Review Article

iMedPub Journals
www.imedpub.com

Annals of Clinical and Laboratory Research
ISSN 2386-5180

2018
Vol.6 No.1:231

DOI: 10.21767/2386-5180.1000231

The Pathways in Endometrial Carcinogenesis and an Overview of its Histology, Grade and Stage

Qin Zhou1, Soobhug Rishikesh Singh[1*], Soobhug Shalini Devi Tina[2], Jing Wena[1], Zhou Yiying[1] and Mac Sandrie Mariella[3]

[1]Department of Obstetrics and Gynecology, The First Affiliated Hospital of Chongqing Medical University, Chongqing, P.R China

[2]Department of Obstetrics and Gynecology, JN Hospital, Mauritius

[3]Department of General Surgery, The First Affiliated Hospital of Chongqing Medical University, Chongqing, P.R China

[*]**Corresponding author:** Soobhug Rishikesh Singh, Department of Obstetrics and Gynecology, The First Affiliated Hospital of Chongqing Medical University, Chongqing, P.R China., Tel: +86 13101394370; E-mail: soobhugrishikesh@ymail.com

Received: March 27, 2018; **Accepted:** April 01, 2018; **Published:** April 07, 2018

Citation: Zhou Q, Singh SR, Tina SSD, Wena J, Yiying Z, et al. (2018) The Pathways in Endometrial Carcinogenesis and an Overview of its Histology, Grade and Stage. Ann Clin Lab Res Vol.6: No.1: 231.

Abstract

Endometrial carcinoma is the most common female genital tract cancer in the developed countries. It is classified as Type I and II endometrial cancer. Understanding of the pathogenesis of each type plays a pivotal role in identifying their precursors. The histological subtype, grade and stage guide the treatment strategies and portend the prognosis in endometrial carcinoma. Hysterectomy is regarded curative in early stage disease. By contrast, uterine serous carcinoma is the most aggressive histologic subtype associated with a low 5-year overall survival rate. Substantial rise in uterine corpus carcinoma parallels with the increase in obesity and diabetes. As they share similar etiologies, measures can be adopted to tackle the modifiable risk factors. No screening consensus is available for low or average risk populations.

Keywords: Endometrial carcinoma; Histology; Grade; Stage

Literature Review

Endometrial cancer is the leading and the second most fatal gynecologic malignancy in the United States. The American Cancer Society, relying on numerical models, has predicted about 63,230 new diagnoses and 11,350 deaths in 2018. From available data during 2011 through 2015, the death rate of uterine corpus cancer has been steadily rising by approximately 2% annually [1]. It is expected that the endometrial cancer incidence will overstep colorectal cancer to become the third most common malignancy in women in the United States by 2030 [2].

The mean age of women with endometrial carcinoma is 63 years and, above 90% are more than 50 years [3]. Most of these patients are diagnosed early, usually at Stage I-II, which carries a favorable outcome with a high 5-year overall survival rate of 96% [4]. In 1983, on the basis of clinical, endocrine-metabolic and morphologic features, Bokhman proposed a dualistic model to classify endometrial carcinoma. As a result, Type I and II endometrial cancers have been distinguished [5]. Type I emerges from high estrogen state, and Type II is independent of the latter [6].

Type I carcinoma and its pathogenesis

Type I endometrial carcinomas are predominantly endometrioid adenocarcinoma and amount to 80-90% of endometrial tumors. They are low-grade tumors that are diagnosed in Stage 1 and carry a good prognosis. However, the outcome is worse for patients with high grade or advanced disease [7,8]. Type I tumors develop from an estrogen-rich milieu. Obesity, diabetes mellitus, nulliparity, early menarche, late menopause, old age, unopposed estrogen exposure, tamoxifen therapy, polycystic ovarian syndrome, and family history of breast cancer or Lynch disease are strong risk factors that create an estrogenic background [9-11].

Obesity is an alarming health concern in the developed countries. About 40% of postmenopausal women are either overweight or obese. It is a well-established risk factor for endometrial tumorigenesis. Excess adiposity promotes peripheral aromatization of androgen to form a surplus of estrogen [12]. Under normal conditions, estrogen stimulates endometrial proliferation while progesterone counteracts the effect of estrogen. Lack of progesterone relative to an increased estrogen level may rocket glandular epithelial proliferation in the endometrium. Excessive endometrial growth may promote mutations in the proto-oncogenes and tumor suppressor genes. As the apoptotic pathway is disturbed, these mutated cells persist, multiply and eventually form endometrial cancer [13]. Obesity can also help in the development of endometrial cancer through insulin resistance, hyperinsulinemia, excess circulating steroid hormones, and localized inflammation [14].

Diabetes is as important as obesity in the genesis of endometrial cancer. The metabolic alterations in diabetes mellitus start many years before clinical symptoms become apparent. The disease develops due to insulin resistance in the liver, skeletal muscle and adipocytes. In the hepatocytes, insulin resistance fails to inhibit glycogenolysis resulting in increased glucose output from the liver. At the same, glucose uptake and its metabolism by the skeletal muscles and adipocytes are impaired. Therefore, the net outcome of insulin resistance is systemic hyperglycemia. In turn, the beta cells of the pancreas try to overcome this state of excess blood glucose level by secreting additional insulin. The result is hyperinsulinemia, hyperglycemia but persisting peripheral insulin resistance [15]. In 2012 diabetes mellitus and obesity contributed to 38.4% of endometrial cancers globally [16].

In the endometrium, insulin can attach to insulin or endothelial growth factor receptors to enhance endometrial cell proliferation, prevent apoptosis, and promote expression of vascular endothelial growth factor and angiogenesis. Gradually this leads to the development of endometrial cancer. Insulin can also promote endometrial carcinogenesis by direct or indirect actions on endogenous estrogen production [17]. Usually 30-50% of circulating estrogens in plasma are bound to sex-hormone binding globulin [SHBG] and, thus rendered inactive. Hyperinsulinemia results in decreased production of SHBG from the liver. The consequence is an elevated level of free estrogen in the blood [18]. Increased blood insulin levels also stimulate androgens production and promote their peripheral conversion to produce estrogens. In addition, insulin stimulates expression of estrogen receptors in the endometrium and increases its sensitivity to estrogens. Ultimately this results in endometrial cancer [19]. In their study Pavelic et al. found that the expression of insulin-like growth factor (IGF-2) and its receptor (IGF-1R) were elevated in endometrial adenocarcinoma stages III and IV than in stages I and II, endometrial hyperplasia or normal endometrium [20]. In short, prior literatures have advocated that the risk of endometrial malignancy in patients suffering from diabetes is two-fold higher than in normal individuals [19].

