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Influence of Radiology for Staging, Treatment and Surgery for Endometrial Carcinoma

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Abstract
The predominance of Endometrial Carcinoma (EC) has made FIGO staging the disease to alter the course of treatment accordingly. The multiple staging was made possible by different radiological techniques which are also used for assistance during surgery. In this review, the prevalence of EC, their staging, healthcare expenditure was highlighted. Further, incorporation of ultrasound, CT and MRIradiological techniques for staging and surgical procedure for EC was elucidated. Finally, we conclude by providing scope for improvement in treatment and surgery of ECs.
Keywords: Endometrial Carcinoma; Radiology; MRI; Staging.

1. Introduction

1.1 Uterus and Endometrial Carcinoma

The cancer that begins in the uterus is called as endometrial carcinoma [1]. A uterus is a pear-shaped pelvic organ that is responsible for the development of fetus, which is otherwise called as gestation and other functions such as menstruation, labor and delivery. It has a triangularly shaped cavity on the coronal cut area as shown in Figure 1. At times, the development of this utero might be incomplete and it is termed as Mullerian Anamoly which has many types of variants that ranges from uterine septum to uterine didelphys which is otherwise called as double uterus.In a female the uterus is anatomically located in the pelvis that is immediately posterior to the bladder and anterior to the rectum. It has been subdivided into four anatomically main segments namely, the fundus, a curved and broad area which serves the purpose of connecting the fallopian tubes to the uterus, the body of the uterus which is termed as corpus, and the principle part of the uterus which starts directly below the fallopian tubes and that keep continues to downwards, known as isthmus, which is a lower neck region of the uterus, and cervix which moves downwards from the isthmus leading to the vagina [2].

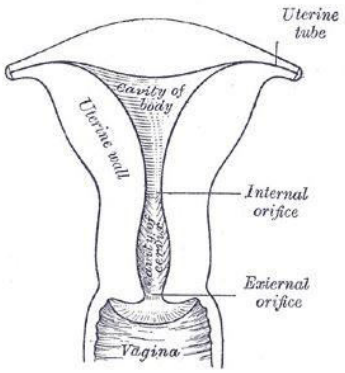

Figure 1: Schematic illustration of anatomy of posterior half of uterus and upper part of vagina.

There are several ligaments that supports the uterus in the functioning, which includes the round ligament, cardinal ligament, broad ligament, utero ovarian ligament, and uterosacral ligaments. Further, urogenital diaphragm, pelvic diaphragm and the perennial body supports the uterus [2]. The positions of the uterus may normally vary such as anteverted/ extroverted or ant flexed or retroflexed or even in the midline, and during pregnancy it could be rotated. In most of the women the uterus lies in the anteverted or anteflexed position. The uterus has basically three tissue

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layers that are endometrium, mytometrium and perimetrium. The endometrium comprises of the inner lining and consists of the basal endometrium. This layer is a functional one that responds to the reproductive hormones. The shedding of this layer leads to the menstrual bleeding. Any damage in the endometrial layer leads to the occurrence of fibrosis which is called as Ashermansyndrome and adhesions [2].

This endometrial cancer begins in the endometrium of the uterus. The endometrium is layer of cells which lines the uterus. This cancer is often referred as uterine cancer. If the uterus is in the tipped position, it usually causes a minor incontinence, fertility dysfunction, pelvic pain and also inconvenience in inserting tampons.During pregnancy, this may lead to uterine incarceration [3].

The endometrial cancer usually happens in the women who are over the age of 40. The women who are at their post-menopause stages have the high risk of the endometrial cancer. The risk is also higher in the cases of the women who got their first period early, who went through the menopause in the later stage of their lives, the women who suffer from obesity, who has the records of high blood pressure and diabetes, the women who have few or no children, suffering the case of infertility, or who is associated with the family having the history of infertility, irregular periods and growth of abnormal cells in the endometrium, and who has the records of having breast cancer, colorectal cancer etc [4].

1.2 Global Prevalence and Symptoms

The endometrial cancer is attributed as one of the most common type of cancer in the female population. It is also ranking seventh most common neoplasm around the world and the fourth most common cancer among women in the world and remains as the most frequently diagnosed gynecologic malignancy. It records its highest incidence in the North America and Europe. In a historical point of view, a considerable rise in the incidence and prevalence of the endometrial cancer in the regions of North America between the year 1960 and 1975. The hormone therapy used in the post menstrualis reportedly the cause of the increase in the exogenous estrogen resulting in the endometrial carcinoma [4].

