategy

PAP test reduces more than 50% incidences of mortality in CRC. HVP vaccination and using condom during sexual intercourse (especially with contaminated partners) are strongly recommended in CRC management. In early stage, surgery (using the loop electrosurgical excision procedure, a laser, or a cold knife), laparoscopic and open surgery are done. In late CRC, radical trachelectomy, chemotherapy (e.g.- cisplatin and topotecan) and/or radiation therapy are used. However, radioactive implants are placed in the cervix to destroy the cancer (brachytherapy). In addition, pelvic exenteration is also done, if radiation therapy lefts cancer in pelvic organs (vagina, uterus, fallopian tubes, ovaries, bladder, urethra, rectum, and anus.).

Vaginal (VGC) and vulvar (VLC) cancers

Primary vaginal cancer accounts for 2-3% of all female genital tract malignancies therefore; it is very rare [2]. VGC accounts for only about 1% of gynecologic cancers. It actually occurs in woman after 60 years of old. VGC usually arise as secondary spread of malignancy from other adjacent organs, such as cervix, endometrium, bowel, ovary, vulva and urinary tract. The most common subtype of primary VGC is squamous carcinoma (80 - 90%) (develops in the flat, skin like cells that line the vagina), then followed by adenocarcinoma (develops from gland cells), rare type carcinoma (usually comes from diethylstilbestrol effects), sarcoma and melanoma [3]. VGC may be caused by human papillomavirus (HPV). Abnormal bleeding from the vagina especially, during or after sexual intercourse, between menstrual periods, or after menopause is the most common symptoms in VGC. Sores, watery discharge and pain during sexual intercourse and frequent urge to urinate and pain during urination are also seen in VGC.

Vulval cancer (VLC), usually a type of skin cancer, develops in the area around the opening of the vagina (begins on the surface of the vulva) and is rare as it accounts for 4 - 5% of gynecologic cancer [4]. Squamous cell carcinomas accounts about 90%, while melanomas and adenocarcinomas by 5% each in VLC. It is typically a disease of the younger to older women [5]. An increased incidence of VLC seemed to be exposure to HPV (90% cases), which is the causal factor of increased incidence of vulva intraepithelial neoplasia (VIN) [2,6]. However, precancerous changes (dysplasia) in vulvar tissues, lichen sclerosus (itching and scarring of the vulva), VGC and cervix cancer (CRC), heavy cigarette smoking and chronic granulomatous disease (a hereditary disease that impairs the immune system) are other plugged causes of VLC. Untreated, VLC may invade the vagina, urethra, anus and even into lymph nodes. Lump or sores (may produce watery discharge), melanomas (bluish black or brown) and itching are the most common symptoms in VLC.

Vulvar or vaginal mass/lump, pruritus, vaginal discharge, pain and post-coital bleeding are the most common symptoms in VGC and VLC. Non-invasive imaging (computerized tomography (CT), ultrasound, magnetic resonance imaging (MRI), positron emission tomography (PET), papanicolaou (PAP) test and nodal assessment have been performed as diagnosis in the both cases. However, chest X-ray (CXR) with abdominal shield, ultrasonography and magnetic resonance imaging (MRI) are thought to be safe during pregnancy [7].

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Treatment strategy

For surgical purpose, modern general and local anaesthetic agents are safe in pregnancy, and they have not proven to be teratogenic in humans. The VLC surgery for pregnant and non-pregnant patients is same. The cornerstone to management of VLC is radical vulvectomy with adequate excisional margin and groin node dissection if depth of tumor invasion is > 1 mm. On the other hand, radical hysterectomy, upper vaginectomy and pelvic lymphadenectomy are performed in VGC surgery. However, an increased risk of intraoperative blood loss and thromboembolic event due to increased vascularity during pregnancy may occur [8].