Nulliparity is another risk factor in the development of endometrial cancer. Endometrial cancer risk is decreased by 20%-40% in parous women than in nulliparous ones [21]. As the number of full term pregnancies increases the risk of endometrial cancer decreases. Several hypotheses have been postulated to account for the beneficial effects of parity. High progesterone milieu during pregnancy may prevent estrogen induced endometrial proliferation and, contribute to the differentiation and apoptosis of the endometrial cells. Also childbirth or postpartum involution of the uterus may cause shedding of precancerous or cancerous cells from the endometrium. These protective effects occur during the reproductive years of parous women. Parity is thought to change the course of the endometrial cancer risk by altering risk factors such oral contraceptive use, age at menopause, obesity and hormone replacement therapy [22].

Most endometrial carcinoma cases are sporadic, but some women are genetically predisposed for the disease. Lynch syndrome and Cowden syndrome are associated with family history of endometrial cancer [23]. Lynch syndrome is a heterozygous, autosomal dominant disorder arising as a result of an inherited germline mutation in one of the DNA mismatch repair genes MLH1, MSH2, MSH6 or PMS2 [24]. These MMR proteins act as heterodimers which identify and repair DNA mispaired errors by removing and resynthesizing of nucleotides [25,26]. Patients with Lynch syndrome present with microsatellite instability (MSI) [27]. Mutations and MSI impair the cell cycle functioning, transcription, signaling transduction, immune surveillance and lead to further damage of the DNA repair pathways. Finally, the risk of tumorigenesis is increased [28]. Women suffering from Lynch syndrome are more vulnerable for endometrial cancer than colorectal cancer [29].

On a molecular level, Type 1 endometrial carcinoma develops from mutations in phosphatase and tensin (PTEN), K-ras, β-catenin, *PIK3CA*, and microsatellite instability [30]. PTEN homolog, located on chromosome 10, is a tumor suppressor gene. Deletion of PTEN leads initially to endometrial hyperplasia, while *PIK3CA* mutations play an active role for its transition to atypical endometrial hyperplasia and finally the development of low grade, endometrioid adenocarcinoma [31]. The molecular classification of endometrial carcinoma comprises four subgroups based on somatic mutation rates, frequency of copy number alterations, and microsatellite instability status [32]. These are DNA polymerase epsilon (POLE) ultramutated, microsatellite instability hypermutated, copy number low, and copy number high. The copy number high group is composed of most of serous and grade 3 endometrioid tumors [33].

Type II endometrial carcinoma and its pathogenesis

Type II tumors or non-endometrioid endometrial carcinoma make up the remaining 10-20% of cancer of the corpus uteri [34,35]. They consist of a heterogeneous, poorly differentiated group of tumors of high grade endometrioid, uterine serous and clear cell carcinomas, and uterine carcinosarcomas [36,37]. Non-endometrioid tumors are estrogen-independent in development and growth, and arise in an atrophic endometrium [38]. Despite accounting for only 10% of the endometrial cancer, Type II tumors behave aggressively and portends a dismal prognosis. They are frequently locally advanced and/or carry the propensity for extrauterine dissemination [37,39,40]. In these situations, survival is less than six months even if aggressive chemotherapy and radiation are performed [36].

The epidemiology of Type II cancers is poorly defined due to their low incidence. However, some studies have attempted to elucidate that these tumors are more likely to develop among older, normal weight, multiparous women and, of African American origin when compared with Type I endometrial carcinoma. Carcinogenesis of Type II tumors probably bypasses the estrogen pathway as normal-weighted and multiparous women are less exposed to estrogen than obese and nulliparous women [35]. On a molecular level, immunostaining

has shown that non-endometrioid tumors might develop as a result of mutations in TP53, ErbB2 and p16 proteins [36]. There is overexpression of mutated ErbB2 and p53 genes in black compared to white women [10].

Several reports have found that women suffering from breast cancer are predisposed to develop uterine serous carcinoma, carcinosarcomas and grade 3 endometrioid tumors. Radiation of adjacent organs, Li-Fraumeni and Lynch syndromes, and mutations in cancer predisposing genes may be the rationale [41]. In another study it has been suggested that BRCA mutations, which are a cause of breast cancer, may be frequently found among uterine serous carcinomas [10,42]. Although an inherited factor has been privileged for the development of endometrial cancer in women with family history of breast cancer, non-genetic cause may also account for its occurrence [43]. This relationship is observed in women, using tamoxifen, who develop uterine serous cancer and carcinosarcomas [41]. Tamoxifen exert anti-estrogenic effect on breast cancer whereas estrogenic activity on the endometrium [44]. Gradually it leads to the formation of benign endometrial polyps, which may undergo malignant transformation to yield serous carcinomas and carcinosarcomas. Tamoxifen can also produce DNA adducts and lead to tumorigenesis via non-hormonal effects [41]. **(Table 1).**

Table 1 Summary of differences between Type I and II endometrial cancer.

Parameters	Type I	Type II
Prototype	Endometrioid adenocarcinoma	Uterine serous carcinoma
Histological subtypes	Endometrioid adenocarcinoma Mucinous carcinoma	Uterine serous carcinoma Clear cell carcinoma Carcinosarcoma
Milieu	Estrogen dependent	Atrophic endometrium
Age at diagnosis	Perimenopause	Late post-menopause or senile
Racial distribution	Whites	Blacks African American
Clinical course	Non-aggressive	Aggressive
Tumor grade	Low	High
Common mutations	PTEN, K-ras, β-catenin, *PIK3CA*	TP53, ErbB2, p16, BRCA
Molecular subtypes	Microsatellite stable Microsatellite instable POLE	Copy number high
Prognosis	Favorable	Poor

Most women with endometrial carcinoma chiefly complain of abnormal uterine bleeding. Those above 50 years report postmenopausal bleeding, while younger ones present with intermenstrual bleeding, heavy menstrual bleeding or a change in bleeding pattern. Rarely, pelvic pain and vaginal discharge may be presenting symptoms [45]. Despite that most women with endometrial carcinoma are diagnosed at an early stage, they constitute a heterogeneous pool with regard to histological subtype, grade, and prognosis [33].

Transvaginal sonography is the initial imaging tool to evaluate presumed endometrial cancer [13]. An endometrial thickness greater than 4 mm warrants endometrial biopsy [46]. Preoperative endometrial sampling by office Pipelle or curettage remains the cornerstone in diagnosing endometrial carcinoma [47]. Nowadays, office-based blind biopsy techniques- Novak curette, suction samplers (Pipelle, Vabra) and brush- are increasingly being used instead of dilation and curettage [28]. These office procedures are anesthesia free. The diagnostic accuracy of office endometrial sampling is 85%-98% with regard to dilation and curettage [48]. Office hysteroscopy guided biopsy or hysteroscopic endometrial resection or dilation and curettage are performed when the initial specimen is scanty or, the histopathological report is inconclusive or shows hyperplastic changes [28]. From the preoperative biopsy tissue, the tumor type and grade can be determined [49].

