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By Ahmed Salih Alshewered

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Endometrial hyperplasia, benign endometrial tumors and endometrial carcinoma: A review study

Ahmed Salih Alshewered

Misan Radiation Oncology Center, Misan Health Directorate, Ministry of Health/Environment, Misan, Iraq

ORCID ID: 0000-0002-0170-1744

Corresponding author:

Ahmed Salih Alshewered

Email:ahmedsalihdr2008@yahoo.com

ABSTRACT

Background: During the reproductive phase, the endometrium undergoes cyclical structural changes. Endometrial hyperplasia (EH) is a prevalent condition that arises from the combination of estrogen exposure and insufficient progesterone levels. Endometrial cancer (EC) is the second most prevalent gynecologic malignancy. The likelihood of EH progressing to EC ranges from 1% to 29%. The objective of this study is to conduct a comprehensive assessment of various forms of endometrial hyperplasia, benign endometrial tumors, and endometrial cancer (EC).

Methods: From major data bases of published papers like PubMed, Scopus and Google scholar, I collected different articles (original, and reviews) and searching included EH, Benign endometrial tumors and EC. Case reports, series, and clinical images were excluded.

Results: All information about topic selected and summarized in epidemiology, etiology, histopathological classification, anatomy, biological and molecular characters, detection and prevention, clinical manifestation, staging, diagnostic workup, prognostic factors, and management.

Conclusion: Endometrial hyperplasia and endometrial cancer are representing the two commonest problems in women. EH is a major precancerous condition for EC. EC is associated with poor

prognosis if diagnosed late. Epidemiology and outcomes of two conditions are varies and different according to many factors including ethnicity, environment, socioeconomic, hereditary, drugs, hormonal and aging process.

Keywords: Endometrial hyperplasia, Benign endometrial tumors, Endometrial carcinoma, uterus, PCOS

INTRODUCTION

Endometrial hyperplasia (EH) is a prevalent condition that arises from the presence of either naturally occurring or externally introduced estrogen, together with a relative insufficiency of progesterone [1]. It is considered a precursor to endometrial cancer (EC), which is one of the most prevalent gynecological cancers globally [1,2]. Endometrial hyperplasia is a condition characterized by the excessive growth of glands in the endometrium due to an imbalance between estrogenic stimulation and progesterone's counterbalancing effects. Anomalous gland-to-stroma ratio resulting from irregular endometrial growth can lead to various alterations in the architecture of the endometrium [3-5]. The causation of this illness is complex, but the primary factor is long-term exposure to estrogen combined with a relative insufficiency of progesterone. Several risk factors contribute to the development of this condition, including age, nulliparity, obesity, genetic predisposition, comorbid conditions such as diabetes Mellitus, cycle irregularities like PCOS, ovarian tumors, hormone replacement therapy, immunosuppression, infection, and in rare cases, hereditary non-polyposis colorectal cancer or Lynch syndrome [3-5,6,7].

In epidemiology, EH incidence has been documented to be thrice the incidence of endometrial carcinoma [8]. GLOBOCAN's 2021 report provides estimates of the global incidence and mortality rates for 36 different types of cancer, including endometrial cancer, across 185 countries. A total of 417,367 new cases of corpus uteri cancer were recorded, leading to a global prevalence of over 1.2 million instances of endometrial hyperplasia (EH) [2]. A comprehensive investigation conducted by Reed et al. [9] A study on the epidemiology of EH found that females diagnosed with hyperplasia without atypia were typically between the ages of 50 and 54. On the other hand, those with atypia were most reported in the age group of 60-64. It is worth noting that EH is quite rare in individuals under the age of 30.

Endometrial cancer ranks as the second most prevalent gynecologic malignancy. Based on the Surveillance, Epidemiology and End Results (SEER) statistics from 2006 to 2010, it is the fourth most frequent cancer among women in the United States. The age-adjusted incidence rate for this

cancer is 24.3 cases per 100,000 women per year [8]. In 2019, the estimated number of cases for women in the USA was 61,880. The mortality rate, adjusted for age, is 4.7 deaths per 100,000 women year, resulting in an anticipated 12,160 fatalities in 2019 [10]. In developed countries, the age-standardized rate for endometrial cancer is 12.9 per 100,000 people, with a cumulative risk of 1.6% for individuals aged 0 to 74 years. In contrast, in developing countries, the rate is 5.9 per 100,000 people, with a cumulative risk of 0.7%. These findings suggest that environmental factors may play a role in the occurrence of cancer [8].

