Clinical and Pathological Characteristics in Endometrial Cancer

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Abstract

Endometrial cancer is divided into two categories and is one of the most common cancers of the uterus. Type 1 is the most prevalent (70–80%) and has a better prognosis because it is limited to the uterus. Every year, 319.500 cases were reported worldwide, resulting in 76.000 deaths. Endometrial cancer is divided into ten major groups based on histology and four groups depending on the likelihood of recurrence, according to the World Health Organization. Age (post-menopause), race, genetics, lifestyle, parity, diabetes, hypertension, unopposed estrogen therapy, early menarche, and delayed menopause are only a few of the risk factors. Women over 45 years of age who have abnormal uterine bleeding should be evaluated with a histological examination and/or ultrasound, according to the American College of Obstetricians and Gynecologists (ACOG). The ultimate test for diagnosis is an endometrial biopsy. Following that, imaging modalities could be used to help with staging. FIGO stage, histological subtypes, tumor grade, myometrial invasion, lymphovascular space invasion, and age are all prognostic variables. Surgical and non-surgical treatment options are commonly used. Lymphadenectomy is not generally indicated in patients with a low risk of recurrence because of the danger of complications, especially in the elderly.

Keywords: Endometrial cancer, Clinicopathological characteristics, Lymph node metastasis, Risk factors

1. Introduction

Uterine cancer affects roughly 319,500 women worldwide each year, with 76,000 deaths. Uterine cancer is the fourth most common cancer in women in the United States (1). The American Cancer Society projects 12,940 uterine cancer deaths in2021, including endometrial cancer and uterine sarcoma (2). In Indonesia, there were 879 instances of endometrial cancer between 2011 and 2015. Overuse of estrogen, tamoxifen use, nullipara, and obesity are the main risk factors for endometrial cancer (3). Endometrial cancer is divided into two types: type 1 and type 2. Type 1 cancer is more common (70–80 percent) and tends to be limited to the uterus, with a favorable prognosis. Type 2 endometrial cancer, on the other hand, has a significant incidence of spreading and has a poor prognosis. It is characterized by a more severe clinical course and is unaffected by estrogen exposure (4,5). Postmenopausal women are more likely to develop endometrial cancer (6). Lymphatic metastasis has long been recognized as a powerful predictive factor for endometrial cancer patients' mortality. The therapeutic advantages of systemic lymphadenectomy are unknown. (Stlberg and colleagues, 2017) As a result, the goal of this study is to determine which clinical and pathological variables can predict lymph node metastases in endometrial cancer.

2. Anatomy and Embryology of the Uterus

The development of the female reproductive system begins with two paramesonephric ducts that form the fallopian tube and fuse to form the uterus and the superior part of the vagina. The uterus is located inside the woman's pelvic cavity, located posteriorly to the urinary vesica and anteriorly to the rectum. The uterus is divided into 4 segments namely the fundus, corpus, isthmus, and cervix, and is supported by the utero-ovarian, rotundum, latum, Cardinale, and sacrouterina ligament. The position of the uterus varies, including anteversion/retroversion, anteflexion/retroflection, or *midline.* In most women, the position of the uterus is anteflexion and anteversion (7). The uterus is directed by the Uterine artery and ovarian artery, the anterior branch of the iliac internal artery. Inside the endometrium, these vessels will branch out into aa. basalis and spiral artery. The main drainage of the uterine fundus is the paraaortic (8). The autonomic nerve of T11-T12 innervates the uterus, with the sympathetic nervous system of the hypogastric plexus, and its parasympathetically innervated by S2-S4 nerve fibers. The uterus of an average adult woman has a length of 8 cm, a width of 5 cm, and a thickness of 4 mm. Histologically, the uterus has 3 layers of tissue, namely endometrium, myometrium, and serous/perimetrium; consecutively from the inside out (7). The endometrium consists of a layered columnar epithelial tissue with many stem cells in the basal layer (9).