Surgery is the mainstay in the management of endometrial cancer [37]. According to the FIGO 2009 classification, endometrial cancer is surgically staged [50]. Comprehensive surgical staging involves peritoneal washings, extrafascial hysterectomy, bilateral salpingo-oophorectomy, and pelvic and para-aortic lymphadenectomy [48]. Nowadays as peritoneal cytology report no longer affects the surgical staging, surgeons may opt to avoid its collection [51]. Formerly, surgical staging was performed via laparotomy. At present minimally invasive techniques are preferred. Even if laparoscopic approaches are associated with longer operative time, they convey considerable benefits [37]. These advantages are less hemorrhage, lower blood transfusion rate, shorter hospital stay, quicker resumption to daily activities, lesser need for analgesics, higher yield of lymph nodes [52].

The introduction of robotic-assisted surgical staging in 2005 has expanded the armamentarium in the treatment of endometrial cancer [53]. Morbid obesity is a relative contraindication to laparoscopy as cardiopulmonary compromise and poor ventilation resulting from high intra-abdominal pressure may hinder a steep Trendelenburg position. In the robotic approach this obstacle of positioning is overcome by undocking the robotic arms which usually prolongs the length of surgery. Nevertheless, the robotic platform improves the laparoscopic skills of the surgeon and permits challenging operations in the obese and morbidly obese patients [54].

In 2005, the American College of Obstetrics and Gynecology (ACOG) and the International Federation of Obstetrics and Gynecology (FIGO) recommended a comprehensive surgical staging in all patients with endometrial carcinoma regardless of the risk factors [55]. This was decided following results of two retrospective studies that showed improved survival in patients with Stage I, grade 3 or more advanced tumors when complete surgical staging was performed. However, there are no randomized trials which support these data. As a result, the

benefits of systematic lymphadenectomy have been questioned in early-stage endometrial cancer [56]. The latter is defined as tumor confined to the body of uterus with the absence of lymph node metastasis [57]. Further studies have shown that hysterectomy with bilateral salpingo-oophorectomy and lymphadenectomy did not improve survival rate in the low risk group early stage disease [58].

The medical complications that result from lymphadenectomy are ileum obstruction or ileus, and deep venous thrombosis [59]. On the other hand, injuries to the blood vasculatures, lymphocyst formation and lower limb lymphedema are the surgical complications [56,59]. In cases of the aggressive, serous or clear cell carcinomas, hysterectomy, bilateral salpingo-oophorectomy, lymphadenectomy, as well as, omentectomy are mandatory as these tumors have propensity for extrauterine metastasis [48,60]. Endometrial cancer displays several patterns of spread, namely, by direct extension, transtubal dissemination, lymphatic and hematogenous metastases [61]. Endometrial carcinoma extends beyond the uterus, first by spreading into the myometrium then infiltrating the cervical stroma. Lymphatic metastasis initially occurs to the pelvic lymph nodes, including external and common iliac lymph nodes, and then to the pelvic lymph nodes. Hematogenous spread is the channel for distant metastases [45]. Histological subtype, tumor grade and clinical stage in endometrial carcinoma are important prognostic factors that drive the treatment regimen [62]. However, there is a discrepancy in histologic subtype and grade between the pre- and postoperative specimens [63].

Histological subtype

Endometrial carcinoma is a heterogeneous tumor that comprises of a vast array of histological subtypes. These are illustrated in **Table 2** [28].

Table 2 Subtypes in endometrial carcinoma.

WHO 2014 classification of endometrial carcinomas	
Endometrioid carcinoma	Neuroendocrine tumors
Squamous differentiation, Villoglandular, Secretory	Low-grade neuroendocrine tumor
	Carcinoid tumor
	High-grade neuroendocrine tumor
Mucinous carcinoma	Small cell neuroendocrine tumor
Serous carcinoma	Large cell neuroendocrine tumor
Clear cell carcinoma	Undifferentiated tumor
Mixed cell adenocarcinoma	Dedifferentiated tumor

In 2014 the term endometrial adenocarcinoma has been modified to endometrial carcinoma but are still interchangeably used. The term endometrial specifies location in the uterine cavity, while, endometrioid refers to the histologic appearance of the tumor which is similar to the normal proliferative endometrial glands [44]. Endometrioid carcinoma is characterized by proliferation of oval or round endometrial glands with a smooth margin that are lined by stratified or pseudostratified low columnar epithelial cells. Their cytoplasm may be basophilic, amphophilic, or lightly eosinophilic. Also, their nuclear polarity is unchanged. Moreover, the glandular lumen may contain some solid growth whose cells resemble those lining the lumen [64]. Endometrioid carcinoma containing malignant cells with squamous differentiation is the most common variant. The squamous element should not be regarded as part of the solid component that upgrades endometrial carcinoma. The criteria for squamous differentiation are:

1) Keratinization shown by staining,

2) Intercellular bridges and/or,

Three or more of the followings:

- Sheet-like growth without gland formation or palisading
- Well-defined cell borders
- Eosinophilic and thick or glassy cytoplasm
- Reduced cytoplasmic to nuclear ratio when compared with other places within the same tumor [65].

Villoglandular endometrioid carcinomas exhibit long, slender, smooth finger-like papillary growths and a fibro-vascular core. They are lined by columnar epithelial cells with minimal or absent cytological atypia. The nuclei are aligned perpendicular to the basement membrane [66]. Secretory endometrioid adenocarcinoma is lined by epithelium that bear sub-nuclear, glycogen vacuoles that resemble the early secretory endometrium [65]. Like endometrioid carcinomas, mucinous adenocarcinoma is a well-differentiated tumor of low grade. The diagnosis of mucinous tumor is made when the tumor cells contain greater than 50% intracytoplasmic mucin [67].

Together uterine serous and clear cell carcinoma represent 10-15% of all endometrial carcinomas. Despite being of low prevalence, they are associated with a mortality rate of 30%-50% due to their high grade [68]. Histologically, uterine serous carcinoma (USC) is characterized by gland-like or solid structure with or without papillae. The cells show high grade tumors with intense mitotic activity, expressing p53 and *PIK3CA* gene mutations [69]. They are also pleomorphic and often contain psammoma bodies. [70]. Uterine serous carcinoma is an aggressive pathology. It invades the myometrium, lymphovascular space and spread to the peritoneal cavity and distally [71]. Cutaneous metastasis has even been reported which presents as an erythrematous rash on the lower abdomen [72]. Clear cell carcinoma is ranked as the second most common Type II tumor. Nevertheless, it is a rare entity accounting for 1%-6% of uterine corpus carcinomas. It derives its name from the large amount glycogen that is present in its cytoplasm that is washed out during tissue preparation leaving a clear space. Clear cell carcinoma also contains hobnail cells. It is a poorly differentiated tumor which is relatively resistant to chemotherapeutic agents and radiation therapy [73-75].