Estrogen is the primary cause of endometrial cancer, although there are additional risk factors involved. Women with low progesterone levels and high estrogen levels in their blood are at a higher risk, as is well known [11]. Additional causes include: the total number of menstrual cycles experienced throughout one's lifetime, an early onset of menstruation, a late onset of menopause, never having given birth, being overweight, having non-insulin-dependent diabetes mellitus, having hypertension, using estrogen-only hormone replacement therapy or sequential oral contraceptives, taking tamoxifen for breast cancer, and having a genetic predisposition such as hereditary non-polyposis colorectal cancer (HNPCC) [12-20].

According to 2018, and 2020 cancer statistics by GLOBOCAN, the estimated number of newly diagnosed cases of endometrial cancer are 382,069(2.1%), and 417,367(2.2%), respectively. While the number of new deaths are 89,929(0.9%) and 97,370(1%) in 2018, and 2020, respectively [2, 21]. Endometrial cancer affect frequently postmenopausal females, 14% are diagnosed in premenopausal age, with 5% being younger than 40 years [22]. In the United States, the prevalence of hysterectomy among women under the age of 50 is approximately 20 to 30%. However, when considering only women who still have a uterus, the percentages are considerably higher [23]. European countries have reported world-standardized and crude incidence rates of 14 to 26 instances per 100,000 women, while the rates for the USA are 19 and 31 per 100,000 women, respectively. Uterine cancer primarily affects women in the postmenopausal stage, often occurring between the ages of 55 and 85. The age-adjusted incidence rates surpass 90 per 100,000 women among those aged 60 to 74 years, reaching a maximum incidence of 108.4 per 100,000 in women aged 65 to 69 years [24].

There are two different types of EC prototypes: type I, which functions in conjunction with estrogen, and type II, which functions independently of estrogen. There are about 75% of endometrial cancers that are categorized as endometrioid carcinomas. This represents the majority of endometrial cancers. As opposed to clear cell carcinomas, which make for 1% to 5% of instances, serous carcinomas account for 5% to 10% of incidences. The remaining five percent of

cases are comprised of numerous additional histologists, such as uterine sarcomas (including carcinosarcoma, leiomyosarcoma, and endometrial stromal sarcoma), making up the remaining five percent. Mucinous carcinomas account for one to three percent of all cases [10].

Aims of the study is to review of different types of endometrial hyperplasia, benign endometrial tumors and EC.

ANATOMY

The uterus is a muscle organ that is in the real pelvis. It is situated between the bladder and the rectum. The uterus is hollow. According to the average measurements, the adult uterus measures roughly 8 centimeters in length, 5 centimeters in width, and 2.5 centimeters in thickness. It is composed of three distinct components, which are the fundus, the body (corpus), and the cervix, when viewed from an anatomical understanding. To a certain extent, the surface is covered by the peritoneum, while the cavity is lined by the endometrium, which is composed of columnar cells that contribute to the formation of many tubular glands. Throughout the course of the menstrual cycle, the endometrium goes through a process of shifting in thickness. The wall is composed of myometrium, which is made up of smooth muscle fibers. The support is facilitated by the extensive, circular, uterosacral, and cardinal ligaments. The uterine artery is responsible for supplying the main blood vessels to the uterus, whereas the lymphatic drainage of the uterine body mostly takes place through the obturator, internal, and external iliac lymph nodes. The lymphatic arteries that originate from the fundus of the body converge with the ovarian artery and carry lymph fluid to the para-aortic lymph nodes for drainage [26].