3. Endometrial Physiology

The function of the endometrium is to prepare for the implantation process, maintain gestation, and menstruate when implantation does not occur. Postmenstrual processes include inflammatory resolution, angiogenesis, tissue remodeling, and the formation of new tissue. Endometrial cells include stromal, epithelial, vascular, and immune cells. The main hormones that play a role in preparing for pregnancy are 17β-estradiol and progesterone which fluctuate throughout the menstrual cycle. At the beginning of the proliferative phase (days 0–14), the vascular and endometrial tissues undergo extensive proliferation, and primordial follicles maturation into de Graaf. Variations in menstrual cycle periods are caused by follicular phase variations. The main hormone of this phase is estrogen, specifically 17β-estradiol. The main goal of this phase is to stimulate the growth of the endometrial lining, creating an endometrial atmosphere that supports the implantation (9). At the end of the proliferative phase, the LH surge occurs, which is when 17β-estradiol reaches its critical level of 200 pg /ml, then the mature follicle ruptures and releases oocytes. The cervical mucus is more numerous and diluted to accommodate sperm cells. Levels of 17β-estradiol decrease at the end of ovulation. The luteal/secretory phase occurs in the last 14 days and is dominated by the hormone progesterone stimulated by LH to prepare the corpus luteum and endometrium for fertilization of the ovum and implantation. When the luteal phase ends, progesterone provides negative feedback to lower FSH and LH levels, which lower 17β-estradiol and progesterone. The endometrium is prepared for fertilization and pregnancy by increasing the vascular supply and stimulating more mucus secretion by lowering tissue thickness, forming complex glandular structures, collecting glycogen, and providing a wider area within the spiral artery. Progesterone levels decrease so that cervical mucus thickening occurs after the fertilization period. When pregnancy occurs, the corpus luteum will maintain hormone levels. Conversely, when implantation does not occur, the corpus luteum regresses, lowering levels of 17β-estradiol and progesterone, resulting in menstruation. Menstrual blood mostly comes from the arteries, containing prostaglandins, debris, and endometrial fibrinolysis (9). Menstruation is generally 3–5 days long with an average volume of 30 ml. The period from regression of the corpus luteum to menstruation and postmenstrual endometrial repair is called the perimenstrual window (9).

Decidualization is the process of transforming the endometrial cells into decidua cells, which serves to provide an endometrial atmosphere that supports embryo implantation and placental development. Decidualization changes the shape of endometrial stromal cells from long to round, by induction of progesterone-dependent protein expression (9, 10). In addition, the endometrium also produces estrogen, androgens, and glucocorticoids. Endometrial stromal are positive cells of androgen receptors in the functional layer (proliferative phase) and basal (throughout the menstrual cycle). Androgen receptors are reduced during the secretory phase, and increase as progesterone decreases. Decreased progesterone due to regression of the corpus luteum triggers menstruation that occurs in 2 phases. The first phase deals with increased exposure to cytokines and prostaglandins, depending on the response of stromal cells to a decrease in progesterone, which is an anti-inflammatory hormone. The second phase is the increase of cytokines and immune cells into the endometrium, activation, and release of *the matrix metalloproteinase* (MMP) enzyme, as well as the destruction of the extracellular matrix. Unlike the first phase, the second phase is not affected by the progesterone (9).

4. Definition and Etiology of Endometrial Cancer

Endometrial cancer is the most frequent malignancy of the corpus uterine (~83%). Malignant subtypes are serous cancer and papillary-serous cancer (4-6%). (4) Type 1 endometrial cancer is the most numerous type of endometrial cancer (~70–80%), consists of endometrioid cancer, *low grade*, diploid, and has hormonal receptors that differentiate moderately or well, tending to be localized in the uterus with a relatively good prognosis. In contrast, type 2 endometrial cancer, includes non-endometrioid, high-grade, aneuploid, poorly differentiated, non-hormonally occurring, devoid of hormone receptors, with a high risk of metastasis and a poor prognosis (4).

Characteristics of type 1 endometrial cancer are obesity, anovulation, nullipara, diabetes mellitus (DM), estrogen-producing neoplasms, as well as exposure to exogenous estrogen. Cyst formations, tubal metaplasia, and gland remodeling can be found that results in more glandular components than stromal. The appearance of endometrial hyperplasia that occurs in type 1 endometrial cancer generally lacks neoplasia morphology and has the characteristics of hyperplasia without atypia. In some cases, the structure of the type 1 cancer gland has neoplastic characteristics (5, 11).

Endometrial hyperplasia without atypia is generally benign, although in 30-40% of cases it can develop into adenocarcinoma. Cancer derived from hyperplasia is type 1 endometrial cancer. Type 2 endometrial cancer is less common (10–20%). Type 2 endometrial cancer generally has non-endometrioid, high-grade histological properties, in the form of papyllaxrosa or clear cells not affected by estrogen and not derived from endometrial hyperplasia, but rather from endometrial tissue atrophy (5)

Type 1 and type 2 endometrial cancers can also be distinguished based on their genetic changes. The most frequent genetic changes in endometrioid cancer involve PTEN. Some studies estimate that PTEN mutations occur early in type 1 endometrial cancer and often coincide with other mutations in phosphatidylinositol-3-OH kinase (PI3K)/AKT, KRAS, ARIDIA, and β-catenin pathways, as well as defects in DNA mismatch repair (MMR). Non-endometrioid endometrial cancer often indicates the presence of aneuploids and mutations in HER2 and TP53. PTEN inactivation generally occurs due to mutations of both alleles, so the function of the gene is lost entirely. PTEN encodes proteins and lipid phosphatase. The activity of lipid phosphatase enzymes induces cell cycle arrest at the G1/S stage. Protein phosphatase enzymes are involved in focal adhesion inhibition, cell dispersion, and migration, as well as inhibition from protein kinase enzyme signaling. Therefore, the disruption of PTEN results in growth disorders and apoptotic escape. PTEN mutations are also found in endometrial hyperplasia. Increased regulation of pro-apoptosis