There are two types of endometrial carcinoma such as Type 1 and Type 2. The type 1 is the estrogen dependent and Type 2 is estrogen independent cancer. The Type 1 cancers is reportedly constituting 85% of the endometrial cancer. The women who are obese are prone to this type of cancer and the complex atypical hyperplasia precedes it. Further, they are low grade endometrioid histology and are related to the uterus alongside with very minimal invasion. The old age patients with atrophic endometrium are most often found to be affected with the type 2 cancer. Their histology mostly comprises of clear cell or high grade serous and they are found to have early stage metastasis. For the patients with type 2 cancer, endometrial cancer is observed to relapse, almost 50% of the time. On molecular level, these two types of cancer are clearly distinguished. The type 1 tumors are found to have PTEN, β-catenin mutations and K-ras and as well as microsatellite instability (MSI). In these cancers, progesterone receptors are found to be in prominent numbers. But as far as the type 2 cancers are concerned, P53 mutations, HER2/neu amplification are found to be observed [5].

Majority of the women population, who are under the age 50 and 60 are diagnosed with the endometrial cancer and the average age is found to be 61. With advancing of age, the probability of developing the cancer also rises. In a demographic analysis, the women in the American countries are found to be affected than the women in the African and Asian countries. The African-American women are found to be more affected than the women of other countries. They are found to have higher mortality rate than the women of America. It is mainly found to be prevalent in high income countries. The age adjusted rates of this disease is going from high to low income economies in the countries that are undergoing transition. However, there is no distinct, overall trend in high income economies [6].

The endometrial cancer shows symptoms at very early stages, such that it is easy to detect the disease earlier. But the overall 5-year survival rate is found to be high and it is lower in the middle economy countries than the high-income countries. There are various lifestyle factors that are involved in the cause of endometrial cancer. Few possible causes include, being overweight and obese, being tall, the increase in the glycemic load, decreased physical activity etc. it is also reported that the influence of sedentary life style causes the cancer. Other causes include, life events, medication and family history are the reasons of the endometrial cancer [7].

The diagnosis of this disease includes, laparoscopy and minilaparotomy which are usually considered as an alternative for the existing diagnosis system. Preoperative clinical and instrumental staging of this disease is done by local and distant diagnosis of the lymph node involvement and it is regarded as the critical step in the designing and outlining the extent and the radicalness of the surgery. The causes such as being obese and having cardiovascular and metabolic disorders are found to further increase the risk of the complications of the surgery. The best approach till date is considered to be the vaginal total hysterectomy [8]. A thorough investigation of the diseases is mandatory before involving nay diagnostic approach in order to refrain from jeopardizing the disease further. Magnetic imaging has been recognized as one of the accurate assessment techniques for the detection of this

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cancer and is proved to have one of the highest accuracies when compared to the other treatment techniques namely sonography and computed tomography. This technique helps in the identification of the assessment of cervical invasion and to identify the enlarged lumboaortic lymph nodes. This helps the gynecological oncologist to plan further surgical procedures that are simple and effective. The MR imaging helps in qualitative study of the disease by using in-depth infiltration into the samples. It helps in the histopathological analysis by the lymph node dissection with anatomical labelling into internal and external iliac, internal obturatory, lumboaortic nodes by the surgeons. The number of the lymph nodes, their location of prevalence, and the quantity of metastatic lymph nodes, could be subsequently documented by the pathologist [8].

1.3 Healthcare Expenditure

The cost of gynecologic cancers was predicted to be $3.8 billion per year, with an average cost of $6,293 per patient. Ovarian cancer ($13,566) had the greatest yearly cost per person, followed by uterine cancer ($6,852) and cervical cancer ($2,312). Hospital inpatient stays (53 percent, $2.03 billion) were the largest component of medical costs, followed by office visits (15 percent, $55 billion) [9].

2. Endometrial Carcinoma Staging

The FIGO (International Federation of Gynecology and Obstetrics) and the American Joint Committee on Cancer TNM staging systems are largely the same when it comes to endometrial cancer staging [10].

Both of them use three parameters to stage (classify) endometrial carcinoma:

The tumor's expanse (size) (T): What is the extent of the cancer's spread within the uterus? Is there any evidence that the cancer has spread to surrounding tissues or organs?