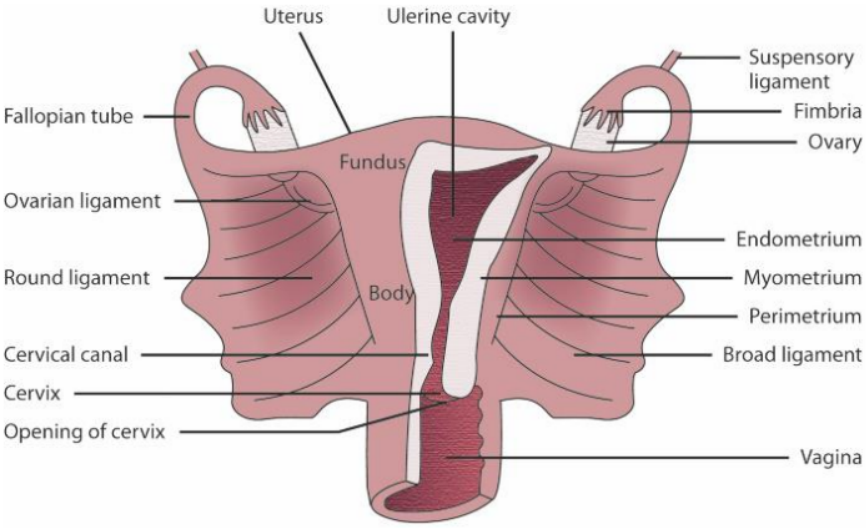

Figure 1. Anatomy of the uterus [25].

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EPIDEMIOLOGY

Endometrial cancer (EC) is the second most prevalent gynecological malignancy, occurring after cervical cancer. It is also the sixth most common cancer in women, ranking below breast, colorectal, lung, cervical, and thyroid cancers. EC accounts for around 4.4% of all cancers and 2% of cancer-related deaths in women [2].

The occurrence rates are particularly elevated in industrialized nations and have been increasing because of the aging of the population and the higher prevalence of obesity [13]. Based on the 2018 cancer data, the likelihood of 1 out of every 35 women (2.8%) acquiring endometrial cancer in their lifetime is reported. The age at which a diagnosis is often made is 62, whereas the age at which death occurs is typically 70 years [21].

Endometrial cancer ranks 14th in terms of mortality, with a cumulative chance of death by age 75 of 0.2%. The USA and Canada had the greatest rates in 2012, estimated at 19.1 per 100,000 people. Northern Europe had an estimated incidence of 12.9 per 100,000 people, while western Europe had an estimated incidence of 15.6 per 100,000 people [8,27]. The rise in endometrial cancer rates in Europe and North America may be attributed to a higher prevalence of obesity and metabolic disorders in these regions, as well as the aging population [28,29]. According to future projections, the number of cases in the USA is expected to rise to 42.13 per 100,000 people by 2030 [30].

In Iraq, it was placed 17th with 611 new cases (1.8% of total cases) and 191 new deaths (0.97% of total deaths). The 5-year prevalence rate was 8.71 per 100,000, corresponding to a total of 1730 cases [31].

ETIOLOGY

The etiology of endometrioid cancer is associated with the exposure of tissues to unopposed elevated levels of hormones, including both exogenous and endogenous estrogens [32]. Endometrial cancer growth is frequently linked to several factors, such as early onset of menstruation, delayed onset of menopause, being overweight, never having given birth, infertility, ovarian tumors that produce estrogen, diabetes mellitus, and hypertension [33]. Despite its anti-estrogenic effects on tissue, tamoxifen has mild estrogenic effects on the uterus, which increases the statistical risk of endometrial cancer in women with breast cancer [34].

Endometrial biopsies that reveal complicated hyperplasia with atypia increase the chance of cancer development by 30–40%; this condition is regarded as a premalignant phase of endometrioid carcinoma and shares its genesis [10].

Having a family history of EC significantly raises the risk, particularly in women under the age of 50. Population studies indicate that a small proportion, specifically around 3-6%, of newly diagnosed endometrial malignancies can be attributed to Lynch syndrome. There is evidence of a genetic tendency for some types of tumors with endometrioid morphology to occur within families. Additionally, individuals diagnosed with endometrial cancer have an elevated risk of acquiring other types of malignancies, particularly in the colon and breast [35-38].

Females with mutations in the MLH1, MSH2, MSH6, or PMS2 genes are at a higher risk of developing endometrial cancer (EC) due to hereditary non-polyposis colorectal cancer (HNPCC) syndrome [39]. The probability of having EC before the age of 50 is 20%, and this probability increases to 60% after the age of 60 [10].

HISTOPATHOLOGICAL CLASSIFICATION

Adenocarcinomas are the most common type of uterine epithelial cancers. The World Health Organization (WHO) has several subgroups within the classification. The most common type of endometrial adenocarcinoma is the endometrioid subtype, which makes up 75% of all cases. Other histological subtypes of endometrial cancer include serous (5-10%), mucinous (1-3%), and clear cell (1-5%) carcinomas. Uterine sarcomas, such as leiomyosarcoma, endometrial stromal sarcoma, and carcinosarcoma (also known as malignant mixed Müllerian tumor or MMMT), are classified as kinds of uterine mesenchymal and mixed malignancies [10, 40].