According to the WHO 2014 classification, a mixed cell carcinoma is defined as an admixture of at least two histotypes

of endometrial carcinoma. The second component should be of Type II origin and, make up at least 5% of the cell type [76]. Also in 2014 WHO stratified neuroendocrine tumors of the endometrium, cervix and vulva into low-grade neuroendocrine tumor and high-grade neuroendocrine carcinoma. High grade tumors affect both the endometrium and cervix, but, they predominate in the cervical rather than the endometrial tissue [77]. The striking features of the neuroendocrine tumor of the endometrium are the signs of neuroendocrine differentiation, marked propensity for distant spread and poor outcome. It is divided into small- and large-cell type neuroendocrine carcinomas.

Macroscopically, small cell neuroendocrine tumors appear as a bulky mass which can invade the myometrium leading to necrosis. Histologically, these tumors demonstrate sheets, cords, nests of heterogeneous small or intermediate sized cells. The latter have scanty or poorly defined cytoplasm, hyperchromatic nuclei, and show high mitotic activity. Interestingly, small cell neuroendocrine tumors express thyroid transcription factor-1 (TTF-1). Patients present with postmenopausal bleeding, menorrhagia, and low or persistent abdominal pain. The aggressive behavior of these tumors result in early metastases to the vagina, fallopian tubes, ovaries, paraaortic lymph nodes, peritoneal cavity, lungs, liver, brain and bones. The prognosis is poor [78]. Like small cell tumors, large cell neuroendocrine tumors also have an increased affinity for the cervix rather than the body of the uterus. Microscopically, they are characterized by organelle nesting, palisading, rosettes, trabeculae, high mitotic activity, necrosis, low nuclear to cytoplasmic ratio and vesicular chromatin. They are large cells with prominent nuclei. During immunohistochemical analysis, they stain positively for Neuron Specific Enolase (NSE), chromogranin A (CgA) and synaptophysin [79]. These tumors are high grade, fast growing and portend an unfavorable outcome [80].

The preoperative endometrial sampling is often discordant from the final specimen. One reason that is advocated is heterogeneity of the tumor cell mass [63]. Few endometrial carcinomas share morphologic features of both endometrioid and serous carcinomas [81]. Some tumors are referred as being ambiguous but stratified in the WHO classification. They show overlapping and confusing histological and immunohistochemical features [82]. Furthermore, only the superficial part of the tumor protruding into the endometrial cavity is scrapped during curettage. However, the tumor mass lying deeper has different histologic and molecular characteristics from the biopsy sample [63]. Another reason accounting for the discrepancy is amount of tissue biopsied. An increasing number of endometrial samplings is being performed by hysteroscopy such that the volume of tissue at biopsy is scanty. It is believed that more tissue is obtained at curettage than at hysteroscopy [83].

Furthermore, there are variations in the quality of the biopsy specimens. The tissues are fragmented or are mixed with hemorrhagic material at biopsy. Fragmentation or blurring of the tissue with artifacts lead to erroneous diagnoses. Differentiation of atypical hyperplasia and endometrial carcinoma is especially challenging [84]. There are some situations where endometrial carcinoma was diagnosed on the basis of biopsy sample but there is absence of tumor in the surgical specimen. This can happen if the patients received neoadjuvant therapy, under dilation and curettage or simple the tumor size is too small. To overcome such dilemma the whole endometrium should be scrutinized at the histopathological examination [28].

Grade

The first International Federation of Gynecology and Obstetrics (FIGO) grading system for endometrial cancer was introduced in 1973 and was based essentially on architecture of the tumor. It was later modified in 1988 with the addition of nuclear atypia [85]. Similar to the histological subtype, grade is also determined from the preoperative biopsy specimen [49]. Endometrioid and mucinous carcinomas are graded according to the amount of non-squamous solid growth and nuclear characteristics in the tumor cell. Uterine serous, clear cell, and undifferentiated carcinomas are all regarded as high-grade tumors [86]. **Table 3** below shows the characteristics of architecture grading [28,87].

Table 3 Characteristics of histological grade.

Grade	Differentiation	Definition
1	Well	≤ 5% non-squamous solid tumor growth
2	Moderate	6%-50% non-squamous solid tumor growth
3	Poor	>50% non-squamous solid tumor growth

If there is significant nuclear atypia, equivalent to nuclear grade 3, the FIGO grade is increased by one grade. For example in the presence of grade 3 nuclear atypia, grade 1 is increased to grade 2, and grade 2 to grade 3.

The nuclear grade is defined by nuclear size and shape, chromatin distribution, and the size of the nucleoli [87,88]. These are described in **Table 4.**

Table 4 Characteristics of nuclear grading.

Grade	Features
1	Uniform round nuclei, evenly distributed chromatin and indistinct nucleoli
2	Irregular oval nuclei, chromatin clumping and moderate size nucleoli
3	Large pleomorphic nuclei, coarse clumped chromatin and prominent nucleoli

Several prior studies have reported variations between the pre- and postoperative tumor grade. Most of the specimen will be upgraded to FIGO grade 2 [89]. This is due to poor reproducibility between grade 1 and 2 tumors, with k values of 0.49-0.65. Firstly, it is hard for the pathologists to distinguish if the solid growth is squamous or non-squamous, particularly in

cases with immature squamous metaplasia. Next, it is very challenging to precisely delineate the limit of non-squamous solid growth of ≤ 5% or >5% in architectural grading that is, Grade 1 or 2 [90]. Moreover, the interpretation of the degree of nuclear atypia is very subjective. The reproducibility of nuclear grading is relatively poor. A k value of 0.22 has been reported [85,90]. Matsuo et al explained that the inaccuracy between the biopsy sample and hysterectomy specimen is the result of sample error. The surgeon fails to biopsy or curettage an underlying high grade tumor [83].

Stage

The International Federation of Obstetrics and Gynecology was first set up in 1958 to stage gynecologic cancers [91]. Endometrial cancer was clinically staged until 1988 when the surgical staging system was adopted. Surgical staging differs from clinical staging in that it is based on the surgico-pathologic findings of the hysterectomy specimen [92]. FIGO staging for endometrial cancer has been lastly refined in 2009 and three major modifications had been made to the 1988 staging system [93]. Firstly, 1988 stages IA and IB were merged to form 2009 stage IA, and similarly Stage IC was named as Stage IB. Secondly, 1988 stage IIA is included in 2009 stage IA or IB depending on the depth of myometrial involvement. Hence the 2009 stage II only represents tumor which has invaded the cervical stroma. Thirdly, Stage C has been divided into stage IIIC1 (presence of positive pelvic).