mechanisms involving Akt-dependent mechanisms mediated through PTEN, as well as decreased regulation of anti-apoptosis mechanisms through Bcl-2. PTEN works in contrast to phosphatidylcholineositol 3-kinase (PI3KCA) to control phosphorylated AKT levels. PTEN mutations increase PI3KCA activation, resulting in phosphorylation of AKT. PI3KCA mutations are found in 36% of endometrial cancer cases (5).

5. Epidemiology

Worldwide, there are an estimated 319,500 cases of uterine cancer per year, and it accounts for about 76,000 deaths per year. From 2006-to 2011, the incidence of endometrial cancer increased by 2.3% annually. Uterine cancer is most commonly diagnosed postmenopausal, with peak incidence occurring between 60-and 70 years of age. Uterine cancer accounts for about 2% of cancer deaths in women in developed countries. Uterine cancer mortality was highest on Caribbean islands (3.3/100,000), Central and Eastern Europe (3.4/100,000), Melanesia (3.8/100,000), Micronesia/Polynesia (2.5/100,000), and the United States (2.2/100,000). Most cases show abnormal uterine bleeding and vaginal discharge. Based on SEER 18 (2004–2011) data, the 5-year survival rate for endometrial cancer is estimated at 81.5% (1).

6. Classification

WHO divides endometrial cancer into ten main groups based on histological morphology. Biological distinctions between endometrial cancer subtypes have been confirmed by several molecular studies.

Endometrioid adenocarcinoma, generally showing glandular, papillary, or solid patterns, is the most histological subtype. The glandular structure is well-formed and exhibits regular luminal boundaries, resembling the structures of the normal endometrial glands. The structures of villi and papillae can generally be distinguished from serous cancer. The area of the solid area determines the degree of histopathology according to the FIGO classification. In 1st-degree cancer, the solid area is < 6%, in 2nd-degree cancer, 6–50%; and >50% in 3rd-degree cancer (12).

6.1. Cancer Musinosum

Pure mucinous cancer contains >50% of cells that have diastase-resistant intracytoplasmic mucus with PAS staining. Focal mucinous differentiation is more commonly found in endometrioid cancers. Although rare, cryptopic or microglandular areas can be found and resemble microglandular hyperplasia of the cervix. Reported association with exogenous estrogen. Mucinous cancer exhibits estrogen receptors (ER) and diffuse positive progesterone receptors (PR), as well as vimentin-positive, which can be from endocervical adenocarcinoma. The Ki-67 index in mucinous cancer is generally low (12).

6.2. Serous Cancer

Endometrial cancer in the form of serous cancer is a common subtype. A mixture of papilar and/or glandular diagnostic instructions with high nucleus degrees are used. Variations in papillae, glandular, and solid structures are common in histological patterns. Tumor cells have a polygonal form, an atypic nucleus, a large nucleolus, and a high mitotic activity. Tumor cells are typically organized irregularly to resemble buds and tufts, however, they can also be hobnail shaped. A villoglandular type of endometrioid cancer and clear cell cancer is included in the differential diagnosis of serous cancer. There is usually a thin papilla-papillae display and no atomic nucleus in the villoglandular variety of endometrioid cancer, whereas clear cell cancer has focused cells with clear cytoplasm, hyaline bodies, and eosinophilic globules. Small, atrophic uteruses are frequently

affected by serous carcinoma, which is commonly accompanied by an atrophic endometrium that can also be detected inside endometrial polyps. Patients with serous cancer are often between the ages of 65 and 70. Immunohistochemical analysis revealed a p53 immunoreactive pattern that is significantly linked to the TP53 mutation. Cases with negative immunohistochemistry usually have frameshift or stop codon mutations, which cause protein shortening that is undetectable by most p53 antibodies. Immunoactivity to Er and PR is usually low or non-existent (12).

6.3. Clear Cell Cancer

Polygonal and hobnail cells with clear or eosinophilic cytoplasms and high levels of nuclear atypia make up clear cell carcinoma. Tubulo-cystic, papillary, and solid histopathological patterns exist. Clear cell cancer papillae are often small and branching, with an ornate stroma. The rich eosinophilic extracellular globular structure and hyaline bodies are also featured. Clear cell carcinoma is a type of cancer that develops in the atrophic endometrium and is frequently found in endometrial polyps. Immunohistochemical examinations show weak/negative positivity to ER and PR, the ki-67 index is at least 25–30%, and generally has positivity to HNF-1β, napsin A, and racemase (AMACR). About 30% of cases indicate a loss of PTEN protein. About 50% of patients are diagnosed in stages II-IV and show a poor prognosis with a 5-year survival rate of less than 50% (12).

