Incidence and Staging of Endometrial carcinoma: Review Article

Amr Ashraf Nasr Refaie, Amr Ahmed Abdelrahman, Tarek Mohamed Elbehiedy, Hussein Mohamed Abdeldayem,

Obstetrics and Gynecology Department, Faculty of Medicine, Zagazig University, Egypt

Corresponding author: Amr Ashraf Mohamed Nasr Refaie

Email: amrashrefaie@gmail.com, **Mobile:** 01000089660

Abstract:

The optimal staging of tumors would reflect their biology and patterns of spread, permit accurate prognostication, and facilitate therapeutic decision-making. Pathologists are in a unique position to study each of these characteristics, comment on their ability to apply the criteria in daily practice, and offer suggestions to further improve the FIGO system. This paper selectively reviews some of the more problematic aspects of the current FIGO system, including the following: the distinction of tumors confined to the endometrium from those which are superficially myoinvasive; the method and utility of histologic grading of endometrial adenocarcinoma; the utility and reproducibility of the diagnosis of cervical epithelial and stromal invasion; the striking heterogeneity within and among stage III A, B, and C tumors and their differing prognostic significance. It concludes with recommendations for changes in a future revision of the FIGO staging of endometrial carcinoma.

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Introduction

Endometrial cancer (EC) is a malignancy of the inner epithelial lining of the uterus, with an increasing incidence and disease-associated mortality, worldwide (1).

EC comprises distinct histological subtypes and molecular phenotypes. Historically, EC was categorized as type I (association with unopposed estrogen stimulation, comprising low-grade cells that are more common and have a favourable prognosis) or type II (not estrogen driven, comprising high-grade cells that are less common and have an unfavourable prognosis) (2).

Type I ECs are primarily composed of grade I or grade II endometrioid adenocarcinomas, whereas type II ECs include grade III endometrioid adenocarcinomas, serous clear cell, undifferentiated carcinomas and carcinosarcomas (3).

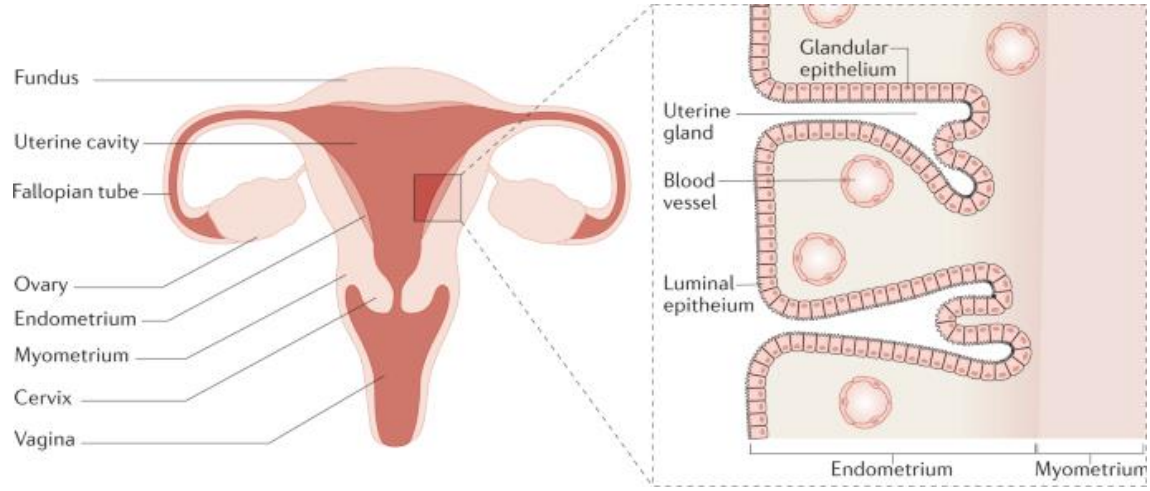

Figure (1): Uterine anatomy. The endometrium is the inner lining of the uterus. Endometrial cancer arises from the endometrial glandular epithelium **(4)**.

Incidence and mortality

EC was diagnosed in 417,367 women in 2020, worldwide, with the highest disease burden in North America and Western Europe. The incidence of EC is rapidly increasing. The high incidence rate in North America and Western Europe could be attributed to a high prevalence of lifestyle risk factors for EC, such as obesity, which is associated with ~50% of EC cases **(5)**.

According to the International Agency for Research on Cancer, the incidence rate of endometrial cancer is increasing rapidly and is estimated to increase by more than 50% worldwide by 2040. The incidence rates have been reported to have an increasing trend in the USA and several European countries since around 2000 **(6, 7)**.