The spread of the infection to neighboring lymph nodes (N): Has the malignancy spread to the lymph nodes in the para-aortic area? These lymph nodes might be found in the pelvic or surrounding the aorta.

After T, N, and M, there are numbers or letters that provide extra information about each of these elements. Higher figures indicate that the cancer has progressed. After determining a person's T, N, and M categories, the information is merged in a procedure called stage grouping to assign an overall stage [11].

The pathologic stage is used in the staging scheme in the table below. It's discovered by studying tissue taken following surgery. Surgical staging is another term for this. The cancer will be assigned a clinical stage if the surgery isn't possible immediately away. This is based on a physical exam, biopsy, and imaging tests performed before to surgery [12, 13].

3. Traditional Treatment Methods for Endometrial Carcinoma

The most essential element in deciding on therapy is the stage (amount) of endometrial cancer. Other considerations such as age, overall health, type of cancerand whether the patient wants to have children, can all influence the options for treatment.

The first treatment for patients with endometrial cancer receives surgery. The uterus, ovaries, and fallopian tubes are all removed during the procedure. (This is known as a TH/BSO, or complete hysterectomy bilateral salpingo-oophorectomy.) To further evaluate the spread of cancer pelvis lymph nodes and area around aorta may also be extracted (a pelvic and para-aortic lymph node dissection [LND] or sampling) [14].

Stage I endometrioid cancers:

Staging the cancer and planning of surgery to remove the cancer is the standard treatment. Radiation will almost certainly be recommended after surgery for women with higher-grade malignancies. It is possible to utilizepelvic radiotherapy,vaginal brachytherapy (VB), or both.

Women who are unable to have surgery owing to other medical issues or who are fragile as a result of their age are frequently treated with just radiation (external radiation and/or vaginal brachytherapy).

Fertility-sparing treatment for stage IA grade 1 endometrioid cancers:

Surgery may be postponed for young women who still wish to have children while progestin medication is used to treat the malignancy. Treatment with progestin may diminish cancer or perhaps disappear for a period of time, allowing the woman to become pregnant [15, 16].

Stage II cancers:

A patient with stage II cancers, a radical hysterectomy is performed in which the uterus and parts surrounding it will be involved in surgery. After the patient has recovered from surgery, radiation therapy, including vaginal brachytherapy and external pelvic radiation, may be administered. Another approach is to start with radiotherapy and then proceed with a simple hysterectomy, BSO, and possibly LND or lymph node biopsy [17].

Stage III cancers:

If the surgeon believes that all visible cancer can be removed, a hysterectomy is performed, which involves the removal of both the ovaries and the fallopian tubes. A radical hysterectomy is sometimes required for women with

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stage III cancer. A pelvic lymph node dissection and para-aortic lymph node dissection may also be performed. Pelvic washings will be performed, as well as the removal of the omentum.

Stage IIIA - cancer has spread to the serosa (the tissue that covers the uterus) or other tissues in the pelvic, such as the fallopian tubes or the ovaries (the adnexa). Chemotherapy, radiotherapy, or both may be used to treat certain cancers following surgery. The pelvis is irradiated, or the abdomen (belly) and pelvis are both irradiated. Vaginal brachytherapy is also commonly employed.

Stage IIIB: The cancer has spread to the vaginal area at this point. Chemotherapy and/or radiation may be used to treat stage IIIB after surgery.

Stage IIIC2: Cancers that have migrated to the lymph nodes in the pelvic (stage IIIC1) and those that have expanded to the lymph nodes around the aorta are classified as stage IIIC (stage IIIC2). Surgery is followed by chemo and/or radiation therapy [18].

Stage IV cancers:

Stage IVA: Endometrial malignancies at stage IVA have spread to the bladder or colon.

Stage IVB: To prevent severe bleeding, a hysterectomy including removal of both fallopian tubes and ovaries may still be necessary. For this reason, radiation therapy may be employed. Hormone therapy may be utilized if the cancer has progressed to other places of the body. High-grade malignancies and tumors with no detectable progesterone or oestrogen receptors on cancer cells, on the other hand, are unlikely to react to hormone therapy [19]. Some women may benefit temporarily from chemo medication combinations. doxorubicin, carboplatin, Paclitaxel, or cisplatin are the most commonly prescribed medications. These medications are frequently used in tandem. Chemotherapy for stage IV carcinosarcoma is frequently the same. It is also possible to mix cisplatin, ifosfamide, and paclitaxel [13].