6.4. Mixed Cancer

Mixed cancer is a combination of 2 or more histological subtypes, in which at least one of the subtypes belongs to type II endometrial cancer. The most combination is endometrioid-serous and endometrioid-clear cells. The minimum percentage of minor components has been defined as at least 5% of all tumor components. Pathogenesis of endometrioid-serous mixed cancer is thought to occur through the progression of endometrioid cancer into serous cancer. Immunohistochemical studies reveal weak/negative ER and PR positivity, a ki-67 index of at least 25–30%, and generally positive HNF-1, napsin A, and racemase expression (AMACR). PTEN protein loss is seen in approximately 30% of cases. About half of patients are diagnosed in stages II-IV, and their prognosis is poor, with a 5-year survival rate of fewer than 50%. (12).

6.5. Undifferentiated Cancer

Monomorphic type undifferentiated cancer subtypes and dedifferentiated malignancies are distinguished in the most recent WHO classification. A myxoid matrix resembling a carcinoma is indicated by an undifferentiated malignant stroma. High-grade neoplasm is a differential diagnosis (sarcoma, malignant lymphoma, and neuroendocrine cancer). Undifferentiated components penetrate the myometrium in general, whereas low-grade components border the endometrial cavity. There is no evidence of ER or PR positive. Any high-grade endometrial neoplasm, including biphasic carcinoma (mixed malignant Mullerian tumor/MMMT), is a differential diagnosis for undifferentiated cancer. Histologically, MMMT generally contains malignant mesenchymal tissue, which mixes with malignant epithelial components. The findings are inversely proportional to cancer dedifferentiation which suggests a clear boundary between the two components. MMMT components are generally more heterogeneous than dedifferentiated cancers. Tumor components are generally high-grade and can show epithelial and mesenchymal differentiation. The prognosis of MMMT is relatively poor (12).

6.6. Neuroendocrine Cancer

Neuroendocrine cancer is the latest subtype in the WHO classification, which is relatively rare with a median age of 60–65 years. Small Cell Neuroendocrine Cancer (SCNEC) growth patterns can be diffuse, trabecular, or rosette-like. Large Cell Neuroendocrine Cancer (LCNEC) consists of a focused firmly-bound cell, trabecula, generally with extensive necrosis. To establish the diagnosis of neuroendocrine cancer, neuroendocrine growth patterns must be found. Immunohistochemical examinations generally show at least positivity to sinaptofisin or chromogranin A. The prognosis of SCNEC and LCNEC is relatively poor. Differential diagnoses of SCNEC and LCNEC include other high-degree neoplasmic subtypes, including undifferentiated cancers (12).

7. Risk Factors

Age, race, and genetic predisposition are risk factors that cannot be changed, whereas diet, lifestyle, nullipara, obesity, diabetes, hypertension, and hormone replacement therapy are risk factors that can be changed. Early menarche age, late menopause age, and estrogen replacement therapy are all linked to an increased risk of endometrial cancer (13).

7.3. Age

The average age of postmenopausal women is 60 years. Cancer is most common between the ages of 75 and 79. Endometrial cancer is more common in women under 40 years old who are premenopausal, have an anovulation cycle, and/or have a hereditary susceptibility (14).

7.4. Race

The highest incidence is found in North America and Northern Europe, and the lowest in Asia and Africa. In the United States, whites have a higher risk than African-Americans (2.88% vs. 1.69%). African-American Race tends to suffer from type II and further stage endometrial cancer (14).

7.5. Obesity

The conversion of androgens into excess estrogens in adipose tissue contributes to an increased risk of obesity. Excess estrogen promotes the proliferation of endometrial cells, which leads to carcinogenesis. It also increases persistent anovulation, which is linked to an increased risk of endometrial cancer (14). Obesity/adiposity is one of the risk factors for endometrial cancer, according to Raglan et al. The findings were further corroborated by the World Cancer Research Fund's 2013 Continued Update Project, which found that body fat levels are linked to endometrial cancer in postmenopausal women due to elevated estrogen, hyperinsulinemia, and chronic inflammation (15).

7.6. Parity

Raglan et al. also discovered that women who gave birth to nullipara had a 40% lower incidence of endometrial cancer. According to a meta-analysis, there is a non-linear negative association between parity and the risk of endometrial cancer. It's assumed to be caused by the alteration, which is characterized by a rise in progesterone during pregnancy, which protects the endometrium (15).

7.7. Diabetes Mellitus

Hyperinsulinemia may have a causal relationship with endometrial cancer either through the mitogenic effect directly or through increased estrogen levels that occur due to decreased levels of Sex Hormone Binding Globulin (SHBG) (15, 16). In addition to DM, other conditions included in metabolic syndrome have also been shown to increase the risk of endometrial cancer (14).