The two major factors that contribute to an increase in the incidence of endometrial cancer in high-income countries are increased prevalence of obesity and extended life expectancy. Other determinants such as the widespread decrease in use of estrogen plus progestin menopausal hormone therapy—have also been proposed as the cause of the increased incidence rates of endometrial cancer in North America **(8)**.

On the basis of a 2016 pooled analysis of epidemiological studies from 1971–2014, EC-associated mortality has increased by an average of 1.9% per year. In the USA, the number of women diagnosed with EC by 2030 will double to 122,000 cases per year if current trends continue **(9)**.

As of 2020, uterine cancer is the fourth most common female neoplasm in Europe, with an incidence of 12.9–20.2 per 100,000 women and a mortality of 2.0–3.7 per 100,000 women **(10, 11)**.

Risk factors

Increased risk of EC is associated with increased age, certain ethnicities, higher BMI, endogenous or exogenous oestrogen exposure, tamoxifen use, early menarche, late menopause, lower parity, metabolic syndrome, family history and genetic predisposition. By contrast, a lower risk of EC is associated with normal BMI, higher parity and oral contraception use **(12)**.

- **Health and lifestyle factors**

Prolonged unopposed oestrogen exposure (such as with oestrogen replacement therapy, chronic anovulation or tamoxifen treatment), and age ≥55 years are very well-known risk factors for EC. In developed countries, an increasing rate of obesity has been paralleled by an increasing incidence of EC **(5, 13)**.

The association between obesity and EC is well established and is particularly pronounced for endometrioid EC, with approximate relative risks of 1.5 for those with overweight, 2.5 for those with class 1 obesity (BMI 30.0–34.9 kg/m^2), 4.5 for those with class 2 obesity (BMI 35.0–39.9 kg/m^2) and 7.1 for class 3 obesity (those with BMI ≥40.0 kg/m^2) **(9)**.

- **Genetic factors**

Some germline mutations increase the risk of EC, of which Lynch syndrome has the strongest association. This autosomal dominant syndrome is characterized by a germline mutation in one of the mismatch repair (MMR) genes: *MLH1* (encoding MutL homologue 1), *MSH2* (encoding MutS homologue 2), *MSH6* (encoding MutS homologue 6) or *PMS2* (encoding postmeiotic segregation increased 2) **(14)**.

Pathophysiology

Endometrial cancer research has gained some momentum in recent years and insights obtained from those studies have significant implications in the clinic. Endometrioid adenocarcinoma progresses through a premalignant phase of intraepithelial endometrial neoplasia in a large proportion of cases, such as hyperplasia with atypia **(15)**.

Most endometrial carcinomas arise as a result of a sequence of somatic DNA mutations, such as *PTEN*, mismatch repair genes, and *TP53* mutations. Mutations in the tumor suppressor *TP53* have been shown to play a pivotal role in serous endometrial cancer. Of note, human epidermal growth factor receptor 2 (HER2) amplification and homologous repair deficiency are also frequently found in this group **(16, 17)**.

Within the subgroup of mismatch repair deficient cancers, the most frequent cause of loss of expression of one or more of the mismatch repair genes is *MLH1* promotor hypermethylation, and other MMRd cancers are caused by double somatic hits. Lynch syndrome, a germline mutation of

one of the mismatch repair genes, is found in 3% of all endometrial cancers, and in 10% of those with mismatch repair deficiency **(18)**.

Histopathology

Histopathologic types

Histopathologic typing should be performed using the latest WHO classification of tumors. All tumors are to be microscopically verified **(19)**.

The histopathologic types of endometrial carcinomas are **(19)**:

- Endometrioid carcinoma: adenocarcinoma; adenocarcinoma-variants (with squamous differentiation; secretory variant; villoglandular variant; and ciliated cell variant)
- Mucinous adenocarcinoma
- Serous adenocarcinoma
- Clear cell adenocarcinoma
- Undifferentiated carcinoma
- Neuroendocrine tumors
- Mixed carcinoma (carcinoma composed of more than one type, with at least 10% of each component).