Carcinosarcoma is the most common form of uterine mesenchymal and mixed tumor, accounting for 45% of cases. Leiomyosarcoma is following at 40%, and endometrial stromal sarcoma is at 10-15%. Carcinosarcomas are currently classified and managed as high-grade carcinomas, which has led to unfavorable outcomes because of their rapid and aggressive dissemination [40].

Non-endometrioid histological categories have a more unfavorable prognosis in comparison to endometrioid cancers. This class is comprised solely of serous and clear cell carcinomas. Serous adenocarcinoma, previously referred to as uterine papillary serous carcinoma, shares similar histological characteristics with its ovarian counterpart. The entity in question may be misidentified as the papillary villoglandular subtype of endometrioid adenocarcinoma, which has a far more favorable prognosis. Endometrioid adenocarcinomas are routinely diagnosed at a later stage compared to this condition [10]. Clear cell carcinoma (CCC) is often associated with a dismal prognosis, often being diagnosed at more advanced stages [41]. Recent genetic study suggests that clear cell carcinoma of the endometrium is not a biologically uniform group. The tumors in question can be classified as either MSI or microsatellite stable, and they share genetic characteristics with serous tumors or endometrioid malignancies [42, 43].

BIOLOGICAL AND MOLECULAR CHARACTERS

In 1983, Bokhman recognized two unique kinds of EC in the past. Cancers of Type I are reliant on estrogen, often triggered by hyperplasia, and commonly have low-grade endometrioid histology. Fibroids commonly develop in an estrogen-rich environment, which is often observed in obese women or during the premenopausal and perimenopausal periods. They typically possess a positive perspective. Type II tumors are estrogen-independent and develop in atrophic endometrium, most commonly as a result of endometrial intraepithelial carcinoma (EIC). These tumors commonly belong to the serous and CCC subtypes. Women who have type II tumors generally have older age, are in the postmenopausal stage, and have high-grade, very invasive malignancies with a negative prognosis [10]. Endometrial cancers frequently exhibit molecular abnormalities, which might encompass:

Loss of PTEN.

1. The SNPs of TP53, KRAS, and PIK3CA.
2. The MSI.
3. The overexpression of ERBB2, epidermal growth factor receptor (EGFR), and P16 [44, 45].

TP53 mutations have been observed in up to 90% of instances of type 2 malignancies, including both invasive and intraepithelial carcinomas. This suggests that TP53 mutations are an early event in the development of these tumors. Additionally, a substantial part of serous carcinomas exhibits an increase in the expression of the ERBB2 protein, and around 20-30% of tumors display an amplification of the ERBB2 gene. PTEN is commonly altered in endometrioid endometrial cancer, with a frequency ranging from 37% to 61%. PTEN deficiency, resulting in the activation of the PI3K-AKT-mTOR signaling pathway, has been observed in 32-83% of endometrioid-type endometrial cancer cases [46].

DETECTION AND PREVENTION

Currently, there are no precise metrics established for the prevention of endometrial cancer, except from the recommendations to abstain from using unopposed estrogen and to avoid weight gain. Patients with confirmed hyperplasia with atypia should undergo prophylactic hysterectomy. In addition, individuals who carry the HNPCC type 2 gene should consider both prophylactic hysterectomy and oophorectomy, as they face a significant chance of developing endometrial cancer either simultaneously or in the future. It is increasingly distinguished that population

lifestyle advice to avoid obesity and encourage physical exercise could be essential to counteract the rising incidence of EC [47].

Typically, there have been no screenings conducted for EC. Population screening is not effective due to the early symptoms and positive prognosis of this malignancy [48]. However, it is recommended to promptly analyze every patient experiencing postmenopausal or atypical vaginal bleeding using vaginal ultrasound and endometrial biopsy. Furthermore, there have been suggestions to screen women with breast cancer who are using tamoxifen. However, the presence of EH (endometrial hyperplasia) on ultrasonography results in many false-positive results. This, in turn, leads to numerous invasive diagnostic procedures for asymptomatic tamoxifen users. A prospective analysis of 247 female tamoxifen users revealed that out of 52 asymptomatic women with a thicker endometrium, the majority had an atrophic endometrium and just one had a tumor. Additionally, among the 20 patients with vaginal bleeding, endometrial cancer (EC) was found in two cases [49].