7.8. Estrogen Exposure

Type I endometrial cancer is linked to long-term exposure to exogenous estrogen (hormone replacement therapy) and endogenous estrogen (chronic anovulation, tumors, and obesity). Other variables linked to higher estrogen exposure include early menarche (age 12 years), nullipara, infertility, late menopause, and persistent anovulation (e.g., related to PCOS). Tamoxifen has also been linked to an increased risk of endometrial cancer. Tamoxifen is an estrogen receptor modulator that functions as an estrogen antagonist in breast tissue but as an estrogen agonist in endometrial tissue. Tamoxifen users have a 2-3 times higher risk of breast cancer than the general population (14).

7.9. Genetic Predisposition

About 5% of cases result from genetic mutations that generally occur in the 10-20 years before sporadic endometrial cancer. Lynch syndrome, or hereditary non-polyposis colorectal cancer, is the dominant autosomal syndrome resulting from germline mutations in one of four DNA mismatch repair genes (MLH2, MSH2, MSH6, or PMS2). (17–19) Lynch syndrome patients have a risk of endometrial cancer of about 60% (20). Genetic mutation screening needs to be considered, particularly in patients <50 years of age with a history of family members. A total hysterectomy procedure with salpingo-oophorectomy has been known to lower the risk of endometrial cancer in Lynch syndrome patients, and the procedure has been recommended by the National Comprehensive Cancer Network (NCCN). Increased risk and onset of younger age, led the American Cancer Society to recommend screening for endometrial cancer annually through biopsy starting at age 35. Guidelines from the NCCN also recommend screening annually, particularly for women who refuse hysterectomy prophylactic procedures and bilateral salpingo-oophorectomy. Transvaginal ultrasound examination is not recommended as a screening modality (14, 18). Cowden syndrome is characterized by mutations in the Phosphatase and Homologous Testin (PTEN) genes. In populations with Cowden syndrome, endometrial cancer is generally diagnosed after reproductive age. Endometrial biopsy and/or transvaginal ultrasound per year from age 30–to 35 years are recommended as screening modalities (14, 21).

8. Diagnosis

American College of Obstetrics and Gynecology and the Society of Gynecologic Oncology agree that endometrial cancer screening is only recommended in patients with Lynch syndrome. Pap smears are not a reliable modality for endometrial cancer screening. Diagnosis enforcement begins with comprehensive anamnesis of risk factors and symptoms, including a history of previous treatment or surgery as well as a family history. The most frequent main symptom is abnormal uterine bleeding. Other findings such as increased vaginal secretions or incidental findings in the form of endometrial thickening on ultrasound can be found. Patients can develop pyometra, a severe uterine infection. Patients with advanced intraperitoneal endometrial cancer may complain of abdominal-pelvic pain, abdominal distension, rapid satiety, changes from urinary gastrointestinal or vesica function, dyspareunia, and tightness due to pleural effusion (14, 22).

Abnormal cytology findings may include the presence of endometrial cells, atypical glandular cells, or adenocarcinoma in situ. Endometrial cancer can also be diagnosed after a hysterectomy procedure (14). Any cause of postmenopausal bleeding is further evaluated, especially if there are risk factors. ACOG recommends evaluation of endometrial cancer with histopathology or ultrasound in women > 45 years of age with abnormal uterine bleeding, or women <45 years with a history of *unopposed* estrogen exposure. After anamnesis, a comprehensive physical examination needs to be performed. In early-stage patients, a physical examination is generally normal. Supraclavicular or inguinal Lymph Nodes (LN) can be palpated. Ascites and Upper quadrant abdomen pain can represent omental caking. Inspeculo examination is done for visualization of the cervix and vagina. Bimanual pelvic examination is performed to evaluate the size and mobility of the uterus, as well as enlargement of the adnexa structure or parametric thickening.

An endometrial biopsy is a definitive examination to establish a diagnosis of endometrial cancer. If a negative or non-diagnostic result is obtained in a patient, other examinations such as hysteroscopy with dilation and curettage are needed for further evaluation. Imaging modalities such as ultrasound do not need to be done before a biopsy examination. When the thickness of the endometrium is <5 mm on TVUS, endometrial biopsy generally does not give significant results. However, type 2 endometrial cancer can come from a thin and atrophic endometrium, so patients who are struggling still need to undergo a biopsy (14)(22).