Discussion

Endometrial carcinoma is distinct from other gynecologic malignancies by its double staging feature: clinical and surgical staging [94]. Clinical staging is completed on the basis of Magnetic Resonance Imaging (MRI) findings. MRI delineates the depth of myometrial involvement, extent of cervical stromal invasion and metastases to the lymph nodes and organs [49]. Several associations have highlighted the importance of MRI in the assessment of endometrial cancer. According to the American College of Radiology MRI allows precise evaluation of the disease. The National Comprehensive Cancer Network recommends MRI when involvement of cervical stroma is suspected, and in Type II tumors. The European Society of Urogenital Radiology advises MRI in intermediate and high risk disease, suspected advanced tumors and, prior to lymphadenectomy [95]. Based on clinical stage, treatment is tailored to avoid extensive surgery in low-risk disease [96].

There are several instances where clinical staging is pivotal in the management of endometrial carcinoma. An increasing number of young women, below the age of 40 years, who are being diagnosed with endometrial cancer wish to preserve their fertility [97]. High dose progestin is recommended in these women with clinical stage IA and grade 1 disease [98]. They are followed by repeated D&C, and hysterectomy is indicated in the event of failure to conservative treatment [99]. Furthermore, endometrial carcinoma is generally linked to diabetes mellitus, hypertension, dyslipidemia, obesity or metabolic syndrome. These medical co-morbidities may contraindicate primary surgery. In such situations treatment strategies solely depend on clinical staging [4]. Moreover, uterine serous carcinoma has a low overall survival rate. Based on findings of clinical staging, neoadjuvant chemotherapy may be administered prior to debulking surgery. Not only it shrinks the tumor burden, but it also decreases the extent of aggressive surgery, operating time, hospital stay and improves the patients' quality of life by reducing postoperative morbidities [100].

However, there are several limitations that lead to a discrepancy between clinical and surgical staging. Lymphovascular space involvement is strongly linked with lymph node metastases and a higher recurrence rate. Preoperative imaging studies fail to recognize lymphovascular space invasion and the diagnosis is only made at histopathological examination of the hysterectomy specimen [49]. Furthermore, a large tumor usually exhibits an increased tumor index. Such large tumor is associated with expansion of the uterine cavity and thinning of the myometrium. As a result, the percentage of myometrial invasion is overestimated [57]. Peritumoral inflammation may also lead to overestimation of the depth of myometrial invasion [49]. On the contrary leiomyomas and adenomyosis decrease the accuracy MRI [101].

The tumor volume or size is directly related to its stage. The smaller the tumor, the lower is the stage. In relation with this fact, MRI- invisible and –visible tumors were compared. If MRI fails to delineate any residual tumor in women following biopsy for endometrial cancer, this may indicate that these patients have a reduced tumor burden compared to MRI-visible tumors [102]. As MRI is performed after biopsy this may be a reason for under-staging of endometrial carcinoma when compared to the hysterectomy specimen. Besides MRI, uterine serous carcinoma also poses a challenge to practitioners. Based on preoperative histology it is difficult to forecast extrauterine dissemination for serous carcinomas. After completion of surgery, 70% of uterine serous tumors are upstaged [103].

Conclusion

Hitherto screening for endometrial cancer is not recommended in asymptomatic, low or medium risk population. Only women with Lynch syndrome who are above 35 years old are screened annually by endometrial biopsy and pelvic sonography. As a strong correlation has already been established between obesity and diabetes, and endometrial tumorigenesis, policy makers should implement structural programs at modifying the risk factors of the non-communicable diseases (NCD). Healthy diet and an active lifestyle can help to halt the progression of obesity and diabetes globally. A paradigm shift is required from the government whereby more emphasis is laid upon disease prevention by enhancing awareness of non-communicable diseases and tackling modifiable risk factors. At the surgical level, sentinel lymph node biopsy holds promises where truly metastatic lymph nodes might be recognized thereby reducing

unnecessary lymphadenectomy. Furthermore, molecular biology can shed insight on the genetic where targeted therapy can be used.

Acknowledgement

We would like to be thankful to all those who have contributed in this manuscript. We are also very grateful for the support provided in this work by The First Affiliated Hospital of Chongqing Medical University (Grant No.2015 qdlx_12), the study of the relationship between miR-99a and insulin-induced endometrial carcinoma, Dr. Qin Zhou.

Conflict of Interest

There is no conflict of interest to declare. This study was not funded by any agency.