Gene carriers undergoing screening for HNPCC syndrome who choose not to have preventive surgery have demonstrated enhanced effectiveness by employing annual endometrial biopsies in conjunction with vaginal ultrasonography [50].

A study was conducted to monitor and assess 175 individuals with genetic mutations using vaginal ultrasonography and endometrial biopsy. The results showed that 94% of cases of endometrial cancer (EC) were found through surveillance, while 74% were detected using endometrial biopsies. Out of the 14 cases of EC, 11 were detected through surveillance and 8 through endometrial biopsies. Furthermore, vaginal ultrasonography accurately identified just four individuals with EC, while failing to detect six other cases. The endometrial biopsy identified 14 more instances of probable precancerous hyperplasia [51].

CLINICAL MANIFESTATION

Abnormal uterine bleeding is the primary symptom that ladies with EC commonly experience. Due to the occurrence of blood loss, which serves as an initial indication of endometrial growth, 75% of women present with early-stage illness. Around 15-20% of women who experience postmenopausal bleeding are diagnosed with endometrial cancer (EC). The symptom is characterized by an excessive and thin discharge that lacks specificity. In women who are premenopausal or perimenopausal, the primary symptom that may be observed is irregular menstrual cycles or excessive menstrual bleeding (menorrhagia). Screening cervical cytology is not typically used as a diagnostic tool; however, it is possible to occasionally detect malignant endometrial cells in routine Papanicolaou (Pap) screens [10].

The presence of normal-appearing endometrial cells in a Pap smear of a postmenopausal female can indicate the presence of malignancy. A recent study analyzed 1183 Pap cytology samples and found that 2.7% of cases with normal endometrial cells, 18.4% of cases with atypical endometrial cells, and 100% of patients with EC cells had severe endometrial lesions [52].

A recent study demonstrated the diagnosis of endometrial and ovarian malignancies by analyzing the genetic material in the liquid obtained from the Pap test [53]. Women in more advanced stages of endometrial cancer may experience abdominal symptoms, pelvic and/or lower back discomfort, lymphedema, or symptoms related to secondary disease [10].

STAGING

Following the identification of a malignancy, the preoperative examination and staging workup are conducted. The definitive staging, as per the FIGO system (figure 2), relies on the surgical and pathological findings.

Federation of Gynecology and Obstetrics Surgical Staging System for Endometrial Carcinoma

Stage and Grade		Description
I		Tumor confined to the corpus uteri (and/or cervical mucosa)
IA	(G1, 2, 3)	No or less than half myometrial invasion
IB	(G1, 2, 3)	More than half myometrial invasion
II	(G1, 2, 3)	Tumor invades cervical stroma but does not extend beyond the uterus[a]
III		Local and/or regional spread of the tumor
IIIA	(G1, 2, 3)	Tumor invades the serosa of the corpus uteri or adnexa
IIIB	(G1, 2, 3)	Vaginal or parametrial involvement
IIIC	(G1, 2, 3)	Metastasis to pelvic or paraaortic lymph nodes
IIIC1	(G1, 2, 3)	Positive pelvic lymph nodes
IIIC2	(G1, 2, 3)	Positive paraaortic lymph nodes with or without pelvic nodes
IV		Tumor invades bladder or bowel mucosa, or distant metastasis
IVA	(G1, 2, 3)	Tumor invasion of bladder or bowel mucosa
IVB	(G1, 2, 3)	Distant metastasis, including intraabdominal metastases or inguinal lymph nodes
FIGO Histological Grading		
G1		<5% nonsquamous or nonmorular solid growth pattern
G2		5%-50% of a nonsquamous or nonmorular solid growth pattern
G3		>50% of a nonsquamous or nonmorular solid growth pattern

Figure 2. Classification of EC [10].

DIAGNOSTIC WORKUP [10]

1. When documenting a patient's medical history, it is important to gather information regarding any risk factors that are linked to endometrial cancer. The risk factors for this

condition encompass obesity, hypertension, diabetes mellitus, unopposed estrogen use, tamoxifen use, nulliparity, a family history of colon, endometrial, breast, or ovarian malignancies, and past pelvic irradiation (particularly for sarcomas).