If a diagnosis of endometrial cancer has been established, a thoracic X-ray can be performed to detect pulmonary metastasis. CT scans, MRIs, or PET/CT may be considered for degree assessment and metastatic evaluation, but are limited in assessing LN involvement. In cases of serous type endometrial cancer and clear cells on biopsy, radiographic examination is generally more favorable because type 2 endometrial cancer tends to have metastasized at the time of diagnosis, so in cases found unresectable, the main therapeutic options with radiotherapy and/or chemotherapy and surgery that are more invasive (laparotomy and cytoreduction) can be considered. MRI examinations are proved useful in evaluating the degree of myometrial invasion, cervical involvement, and lymph node involvement in young patients who may need ovarian preservation (14, 22). Saline infusion sonohysterography may also be used to evaluate the endometrial cavity. This examination is relatively rare but can be considered if the results of an endometrial biopsy or transvaginal ultrasound are considered inadequate to establish the diagnosis (22).

9. Stage Determination

The stage of endometrial cancer is determined based on the 2009 FIGO classification (Table 3). Prognostic factors include FIGO stage, histological subtype, degree, myometrial invasion, lymphovascular space invasion (LVSI), and age. As many as 75-85% of endometrial cancer cases are type 1. The rest is type 2 endometrial cancer.

Table 1. Staging of endometrial cancer according to FIGO 2009

Stage	Definition
IA	Tumor confined to the uterus, myometrial invasion is not obtained or < 50%
IB	Tumor confined to the uterus, myometrial invasion ≥ 50%
II	Invasion of the cervical stromal, but does not pass through the uterus
IIIA	Tumor invading serous or adnexa
IIIB	Vaginal and/or parametric involvement
IIIC1	Pelvic LN involvement
IIIC2	Para-aortic LN involvement
IVA	Tumor invade the vesica urinary and/or intestinal mucosa
IVB	Distant metastases, including abdominal metastases and/or inguinal LN

10. Management

Endometrial cancer management can be grouped into surgical therapy and non-surgical therapy.

10.1.Endometrial hyperplasia

Hysterectomy can be performed with/without bilateral salpingo-oophorectomy. ACOG does not recommend supracervical procedures as a therapeutic option because they leave residual tumors. The definitive therapy of complex atypical endometrial hyperplasia is hysterectomy. Other options include abdominal procedures and minimally invasive procedures such as laparoscopy. Patients with endometrial hyperplasia without atypia, multiple comorbidities that complicate surgery, or want fertility preservation, may be considered for non-surgical therapy, most often progesterone therapy for tumor stabilization and prevention of progressions to endometrial cancer. The use of levonorgestrel IUD or oral progesterone (medroxyprogesterone 10 mg/day for 10–14 days/month) is an option for low-moderate-risk endometrial hyperplasia therapy. In general, the American Academy of Family Physicians recommends therapy for 6 months, with endometrial tissue retrieval every 3 months for evaluation (22).

10.2. Endometrial Cancer

The main therapies in cases of endometrial cancer are total hysterectomy with bilateral salpingo-oophorectomy, para-aortic and pelvic lymphadenectomy, and pelvic washing to determine the stage. Vaginal hysterectomy in general is not recommended because it can inhibit the abdominal survey and lymphadenectomy process (22). The decision of lymphadenectomy and the extent of lymphadenectomy can be determined based on the findings of hysterectomy. The criteria for low LN metastatic risk are myometrial invasion < 50%, tumor size < 2 cm, or G1-2. Sentinel Lymph Node Mapping (SLNM) can determine the need for adjuvant therapy and decrease lymphadenectomy-related morbidity and long-term sequelae of unnecessary adjuvant therapy. In cases of early-stage non-endometrioid cancer, abdominal cavity review, bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy, omentectomy, and peritoneal biopsy with maximum debulking are recommended, due to the high tendency of spread to the upper abdomen. The standard surgery is laparoscopy with total hysterectomy, without vaginal cuffs, and bilateral salpingo-oophorectomy. Lymphadenectomy is not recommended at low recurrence risk but is recommended in moderate and high-risk groups for stage determination and adjuvant therapy. Palliative surgery may be considered in patients with metastasis. Progestin therapy (medroxyprogesterone acetate 400–600 mg/day or megestrol acetate 160–320 mg/day or levonorgestrel IUD) is a therapeutic option in this group (23).

Early-stage adjuvant therapy is adjusted based on risk groups and prognostic factors, including radiotherapy and/or chemotherapy. (22) Postoperative pelvic radiation in stage I endometrial cancer may provide locoregional control. Vaginal brachytherapy in stage IA endometrioid endometrial cancer showed no improvement in survival compared to observation. The addition of pelvic radiation was shown to improve locoregional control, but did not affect overall survival and was associated with increased acute toxicity to the gastrointestinal system and urinary tract. Postoperative pelvic radiation is considered standard therapy in high-risk endometrial cancer. Single adjuvant chemotherapy promotes poor local control, so it is combined with pelvic radiation. Combination adjuvant treatment (4 cycles of platinum-based chemotherapy before/after radiotherapy) was shown to improve *disease-free survival* and *overall survival*. In endometrial cancer with metastasis, surgical or radiation therapy may be performed, especially in single/isolated pelvic recurrence or metastasis at only one location. In patients with recursion outside the pelvis, chemotherapy or hormonal therapy may be an option for palliative therapy (23, 24).