FIGO staging classification

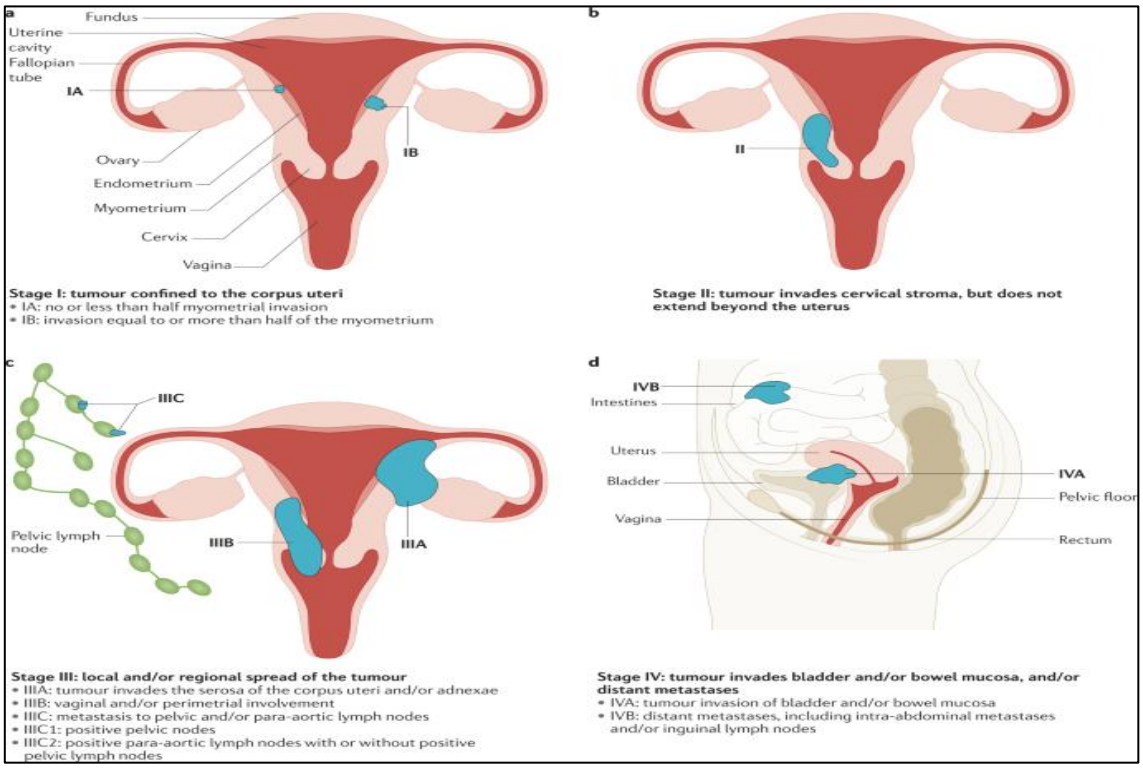

Figure (2): Staging of endometrial cancer **(4)**.

Table (1): FIGO staging **(15).**

FIGO stage
I[a] Tumor confined to the corpus uteri **IA**[a] No or less than half myometrial invasion **IB**[a] Invasion equal to or more than half of the myometrium
II[a] Tumor invades cervical stroma, but does not extend beyond the uterus[b]
III[a] Local and/or regional spread of the tumor • IIIA[a] Tumor invades the serosa of the corpus uteri and/or adnexa[c] • IIIB[a] Vaginal involvement and/or parametrial involvement[c] • IIIC[a] Metastases to pelvic and/or para-aortic lymph nodes[c] • IIIC1[a] Positive pelvic nodes • IIIC2[a] Positive para-aortic nodes with or without positive pelvic lymph nodes
IV[a] Tumor invades bladder and/or bowel mucosa, and/or distant metastases • IVA[a] Tumor invasion of bladder and/or bowel mucosa • IVB[a] Distant metastasis, including intra-abdominal metastases and/or inguinal nodes

- **a** Either G1, G2, or G3.
- **b** Endocervical glandular involvement only should be considered as Stage I and no longer as Stage II.
- **c** Positive cytology has to be reported separately without changing the stag

Diagnosis, screening and prevention

Clinical presentation and diagnostic assessment

Among perimenopausal and postmenopausal women, postmenopausal bleeding (PMB) accounts for approximately two-thirds of all gynaecological visits and is a common symptom of EC. Indeed, one meta-analysis found that PMB occurred in ~90% of patients with EC; however, it led to a diagnosis of EC in only 9% of cases **(20)**.

Although abnormal uterine bleeding is the most common symptom of EC, bleeding can be accompanied by vaginal discharge and pyometra (uterine infection) in some women. Patients diagnosed with advanced EC might also present with symptoms similar to those of advanced ovarian cancer, such as pain and abdominal distension along with either constipation or diarrhoea **(21)**.

Diagnostic work-up is recommended to rule out EC in all women presenting with PMB. The standard work-up to investigate and determine the cause of PMB may comprise pelvic ultrasonography, endometrial biopsy or dilatation and curettage (D&C; involves cervical dilation with scraping of the endometrial lining) with or without hysteroscopy **(22)**.

Measurement of the endometrial thickness using transvaginal ultrasonography should be performed in the sagittal plane at the thickest point; most authors consider 5 mm as the normal upper limit for endometrial thickness in postmenopausal women, and this cut-off value has a sensitivity of 96% and a specificity of 61% for EC in post-menopausal women with abnormal uterine bleeding **(4)**.