References

1. Siegel RL, Miller KD, Jemal A (2018) Cancer statistics, 2018. CA Cancer J Clin. 68: 7-30.
2. Prescott J, Setiawan VW, Wentzensen N, Schumacher F, Yu H, et al. (2015) Body mass index genetic risk score and endometrial cancer risk. PLoS One. 10: e0143256.
3. Colombo N, Preti E, Landoni F, Carinelli S, Colombo A, et al. (2011) Endometrial cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Onco 22: vi35-9.
4. Tangjitgamol S, Khunnarong J, Srijaipracharoen S (2014) Medical morbidities in endometrial cancer patients. Int J Gynecological Cancer : official j Int Gynecological Cancer Society 24: 1623-1627.
5. Bokhman JV (1983) Two pathogenetic types of endometrial carcinoma. Gynecol Oncol 15: 10-17.
6. Sherman ME (2000) Theories of endometrial carcinogenesis: a multidisciplinary approach. Modern pathology : An official journal of the United States and Canadian Academy of Pathology, Inc. 13: 295-308.
7. Dedes KJ, Wetterskog D, Ashworth A, Kaye SB, Reis-Filho JS (2011) Emerging therapeutic targets in endometrial cancer. Nat Rev Clinical Oncol 8: 261-271.
8. Dowdy SC (2014) Improving oncologic outcomes for women with endometrial cancer: realigning our sights. Gynecol Oncol 133: 370-374.
9. Abu-Zaid A, Alsabban M, Abuzaid M, Alomar O, Al-Badawi IA, (2017) ABO blood group and endometrial carcinoma: A preliminary single-center Experience from Saudi Arabia. Cureus. 9: e1959.
10. Yang HP, Wentzensen N, Trabert B, Gierach GL, Felix AS, et al. (2013) Endometrial cancer risk factors by 2 main histologic subtypes: the NIH-AARP Diet and Health Study. Am J Epidemiol 177: 142-151.
11. Helder-Woolderink J, de Bock G, Hollema H, van Oven M, Mourits M (2017) Pain evaluation during gynaecological surveillance in women with Lynch syndrome. Familial Cancer 16: 205-210.
12. Cymbaluk-Ploska A, Chudecka-Glaz A, Pius-Sadowska E, Sompolska-Rzechula A, Machalinski B, et al. (2018) Circulating serum level of Visfatin in patients with endometrial cancer. BioMed Res Int. 18: 179.
13. Felix AS, Weissfeld JL, Pfeiffer RM, Modugno F, Black A, et al. (2014) Endometrial thickness and risk of breast and endometrial carcinomas in the prostate, lung, colorectal and ovarian cancer screening trial. Int J Cancer 134: 954-960.
14. Arem H, Park Y, Pelser C, Ballard-Barbash R, Irwin ML, et al. (2013) Prediagnosis body mass index, physical activity, and mortality in endometrial cancer patients. J National Cancer Inst. 105: 342-349.
15. Martin SD, McGee SL (2018) Metabolic reprogramming in type 2 diabetes and the development of breast cancer. J Endocrinol 237: R35-R46.
16. Pearson-Stuttard J, Zhou B, Kontis V, Bentham J, Gunter MJ, et al. (2018) Worldwide burden of cancer attributable to diabetes and high body-mass index: a comparative risk assessment. Lancet Diabetes Endocrinol. 6: 95-104.
17. Bray GA (2002) The underlying basis for obesity: relationship to cancer. J Nutrition 132: 3451s-3455s.
18. Akhmedkhanov A, Zeleniuch-Jacquotte A, Toniolo P (2001) Role of exogenous and endogenous hormones in endometrial cancer: review of the evidence and research perspectives. Ann N Y Acad Sci 943: 296-315.
19. Lai Y, Sun C (2018) Association of abnormal glucose metabolism and insulin resistance in patients with atypical and typical endometrial cancer. Oncol Let 15: 2173-2178.
20. Pavelic J, Radakovic B, Pavelic K (2007) Insulin-like growth factor 2 and its receptors (IGF 1R and IGF 2R/mannose 6-phosphate) in endometrial adenocarcinoma. Gynecol Oncol 105:727-735.
21. Wan-Nor-Asyikeen WA, Siti-Azrin AH, Jalil NA, Othman NH, Zain AA (2016) Endometrial cancer in hospital Universiti Sains Malaysia. Asian Pacific Journal of Cancer Prevention : APJCP. 17: 2867-2870.
22. Schonfeld SJ, Hartge P, Pfeiffer RM, Freedman DM, Greenlee RT, et al. (2013) An aggregated analysis of hormonal factors and endometrial cancer risk by parity. Cancer 119: 1393-401.
23. Masuda K, Hirasawa A, Irie-Kunitomi H, Akahane T, Ueki A, et al. (2017) Clinical utility of a self-administered questionnaire for assessment of hereditary gynecologic cancer. Japanese J Clin Oncol 47: 401-406.
24. Zeimet AG, Mori H, Petru E, Polterauer S, Reinthaller A, et al. (2017) AGO Austria recommendation on screening and diagnosis of Lynch syndrome (LS). Arch Gynecol and Obstetrics. 296: 123-127.
25. Von Salome J, Boonstra PS, Karimi M, Silander G, Stenmark-Askmalm M, et al. (2017) Genetic anticipation in Swedish Lynch syndrome families. PLoS genetics. 13: e1007012.
26. Pecorino B, Rubino C, Guardala VF, Galia A, Scollo P (2017) Genetic screening in young women diagnosed with endometrial cancer. J Gynecol Oncol. 28:e4.
27. Bouguenouch L, Samri I, Belhassan K, Sayel H, Abbassi M, et al. (2016) Lynch syndrome: case report and review of the literature. Pan Afr Med J. 24: 142.
28. Bartosch C, Pires M, Jeronimo C, Lopes JM (2017) The role of pathology in the management of patients with endometrial carcinoma. Future oncology (London, England).13 : 1003-1020.
29. Bruegl AS, Ring KL, Daniels M, Fellman BM, Urbauer DL, et al. (2017) Clinical challenges associated with universal Screening for

Lynch Syndrome-associated endometrial cancer. Cancer prevention research (Philadelphia, Pa). 10: 108-115.

30. Park JY, Nam JH, Kim YT, Kim YM, Kim JH, et al. (2013) Poor prognosis of uterine serous carcinoma compared with grade 3 endometrioid carcinoma in early stage patients. Virchows Archiv : Int J Pathol 2462: 289-296.

31. Yasuda M (2014) Immunohistochemical characterization of endometrial carcinomas: endometrioid, serous and clear cell adenocarcinomas in association with genetic analysis. Obst Gynaecol Res 40: 2167-2176.

32. Le Gallo M, Bell DW (2014) The emerging genomic landscape of endometrial cancer. Clinical Chem 60: 98-110.

33. Barlin JN, Soslow RA, Lutz M, Zhou QC, St Clair CM, et al. (2013) Redefining stage I endometrial cancer: incorporating histology, a binary grading system, myometrial invasion, and lymph node assessment. Int J Gynecol Cancer : Official J Int Gynecolo Cancer Soc. 23: 1620-1628.

34. Becker JH, Ezendam NP, Boll D, van der Aa M, Pijnenborg JM (2015) Effects of surgical volumes on the survival of endometrial carcinoma. Gynecol Oncol. 139: 306-311.

35. Felix AS, Weissfeld JL, Stone RA, Bowser R, Chivukula M, et al. (2010) Factors associated with Type I and Type II endometrial cancer. Cancer causes control : CCC. 21: 1851-1856.

36. Leslie KK, Thiel KW, Goodheart MJ, De Geest K, Jia Y, et al. (2012) Endometrial cancer. Obst Gynecol Clinics N Am. 39: 255-268.

37. Wright JD, Barrena Medel NI, Sehouli J, Fujiwara K, Herzog TJ (2012) Contemporary management of endometrial cancer. Lancet (London, England). 379: 1352-1360.

38. Siu MK, Kong DS, Ngai SY, Chan HY, Jiang L, et al. (2015) p21-Activated Kinases 1, 2 and 4 in Endometrial Cancers: Effects on Clinical Outcomes and Cell Proliferation. PLoS One. 10: e0133467.

39. Foerster R, Kluck R, Rief H, Rieken S, Debus J, et al. (2014) Survival of women with clear cell and papillary serous endometrial cancer after adjuvant radiotherapy. Radiation oncology (London, England).9: 141.

40. Leslie KK, Stein MP, Kumar NS, Dai D, Stephens J, et al. (2005) Progesterone receptor isoform identification and subcellular localization in endometrial cancer. Gynecol Oncol. 96: 32-41.

41. Brinton LA, Felix AS, McMeekin DS, Creasman WT, Sherman ME, et al. (2013) Etiologic heterogeneity in endometrial cancer: evidence from a Gynecologic Oncology Group trial. Gynecol Oncol. 129: 277-284.

42. Kwong A, Ho JCW, Shin VY, Kurian AW, Tai E, et al. (2018) Rapid detection of BRCA1/2 recurrent mutations in Chinese breast and ovarian cancer patients with multiplex SNaPshot genotyping panels. Oncotarget. 9: 7832-7843.

43. Gehrig PA, Bae-Jump VL, Boggess JF, Groben PA, Fowler WC, Jr., et al. (2004) Association between uterine serous carcinoma and breast cancer. Gynecol Oncol. 94: 208-211.

44. Rutgers JK (2015) Update on pathology, staging and molecular pathology of endometrial (uterine corpus) adenocarcinoma. Future oncology (London, England). 11: 3207-3218.