Cisplatin, paclitaxel and 5-fluorouracil (5-FU) are the three most common chemotherapeutic agents used in VGC and VLC. Moreover, Platinum-based chemotherapeutic agents are used in the second and third trimester of pregnancy [9]. To be mentioned that, all chemotherapeutic agents administered during pregnancy usually cross the placenta barrier and are therefore potentially teratogenic. In the organogenesis phase (first trimester of pregnancy) they cause miscarriage or structural abnormalities in fetus. However, there is no such evidence in the second and third trimester with therapeutically agents [10]. Orton, et al [2] suggested that, the use of brachytherapy may be a boost in the treatment of primary VGC.

Radiotherapy is an alternative strategy in VGC and VLC in non-pregnant women. However, it should be avoided during pregnancy as doses in excess of 0.1 Gy have been associated with detrimental effects [11].

The application of regenerative medicine technologies such as – tissue engineering: use of extracellular matrices (ECM) with/without cells; cell engineering: tissue specific stem cells, mesenchymal stem cells and pluripotent stem cells is currently being considered for treating several types of disorders of the female and male reproductive systems including cancers [12].

Although cancer treatments are evident to eliminate damaged oocytes by causing DNA damage and apoptosis but, many cancer treatments increase the risk of premature ovarian insufficiency (POI) and infertility. Radiation exposure is also a notable cause of this event. Genotoxic agent that causes damage to the oocyte DNA may lead to an activation of checkpoint kinase CHEK2, which phosphorlates TAp63 and p53 and triggers the proapoptotic response via PUMA and NOXA. Downstream activation of BAX and inhibition of BCL2-like proteins leads to caspase-dependent apoptosis. Thus, CHEK2 inhibition could be a powerful dual-benefit treatment – improving the killing of cancer cells and protecting ovarian function in patients [13].

Fallopian tube cancer (FLTC)

Fallopian tube cancer (FLTC) develops in the tubes leading from the ovaries to the uterus. It is rare and accounts less than 1% of gynecologic cancers. Women between 50 and 60 years old are more susceptible to FLTC. Those who have long-term inflammation of the fallopian tubes (chronic salpingitis), tuberculosasis and infertility may suffer in FLTC. Adenocarcinomas account more than 95% of FLTC followed by sarcomas (connective tissue). It may lead ovarian cancer (OVC) and may spread to the surrounding areas by the lymphatic system. Vague abdominal discomfort, bloating, and pain in the pelvic area or abdomen, watery discharge from the vagina, ascites (fluid in abdominal cavity) and large mass formation in the pelvis are the symptoms in FLTC. Routine pelvic examination test and CT are done for diagnosis of FLTC.

Treatment strategy

Surgery is a first line effective treatment in FLTC, which includes: hysterectomy (removal of the uterus) and salpingo-oophorectomy (removal of the ovaries and fallopian tubes, adjacent lymph nodes, and surrounding tissues). Radiotherapy is rarely useful in FLTC. However, chemotherapy is usually used after surgery with carboplatin and paclitaxel.

Hydatidiform mole (HDFM)

Hydatidiform mole (HDFM) is a growth of an abnormal fertilized egg or an overgrowth of tissue from the placenta. Usually, it develops from cells that remain in the uterus after a miscarriage or a full-term pregnancy. HDFM is most common in young age (17 to over 35
years). Feeling pregnancy, enlarged abdomen, severe nausea, vomiting, vaginal bleeding, sepsis, shock, and proteinuria (preeclampsia or eclampsia) are the symptoms in HDFM. It may metastasize to other parts of the body. Ultrasonography, X-ray, CT, pregnancy test, human chorionic gonadotropin (hCG) levels test and biopsy are done to diagnose the HDFM.

**Treatment strategy**

Surgery, especially hysterectomy (removal of the uterus) is done. Chemotherapy (methotrexate and/or dactinomycin, etoposide, methotrexate, actinomycin-D, cyclophosphamide and vincristine) and oral contraceptives are frequently recommended in HDFM.

**Bibliography**


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