10.3. Metastasis and Advanced stages

Hormonal therapy may be a therapeutic option in endometrioid endometrial cancer. The response rate of initials therapy with progestagen is about ~25%, while tamoxifen is only ~10%. Predictors of therapeutic response are low histological degrees, longer relapse onset, location and degree of involvement outside the pelvic region, and hormone receptor positivity, so hormone receptor status needs to be determined before hormonal therapy. Hormonal therapy options are progestational agents (megestrol acetate 4x160 mg of medroxyprogesterone acetate 4x200 mg). Hormonal therapy is recommended as an alternative therapy in patients with G1-2 tumors, hormone receptor-positive, and tumors that do not develop rapidly (23).

10.4. Chemotherapy

The most active drugs in cases of endometrial cancer are doxorubicin, platinum agents, and paclitaxel. The combination of doxorubicin + cisplatin (AP) was shown to show better response and progression-free *survival* rates, but no overall survival improvements were obtained compared to doxorubicin in stages III and IV. Doxorubicin, Cisplatin, and Paclitaxel (TAP) showed improvements in response rates, progression-free survival, and overall survival compared to AP but had poor tolerability. No significant survival differences were found between Carboplatin-Paclitaxel (CT) and TAP. The toxicity profile is better on the CT regimen, making it a standard chemotherapy regimen in advanced stage and adjuvant therapy. Drugs that have been evaluated are paclitaxel, liposomal doxorubicin, ifosfamide, oxaliplatin, and ixabepilone. Carboplatin and paclitaxel are standard chemotherapy options in the advanced or metastatic endometrial cancer (23).

10.5. Advanced Monitoring

Most cases of endometrial cancer relapse within 3 years after initial therapy. The pelvic cavity is the site of the most frequent recurrence, mostly in the vagina and a third of cases have relapses outside the pelvic cavity. Most endometrial cancers have a low risk of recurrence, and >50% of recurrence cases are detected through the examination. Endometrial relapse cancer has a poor prognosis except for local relapse. Generally, a physical examination includes a pelvic cavity inspection. Cytology examinations are not proven to be involved in follow-up monitoring. CA-125 levels are not used routinely but can benefit at an advanced stage, serous type, or CA-125 levels that increase when diagnosed. A routine thoracic x-ray is not recommended. Ultrasound and PELVIC CT scans are thought to be involved in the evaluation of patients with symptoms, advanced stages, or patients who clinically have signs of recurrence (23).

11. LN Metastases in Endometrial Cancer

Tumor cells that successfully develop at metastatic sites will form a unique subpopulation of cells, called Metastasis-Initiating Cells (MIC). MIC passes through the metastatic cascade and obtains phenotypes favorable to the development of that cell population through genetic mutations. Tumor metastasis processes include cell migration, local invasion, cell entry into the systemic circulation, arrest at secondary locations, extravasation, and colonization. An important ability in the metastasis process in cellular plasticity. MIC has the same ability as cells in its primary tumor (*tumor-initiating cells*) that can undergo bidirectional transitions into epithelial and mesenchymal cells, avoid apoptosis processes, undergo several dormant cycles, avoid the response of the host immune system, change the metabolic activity of cells to adapt to various oxidative stresses, and form/destroy stromal niches. Metastasis away from a primary tumor generally occurs through hematogenic, lymphatic, and trans-cellomic pathways. In the case of gynecological tumors, tumor

spread can also occur locally, either through destructive invasion of surrounding tissue, intraepithelial pathways, or exfoliation. This process is called a local extension. In the spread of intraepithelial pathways and/or exfoliation, tumor cells may spread early in the course of the disease before primary tumor progression has been completed field (25, 26).

Lymphatic metastasis is one of the most important prognostic factors of endometrial cancer. 5-year progression-free survival of early-stage endometrial cancer without LN metastases is 90%, to 75% in pelvis LN metastases, and up to 38% in para-aortic LN metastases. Of the total incidence, 18% of cases showed metastasis in the pelvis LN, 14.8% of the para-aortic LN, and 3.1% of the para-aortic LN were isolated. Lymphadenectomy has not been done routinely in all cases of endometrial cancer due to the risk of complications, especially in old age. In cases with a high tendency to lymphatic metastasize, lymphadenectomy may be performed with other therapies. Conversely, in the case of low lymphatic metastatic tendency, lymphadenectomy as much as possible is not performed. For this reason, a predictor is needed for the stratification of lymphatic metastasis risk in cases of endometrial cancer. What can be used is the degree of the tumor, histopathology, tumor type, and myometrium invasion. Clinical stage I endometrial cancer with 1st degree has a 3% chance of lymphatic spread for the pelvis LN and 2% for the para-aortic LN. Meanwhile, at the clinical stage equal to 3rd degree, the probability of lymphatic spread increased to 18% for the pelvis LN and 11% for the para-aortic LN. It can be concluded that at the same clinical stage, an increase of 1-3 degrees will increase the risk of LN metastasis by up to 6 times. In the 1st-degree tumor group without myometrial invasion, as well as 2nd-degree tumors with superficial myometrial invasion and size <3 cm, lymphadenectomy is unnecessary because the risk is very low. The risk increases by 20% when the tumor is >5 cm in size (27).