45. Frost JA, Webster KE, Bryant A, Morrison J (2015) Lymphadenectomy for the management of endometrial cancer. The Cochrane database Syst Rev 2015: Cd007585.

46. Breijer MC, Timmermans A, van Doorn HC, Mol BW, Opmeer BC (2010) Diagnostic strategies for postmenopausal bleeding. Obstet Gynecol Int. 2010: 850812.

47. Amant F, Moerman P, Neven P, Timmerman D, Van Limbergen E, et al. (2005) Endometrial cancer. Lancet (London, England). 366: 491-505.

48. Tangjitgamol S, Anderson BO, See HT, Lertbutsayanukul C, Sirisabya N, et al. (2009) Management of endometrial cancer in Asia: consensus statement from the Asian Oncology Summit 2009. The Lancet Oncology. 10: 1119-1127.

49. Freeman SJ, Aly AM, Kataoka MY, Addley HC, Reinhold C, et al. (2012) The revised FIGO staging system for uterine malignancies: implications for MR imaging. Radiographics : a review publication of the Radiological Society of North America, Inc. 32: 1805-1827.

50. Beddy P, O'Neill AC, Yamamoto AK, Addley HC, Reinhold C, et al. (2012) FIGO staging system for endometrial cancer: added benefits of MR imaging. Radiographics : a review publication of the Radiological Society of North America, Inc. 32: 241-254.

51. Milgrom SA, Kollmeier MA, Abu-Rustum NR, Makker V, Gardner GJ, et al. (2013) Positive peritoneal cytology is highly predictive of prognosis and relapse patterns in stage III (FIGO 2009) endometrial cancer. Gynecol Oncol. 130: 49-53.

52. Marnitz S, Kohler C (2012) Current therapy of patients with endometrial carcinoma. A critical review. Strahlentherapie und Onkologie : Organ der Deutschen Rontgengesellschaft 188: 12-20.

53. Cardenas-Goicoechea J, Shepherd A, Momeni M, Mandeli J, Chuang L, et al. (2014) Survival analysis of robotic versus traditional laparoscopic surgical staging for endometrial cancer. Am J Obst Gynecol. 210: 160.e1-.e11.

54. Rabinovich A (2015) Minimally invasive surgery for endometrial cancer. Curr Opn Obst Gynecol 27: 302-307.

55. American College of Obstetricians and Gynecologists (2005) ACOG practice bulletin, clinical management guidelines for obstetrician-gynecologists, number 65, August 2005: management of endometrial cancer. Obstet Gynecol 106: 413-425.

56. Coronado PJ, Rychlik A, Martinez-Maestre MA, Baquedano L, Fasero M, et al. (2018) Role of lymphadenectomy in intermediate-risk endometrial cancer: a matched-pair study. J Gynecol Oncol 29: e1.

57. Sadowski EA, Robbins JB, Guite K, Patel-Lippmann K, Munoz del Rio A, et al. (2015) Preoperative pelvic MRI and serum cancer antigen-125: selecting women with grade 1 endometrial cancer for lymphadenectomy. Am J Roentgenol. 205: W556-W564.

58. Turan T, Kimyon Comert G, Turkmen O, Ureyen I, Fadiloglu E, et al. (2017) Therapeutic value of lymphadenectomy and adjuvant radiotherapy in uterine corpus confined endometrioid-type cancer. J Chin Med Assoc. 26: 30348-30349

59. Cetinkaya K, Atalay F, Bacinoglu A (2014) Risk factors of lymph node metastases with endometrial carcinoma. Asian Pacific J Can Prevention : APJCP. 15: 6353-6356.

60. Kulhan M, Kulhan G, Nayki U, Nayki C, Ulug P, et al. (2016) Assessment of clinicopathological features, evaluation of treatment, and prognosis of clear cell and serous papillary endometrial carcinoma. Ginekologia polska. 87: 570-574.

61. Perrone AM, Girolimetti G, Cima S, Kurelac I, Livi A, et al. (2018) Pathological and molecular diagnosis of bilateral inguinal lymph

nodes metastases from low-grade endometrial adenocarcinoma: a case report with review of the literature. BMC Cancer. 18: 7.

62. Salvesen HB, Haldorsen IS, Trovik J (2012) Markers for individualised therapy in endometrial carcinoma. Lancet Oncology. 13:e353-e361.

63. Trovik J, Wik E, Werner HM, Krakstad C, Helland H, et al. (2013) Hormone receptor loss in endometrial carcinoma curettage predicts lymph node metastasis and poor outcome in prospective multicentre trial. Eur J Cancer. 49: 3431-3441.

64. Malpica A (2016) How to approach the many faces of endometrioid carcinoma. Mod Pathol. 29: S29-S44.

65. Fattaneh AT, Devilee P (2002) Pathology and genetics of tumours of the breast and female genital organs. International Agency for Research on Cancer, WHO, Lyon.

66. Ambros RA, Ballouk F, Malfetano JH, Ross JS (1994) Significance of papillary (villoglandular) differentiation in endometrioid carcinoma of the uterus. Am J Surg Pathol 18: 569-575.

67. Young RH, Scully RE (1992) Uterine carcinomas simulating microglandular hyperplasia. A report of six cases. Am J Surg Pathol 16: 1092-1097.

68. Vogel TJ, Knickerbocker A, Shah CA, Schiff MA, Isacson C, et al. (2015) An analysis of current treatment practice in uterine papillary serous and clear cell carcinoma at two high volume cancer centers. J Gynecol Oncol 26: 25-31.

69. Bashir S, Jiang G, Joshi A, Miller C, Jr., Matrai C, et al. Molecular alterations of PIK3CA in uterine carcinosarcoma, clear cell, and serous tumors Int J Gynecol Cancer. 24: 1262-1267.

70. Lobo FD, Thomas E (2016) Type II endometrial cancers: A case series. J Midlife Health 7: 69-72.

71. Brudie LA, Khan F, Radi MJ, Ahmad S (2016) Serous carcinoma of endometrium in combination with neuroendocrine small-cell: A case report and literature review. Gynecol Oncol Rep. 17: 79-82.

72. Chang ES, Baker WD, Landen CN (2016) Metastatic papillary serous uterine cancer presenting as a rash. Gynecol Oncol Rep. 18 :11-3.

73. Fadare O, Zheng W, Crispens MA, Jones HW, Khabele D, et al. (2013) Morphologic and other clinicopathologic features of endometrial clear cell carcinoma: a comprehensive analysis of 50 rigorously classified cases. Am J Cancer Res. 3: 70-95.

74. Matoba Y, Kisu I, Saotome K, Katayama M, Taniguchi M, et al. (2016) Clear cell carcinoma of the lower uterine segment: A case report. Mol Clin Oncol 5: 701-704.