2. 2. Comprehensive physical assessment, which includes an examination of the vagina and a bimanual pelvic examination.
3. Transvaginal ultrasonography with endometrial biopsy or aspiration curettage.
4. Instruments for endometrial biopsies, including a Vabra aspirator, a tiny Novak curette, and a Pipelle device.
5. It is recommended to either undergo formal dilation and fractional curettage with or without hysteroscopy.
6. CT scan for chest/abdomen/pelvis in stage I and II for evaluation of extra-uterine disease.
7. Routine blood count and chemistries; Ca-125.
8. Positron emission tomography (PET) scan.
9. MRI for depth of invasion.

PROGNOSTIC FACTORS

By doing both retrospective and prospective analysis, multiple studies have identified the main prognostic factors in EC. These factors include tumor stage, patient age, histological cell type, tumor grade, depth of myometrial invasion, and the presence of LVSI [40, 54]. The determination of these factors relies on the degree of solid growth, the way the tumor infiltrates the myometrium, and the existence of necrosis within the tumor cells. A simple binary method, classifying tumors as either low or high risk based on the percentage of solid growth (<50% vs. >50%), showed greater predictive capacity and improved reliability compared to the International Federation of Gynecology and Obstetrics (FIGO) grading system [55]. The FIGO grading system can be used as a binary system by classifying tumors into grades I and II against grade III, which has shown considerable prognostic significance. In addition, this technique has the advantages of being easily replicated and widely recognized by pathologists worldwide [56].

In most studies, the prognostic value of grade was frequently shown to be higher than that of depth of myometrial invasion. A diffusely infiltrating pattern of myometrial invasion is a stronger unfavorable predictor of outcomes compared to the amount of invasion [55].

MANAGEMENT

The primary therapeutic choice is surgical intervention, specifically an abdominal hysterectomy and bilateral salpingo-oophorectomy. This treatment can be performed using laparoscopy, robot-

assisted surgery, or laparotomy. Laparotomy is still predominantly limited to women with advanced cancer, a significantly enlarged uterus, or comorbidities. The 5-year overall survival (OS) rate for women with EC varies depending on the stage of the disease. For patients with stage I EC, the survival rate is between 80-90%. For stage II, the rate is between 60-80%, and for stage III, it ranges from 50-80%. The lower survival rate for stage III is due to the varied degree of the disease in tumors designated as FIGO stage III. Radiotherapy (RT) as the main treatment for females who cannot undergo surgery yields a 5-year overall survival (OS) rate ranging from 50% to 85%, and local control rates between 70% and 90% for stage I illness [10, 57]. RT, or radiation therapy, can greatly enhance the ability to locally control the disease and increase the chances of survival without any signs of the disease recurring. Adjuvant pelvic irradiation should be considered for women who have grade III malignancies with outer 50% myometrial invasion, advanced age, and/or lymphovascular space invasion. Brachytherapy as a standalone treatment may be an option for grade I or grade II illness with invasion of the outer 50% of the myometrium. It may also be considered for grade III disease or cases with unfavorable histopathologies, provided there is no invasion or invasion limited to the inner 50% of the myometrium [58, 59].

Adjuvant chemotherapy, concurrent chemoradiation, or sequential radiotherapy (RT) and chemotherapy may be considered due to their potential to improve relapse-free survival, particularly in stage III cancer. However, the benefits of adjuvant chemotherapy and RT on overall survival (OS) are still a subject of debate [10].

The optimal method for managing individuals with locally advanced pelvic disease has not been definitively determined. Radiation therapy can be given before or following surgical procedures intended to eliminate all observable indications of illness. Metastatic cases or cases of unresectable local illness can be effectively managed using chemotherapy or hormone treatment. Low-grade illness that is positive for estrogen and progesterone receptors can exhibit long-lasting responses to hormone therapy, frequently spanning many years. Endothelial cells exhibit a strong and rapid response to irradiation. Hence, it is recommended to administer palliative radiation therapy to patients who are experiencing symptoms, as it effectively relieves various symptoms such as hemorrhage, vaginal discharge, swelling due to localized disease or lymph node enlargement, pain caused by bone infiltration, and symptomatic brain metastases [59].

CONCLUSION

Endometrial hyperplasia and endometrial cancer are representing the two commonest problems in women. EH is a major precancerous condition for EC. EC is associated with poor prognosis if

diagnosed late. Epidemiology and outcomes of two conditions are varies and different according to many factors including ethnicity, environment, socioeconomic, hereditary, drugs, hormonal and aging process.

Disclosure

None

Ethics approval

This study was approved by Misan Radiation Oncology Center Committee Board (103/ 2020).

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Conflicts of interesting

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