4. Radiological Technique for Diagnosis and Surgery Assistance

To detect the lymph nodes and the distant metastasis in the endometrial carcinoma, Computed tomography and PET techniques are used. To evaluate the degree of this local disease, ultrasound sonography and MRI are utilized. When it comes to detect the tiny, metastatic deposits that are present in the lymph node and omentum. The extrauterine soft tissue involvement in the endometrial cancer can be detected by the CT, MRI and PET techniques [20].

Imaging technique is used for detection, planning and treatment of post-operative residual disease in the patients who are prone to higher risk, in addition to the preoperative staging. The techniques used for monitoring are CT/PET-CT and whereas for the post-treatment monitoring, in the patients that are asymptomatic, who are prone to heavy risk of relapse, PET and PET-CT helps in the surveillance [21].

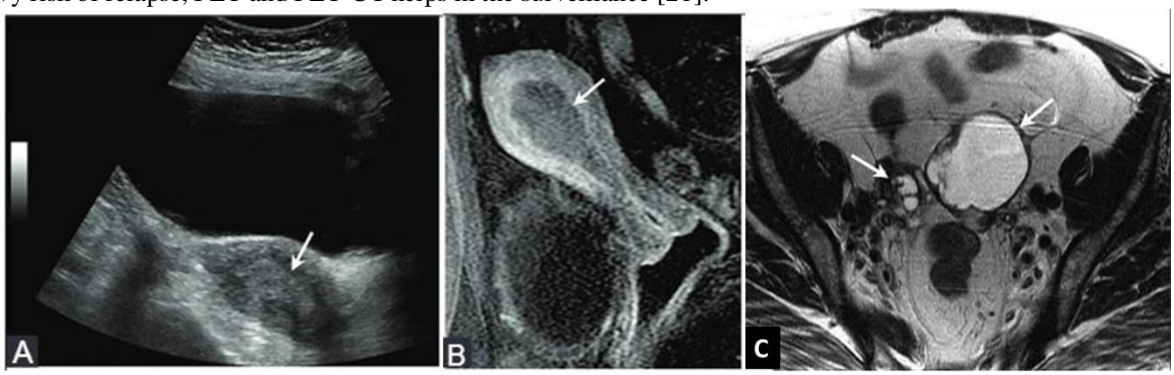

Figure 2: (a) Ultrasound, (b) PET and (c) MRI image of Utereus with Stage III EC adopted with permission from Ref [4].

4.1 Ultrasound

To scruntize the uterine cavity, the endometrium and the adnexa in great details, the transvaginal ultrasound could be utilized. In the women who are aged and elderly, and is associated with the vaginal stenosis, the trans rectal ultrasonography has be done with the transvaginal ultrasound, both in adjunct with each other, thus avoiding the risk of losing the significant ovarian and tubal disease.

In a step by step manner, the ultrasound examination should be done. For the tumor penetration into the cervix stroma, the cervix should be checked in a sagittal plane with a transvaginal ultrasonography probe. From cornu to cornu, the entire body of the uterus should be inspected in detail and from the cervix to the fundus in a transverse plane.

The normal endometrium is smooth, ranging from 1mm thick usually and is distanced from the myometrium by a thin layer of hypo echo. The ultrasound, although can detect the abnormalities in the endometrium, it might not be

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always accurate and it demands confirmation to be done in histological ways. If the thickness of the endometrial layer increases, and higher the post-menopausal stages, there is an increased risk in the endometrial cancer.

According to a meta-analysis by Smith-Bindman et al., a cut-off value of 4–5 mm indicates the value of a carcinoma, with 96 percent sensitivity and 61 percent accuracy. Additionally, the variable echogenicity is caused by areas of bleeding and necrosis, as well as an irregular endometrial myometrial interphase, which indicates cancer-induced myometrium invasion, corroborate the diagnosis of endometrial cancer [22].

4.2 Computed Tomography (CT)

For examining the uterine abnormalities, the CT scans are found to be less useful. The difference between the picture quality would be evident between the CT scan and the MRI in the soft tissue delineation is observed and reported elsewhere [23]. In order to obtain the CT observations, the CT done on the hypodense lesion or an expanded endometrial cavity may give gross images of the endometrial tumor and it could be hard to identify and distinguish from the benign lesions. But otherwise, the CT has the better multiplanar spit and hence it is sought for imaging the Endometrial cancer lesions.