75. Fadare O, Desouki MM, Gwin K, Hanley KZ, Jarboe EA, et al. (2014) Frequent expression of napsin A in clear cell carcinoma of the endometrium: potential diagnostic utility. Am J Surg Pathol 38: 189-196.

76. Kurman RJ, Carcangiu ML, Herrington CS, Young RH (2014) WHO classification of tumours of female reproductive organs. WHO, Lyon, France.

77. Howitt BE, Kelly P, McCluggage WG (2017) Pathology of neuroendocrine tumours of the female genital tract. Curr Oncol Rep. 19: 59.

78. D'Antonio A, Addesso M, Caleo A, Guida M, Zeppa P (2012) Small cell neuroendocrine carcinoma of the endometrium with pulmonary metastasis: A clinicopathologic study of a case and a brief review of the literature. Ann Med Surg 5: 114-117.

79. Shahabi S, Pellicciotta I, Hou J, Graceffa S, Huang GS, et al. (2013) Clinical utility of chromogranin A and octreotide in large cell neuro endocrine carcinoma of the uterine corpus. Rare tumors 3: e41.

80. Ogura J, Adachi Y, Yasumoto K, Okamura A, Nonogaki H, et al. (2018) Large-cell neuroendocrine carcinoma arising in the endometrium: A case report. Mol Clin Oncol. 8: 575-578.

81. Wei JJ, Paintal A, Keh P (2013) Histologic and immunohistochemical analyses of endometrial carcinomas: experiences from endometrial biopsies in 358 consultation cases. Arch Pathol Lab Med 137: 1574-1583.

82. Soslow RA (2010) Endometrial carcinomas with ambiguous features. Semin Diagn Pathol. 27: 261-273.

83. Di Cello A, Rania E, Zuccala V, Venturella R, Mocciaro R, et al. (2015) Failure to recognize preoperatively high-risk endometrial carcinoma is associated with a poor outcome. Eur J Obstet Gynecol Reprod Biol. 194: 153-160.

84. Bourdel N, Chauvet P, Tognazza E, Pereira B, Botchorishvili R, et al. (2016) Sampling in Atypical Endometrial Hyperplasia: Which Method Results in the Lowest Underestimation of Endometrial Cancer? A Systematic Review and Meta-analysis. J Minim Invasive Gynecol. 23: 692-701.

85. Guan H, Semaan A, Bandyopadhyay S, Arabi H, Feng J, et al. (2011) Prognosis and reproducibility of new and existing binary grading systems for endometrial carcinoma compared to FIGO grading in hysterectomy specimens. Int J Gynecol Cancer. 21: 654-660.

86. Hoang LN, McConechy MK, Kobel M, Han G, Rouzbahman M, et al. (2013) Histotype-genotype correlation in 36 high-grade endometrial carcinomas. Am J Sur Pathol. 37: 1421-1432.

87. Lax SF, Kurman RJ, Pizer ES, Wu L, Ronnett BM (2000) A binary architectural grading system for uterine endometrial endometrioid carcinoma has superior reproducibility compared with FIGO grading and identifies subsets of advance-stage tumors with favorable and unfavorable prognosis. Am J Sur Pathol 24: 1201-1208.

88. Bilgin T, Ozuysal S, Ozan H (2005) A comparison of three histological grading systems in endometrial cancer. Arch Gynecol Obstet 272: 23-25.

89. Leitao MM Jr., Kehoe S, Barakat RR, Alektiar K, Gattoc LP, et al. (2008) Accuracy of preoperative endometrial sampling diagnosis of FIGO grade 1 endometrial adenocarcinoma. Gynecol Oncol. 111: 244-248.

90. Scholten AN, Smit VT, Beerman H, van Putten WL (2004) Prognostic significance and interobserver variability of histologic grading systems for endometrial carcinoma. Cancer 100: 764-772.

91. Kim HS, Song YS (2009) International Federation of Gynecology and Obstetrics (FIGO) staging system revised: what should be considered critically for gynecologic cancer? J Gynecol Oncol. 20: 135-136.

92. Abu-Rustum NR, Zhou Q, Iasonos A, Alektiar KM, Leitao MM Jr., et al. (2011) The revised 2009 FIGO staging system for endometrial cancer: should the 1988 FIGO stages IA and IB be altered? Int J Gynecol Cancer. 21: 511-516.

93. Cooke EW, Pappas L, Gaffney DK (2011) Does the revised International Federation of Gynecology and Obstetrics staging system for endometrial cancer lead to increased discrimination in patient outcomes? Cancer 117: 4231-4237.

94. Wang X, Huang Z, Di W, Lin Q (2005) Comparison of D&C and hysterectomy pathologic findings in endometrial cancer patients. Arch Gynecol Obstet. 272: 136-141.

95. Meissnitzer M, Forstner R (2016) MRI of endometrium cancer - how we do it. Cancer Imaging 16: 11.

96. Haldorsen IS, Salvesen HB (2016) What is the best preoperative imaging for endometrial cancer? Curr Oncol Rep 18: 25.

97. Inoue O, Hamatani T, Susumu N, Yamagami W, Ogawa S, et al. (2016) Factors affecting pregnancy outcomes in young women treated with fertility-preserving therapy for well-differentiated endometrial cancer or atypical endometrial hyperplasia. Reprod Biol Endocrinol. 14: 2.

98. Gungor T, Cetinkaya N, Yalcin H, Zergeroglu S, Erkaya S (2016) Clinicopathologic characteristics and treatment features of women with the incidental diagnosis of endometrial adenocarcinoma during infertility follow-up in Ankara, Turkey. Taiwan J Obstet Gynecol. 55: 309-313.

99. Wang F, Yu A, Xu H, Zhang X, Li L, et al. (2017) Fertility preserved hysteroscopic approach for the treatment of stage ia endometrioid carcinoma. Int J Gynecol Cancer 27: 1919-1925.

100. Vandenput I, Van Calster B, Capoen A, Leunen K, Berteloot P, et al. (2009) Neoadjuvant chemotherapy followed by interval debulking surgery in patients with serous endometrial cancer with transperitoneal spread (stage IV): a new preferred treatment? Br J Cancer. 101: 244-249.

101. Beddy P, Moyle P, Kataoka M, Yamamoto AK, Joubert I, et al. (2012) Evaluation of depth of myometrial invasion and overall staging in endometrial cancer: comparison of diffusion-weighted and dynamic contrast-enhanced MR imaging. Radiology. 262: 530-537.

102. Choi HJ, Lee S, Park BK, Kim TJ, Kim CK, et al. (2016) Long-term outcomes of magnetic resonance imaging-invisible endometrial cancer. J Gynecol Oncol 27: e38.

103. Roelofsen T, van Ham MA, de Hullu JA, Massuger LF (2011) Clinical management of uterine papillary serous carcinoma. Expert review of anticancer therapy. 11: 71-81.