Myometrial invasion >50% is an important independent risk factor for determining para-aortic LN metastasis (OR 14.37; sensitivity = 93.3%) and LN pelvis (OR 5.39; sensitivity 84.6%) (28). The findings supported a study in Sweden that stated that myometrial invasion $\geq$50%, non-endometrioid histology, and FIGO degree 3 endometrial cancer are strong independent risk factors for lymphatic metastases in endometrial cancer. Evaluation of myometrial invasion is rarely done because it is difficult to do. Recent studies have shown that evaluation of myometrial invasion with vaginal ultrasound with trained and experienced operators provides examination results with quality, sensitivity, and specificity similar to MRI (27).

Recent Meta-analysis shows that PET/CT delivers the most promising results with 72% sensitivity, 94% specificity, and the highest PPV. However, about 30% of cases of lymphatic metastases still go undetected due to sensitivity limitations. Intraoperative frozen cutting assessment is practical and reliable for determining tumor degree and myometrial invasion depth with an accuracy rate of 89% for tumor degrees and 85% for myometrium invasion depth. The system scores in France to determine the prognosis of lymphatic metastasis in endometrial cancer using several factors: age ($\geq$ 60 years), LVSI, tumor size, depth of myometrial invasion, tumor type, and degree based on histopathology. Assessment with this scoring system still has a high false-positive result. Preoperative SERUM LEVELS of CA-125 have been proposed as one of the predictor factors for looking at the lymphatic metastatic prognosis and endometrial cancer survival. However, the threshold value is still not standardized. A study showed that a ca-125 limit value of 16 IU/ml has a sensitivity of 71% with a PPV of 35%. Because the sensitivity and PPV of this CA-125 level examination are still low, CA-125 cannot be used as the only predictor factor against lymphatic metastases in the endometrial cancer (27).

Table 2. The study of factors that increase the risk of endometrial cancer lymphatic metastasis

Author (Years)	Title	Study Design	Samples	Results
Karalok, *et al* (2017)	*Lymph node metastasis in patients with endometrioid endometrial cancer*	*Retrospective cohort*	*368*	*The risk of lymph node involvement was 30%, even in patients with the highest-risk uterine factors, that is those who had tumors of greater than 2 cm (p=0.005), deep myometrial invasion (p<0.0001), and grade 3 disease (p=0.131), indicating that 70% of these patients underwent unnecessary lymphatic dissection.*
Muallem, *et al* (2016)	*Risk factors of lymph nodes metastases by endometrial cancer: a retrospective once-center study)*	*Retrospective cohort*	179	*The only significant predictors of pelvic and para-aortic lymph node metastases were tumor grade and deep myometrial invasion. G3, myometrial infiltration >50%, and type II endometrial cancer all have a negative correlation with poor progression-free survival (PFS) and overall survival (OS). Tumor size >2 cm is associated with a shorter PFS but not with a shorter OS..*
Stålberg, *et al* (2017)	*Risk factors for lymph node metastases in women with endometrial cancer: a population-based, nation-wide register study – on behalf of the Swedish gynecological cancer group (SweGCG)*	*Retrospective cohort*	1165	*Patients with tumors with MI >50% (RR=4.1; 95 percent CI 3.0-5.6), non-endometrioid histology compared to endometrioid histology (RR 1.8; CI 1.4-2.4), and FIGO grade 3 compared to grade 1-2 tumors had a higher risk of LNM (RR 1.5; CI 1.1-2.0). Because there was no statistically significant link between DNA ploidy status and LNM, DNA ploidy should not be considered when deciding whether or not to remove nodes prior to surgery.*

Conclusion

Endometrial cancer is the most common uterine cancer, with type 1 being the most common. Overuse of estrogen, tamoxifen, nullipara and obesity are the main risk factors for endometrial cancer. Endometrial biopsy is a common and reliable method of diagnosing endometrial cancer. The majority of instances of endometrial cancer relapse within three years of starting treatment. FIGO stage, histological subtype, tumor degree, myometrial invasion, lymphovascular space

invasion, and age are all prognostic variables. Patients can have surgery or non-surgical treatment based on clinical judgments and biopsies in general.

Conflicts of Interest

No declare

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