In the individuals with the high-grade histology, if the extrauterine illness is anticipated, a profound myometrium invasion or a big uterus is found, in the absence of the MRI and PET, a computed tomography should be useful. A CT scan is frequently conducted as a baseline examination, prior to a histologic diagnosis of endometriosis. Intravenous contrast aids in recognizingsoft tissue metastases and vascular structures, as well as distinguishing between them.

A positive correlation between the size of the positive lymph node and metastasis (P0.01) was observed in a study that measured positive and negative pelvic lymph nodes in 32 individuals with node-positive endometrial cancer. 68 of 125 subjects with positive lymph nodes showed a maximum short axis diameter of less than 10 mm. While negative lymph nodes measured 46 of 160 (29%) cases. Patients with solitary metastatic nodes were found to have tumour deposits in nodes less than 10 mm. 85 percent of patients with multiple positive nodes had at least one positive node larger than 10 mm. 8 A single positive node was discovered in 25%–40% of patients with node-positive endometrial cancer, while several nodes were found in 60%–75% of patients with node-positive endometrial cancer.

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4.3 Magnetic Resonance Imaging (MRI)

For anatomical studies of the pelvis and abdomen, MRI is the imaging technique of choice when it is available. Endometrial cancer within the endometrial cavity; tumour infiltration into the myometrium, endocervix, and extensive extension into the parametria; and other pelvic tumour deposits are best detected and evaluated with MRI [25].

Endometrial cancer usually presents as an intermediate signal strength on T2-weighted imaging. Due to the presence of increased cellularity, necrosis, and bleeding within the tumor, it does not have a uniformly strong signal like normal endometrium. There are two layers to the myometrium that surrounds it. The inner myometrial layer, also known as the "junction zone," abuts the endometrium and has a low signal band, whereas the outside myometrium has a more variable look but is usually of intermediate signal.During the early dynamic phase after intravenous contrast, the innermost myometrial layer improves uniformly as a continuous line or "subendometrial stripe." Myometrial invasion is indicated by a disruption of the subendometrial stripe or a complete breach of the junction zone. Deep myometrial invasion is ruled out by an intact junctional zone and a continuous band of early subendometrial enhancement [26].

Myometrial invasion is indicated by a disruption of the subendometrial stripe or a complete breach of the junctional zone. Deep myometrial invasion is ruled out by an intact junctional zone and a continuous band of early subendometrialenhancement.MRI is helpful for analyzing the extrauterine disease and as well as any other structural anatomical detail which is expected to influence the plan, design, execution and severity of primary surgery [27].

5. Reoccurrence of endometrial carcinoma after surgical removal

Recurrent cancer occurs when the cancer rebounds after the initial treatment. It may reoccur in the same location (called a local recurrence), in a surrounding neighborhood (called a regional recurrence), or in a different location (called a regional recurrence) (distant recurrence). Some recurring treatment options are comparable to those that were present when the illness was first given a diagnosis:

1. Bleeding or discharge from the cervix

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2. Pain in the pelvic region, the abdomen, or the backs of the legs
3. Urinating is difficult or painful.
4. Loss of weight
5. Coughing and loss of breath that persists

After being diagnosed with persistent endometrial cancer, the chances of survival are slim. Although total pelvic exenteration has been described as a medication for a restricted population of patients with reoccurring endometrial cancer, there is no information on the utility of other surgical techniques [28]. Patients with remote recurrences are routinely treated with a variety of cytotoxic regimens, however based on previous case studies and the information they provided, response time, and longevity are all quite limited. Pelvic radiation is used to treat limited, discrete pelvic episodes that are typically confined to the vaginal region, yet only a small proportion of cases are surgically treated. According to the studies, surgery shows great promise in treating central pelvic recurrences, and chemotherapy tends to be effective in treating all the other relapse, but with the limitations stated above. The minimal use of surgical intervention with recurring cancer is thought to be related to cynicism about the technique, which is seen as technically demanding, unproductive, and potentially risky. In a study conducted by Campagnutta et al., a conventional surgical technique has been established to demonstrate that abdominal and pelvic complications are possible and efficient treatment of individuals with recurrent endometrial cancer can be done within well-defined boundaries [29].

6. Conclusion

Radiological technique plays a vital role in staging, treatment and surgery for EC patients. Recently, MRI is the most prevalent imaging technique for preoperative assistance and suitable for proper management of patients with ECs.

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