Pelvic ultrasonography can be omitted in patients who already have an endometrial sample showing an invasive cancer. When histopathological findings from endometrial biopsy are insufficient to confirm diagnosis, a D&C should be carried out; of note, biopsy under hysteroscopy has higher accuracy than 'blind' D&C, and remains the gold standard for the diagnosis of EC when possible **(23)**.

Of note, biomarkers of EC, namely, CA-125 or HE4, can be incorporated into routine diagnostic and follow-up practice for EC management owing to lack of evidence in support of their clinical impact **(24)**.

Preoperative staging: imaging

Although EC is a surgically staged disease, preoperative staging using imaging may help to establish those at risk of recurrence and inform surgical management, as imaging can identify myometrial or cervical invasion and lymph node metastasis **(25)**.

Staging using imaging is indicated for patients who present with symptoms suggestive of extrapelvic disease and those with a poor performance status who are unable to independently perform activities of daily life for whom metastatic disease must be ruled out and in consequence surgery would not be an option **(26)**.

MRI is the most accurate imaging technique for preoperative staging of EC owing to its excellent soft tissue contrast resolution. Depth of myometrial invasion and cervical stromal invasion are both important aspects of EC staging and can be determined using dynamic contrast-enhanced MRI (DCE-MRI) and T2-weighted imaging. Diffusion-weighted imaging (DWI) can be carried out in patients who cannot receive intravenous gadolinium, which is typically used for DCE-MRI **(27)**.

In support of the use of DWI, one meta-analysis did not identify differences in the diagnostic performance of DWI compared with DCE-MRI, and combining T2-weighted imaging and DWI was superior to DWI or DCE-MRI alone **(25)**.

CT has low sensitivity (83%) and specificity (42%) for myometrial and cervical stromal invasion, and is generally not used for the initial diagnosis of EC. However, CT is useful in evaluating the extent of disease in women with more advanced disease with extra-uterine spread. For detection of lymph node metastases, both CT and MRI have a sensitivity of 27–66% and a specificity of 73–99% **(25)**.

Integrated PET and CT (PET–CT) is not an appropriate screening tool for detection of primary EC owing to its limited spatial resolution, and is only indicated for initial staging if extra-uterine involvement is suspected or is observed on a preoperative MRI. Moreover, when PET–CT is performed as initial staging, primary intratumoural heterogeneity of [^{18}F]fluorodeoxyglucose (^{18}F-FDG) uptake seems to be a negative prognostic sign, correlating with a greater likelihood of tumour recurrence; these patients may benefit from more aggressive monitoring **(28)**.

In advanced disease, PET–CT may be particularly useful in detecting pelvic and para-aortic lymph node metastasis, with a sensitivity of 51–69% and specificity of 90–100%. In addition, PET–CT with either CT or MRI has higher sensitivity and specificity for detecting recurrence than CT and/or MRI alone. Nevertheless, no correlation was found between early detection of recurrence and overall prognosis. Therefore, integration of PET–CT in the diagnosis and follow-up of EC is not routinely indicated **(29)**.

Management

Estimating the risk of disease recurrence has historically been challenging for EC given variability in surgical practice and the lack of reproducible pathological classification. Consequently, treatment of newly diagnosed EC is variable between regions and across treatment centres. For early-stage disease, the main treatment is surgery. Depending on stage of disease and other risk factors, adjuvant radiotherapy and/or chemotherapy can be used to reduce risk of recurrence **(30, 31)**.

Studies investigating adjuvant endocrine therapy have been small and negative; therefore, endocrine therapy is not recommended in the adjuvant setting. Options for metastatic disease are limited, with both chemotherapy and endocrine therapy considered standard of care. More

recently, immunotherapy alone or in combination has become standard of care, although these therapies are not universally available across all jurisdictions **(32, 33)**.

Surgery

Surgery is the primary treatment for women with localized EC. Surgical staging is used for prognostication and identification of women who might benefit from adjuvant treatment. Total hysterectomy with bilateral salpingo-oophorectomy (BSO) is standard of care and can be performed by an open or a minimally invasive approach. Minimally invasive techniques have similar oncological outcomes, shorter hospital stay and fewer complications compared with open laparotomy in early-stage EC **(34)**.

Lymphadenectomy is a controversial topic in the management of EC. Gynecologic Oncology Group (GOG)-33 found a role for lymphadenectomy in staging EC, and retrospective analysis found a survival benefit for pelvic and para-aortic lymphadenectomy in patients with higher risk histology and for those with intermediate-risk or high-risk disease **(35)**.

The necessity of para-aortic lymphadenectomy (to detect metastatic deposits) is also controversial and can be particularly challenging in patients with obesity. The risk of para-aortic metastases if no metastatic deposits are identified in the pelvic lymph nodes is dependent on other factors, such as LVSI, tumour histology and grade **(36)**.

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