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HISTOLOGY, GRADE AND STAGE OF ENDOMETRIAL CARCINOMA- SYSTEMATIC REVIEW

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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 riskpopulations.
Keywords: Endometrial carcinoma; Histology; Grade; Stage.

Introduction

Endometrial cancer is the leading and the second most fatalgynecologic 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, endocrinemetabolic 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].

Material and methods

The literature search was performed on PubMed, Medline and Google scholar, chosen because they are reliable and easy to read. Keywords were used, either alone or in

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combination using ‘AND’ or ‘OR’, to focus the search on the topic without excluding relevant papers. The reference lists of the articles retrieved were examined to capture any other potentially relevant article.

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]. 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. 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 [8]. 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. Obesity can also help in the development of endometrial cancer through insulin resistance, hyperinsulinemia, excess circulating steroid hormones, and localized inflammation.

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 [9]. 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 [10]. Most endometrial carcinoma cases are sporadic, but some women

are genetically predisposed for the disease. Women suffering from Lynch syndrome are more vulnerable for endometrial cancer than colorectal cancer. On a molecular level, Type 1 endometrial carcinoma develops from mutations in phosphatase and tensin (PTEN), Kras, β-catenin, *PIK3CA*, and microsatellite instability. 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. The molecular classification of endometrial carcinoma comprises four subgroups based on somatic mutation rates, frequency of copy number alterations, and microsatellite instability status. 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 [11].

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 [12]. They consist of a heterogeneous, poorly differentiated group of tumors of high grade endometrioid, uterine serous and clear cell carcinomas, and uterine carcinosarcomas. Non-endometrioid tumors are estrogen-independent in development and growth, and arise in an atrophic endometrium. 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. In these situations, survival is less than six months even if aggressive chemotherapy and radiation are performed [13]. 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 [14]. On a molecular level, immunostaining has shown that non-endometrioid tumors might develop as a result of mutations in TP53, ErbB2 and p16 proteins. There is overexpression of mutated ErbB2 and p53 genes in black compared to white women. Several reports have found that women suffering from breast cancer are predisposed to develop uterine serous carcinoma, carcinosarcomas and grade 3 endometrioid. Radiation of adjacent organs, Li-Fraumeni and Lynch syndromes, and mutations in cancer predisposing genes may

be the rationale. In another study it has been suggested that BRCA mutations, which are a cause of breast cancer, maybe frequently found among uterine serous carcinomas [15]. 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. This relationship is observed in women, using tamoxifen, who develop uterine serous cancer and carcinosarcomas. Tamoxifen exert anti-estrogenic effect on breast cancer whereas estrogenic activity on the endometrium . 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 tumorienesis via non-hormonal effects [16].

(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 [17]. 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. Transvaginal sonography is the initial imaging tool to evaluate presumed endometrial cancer. An endometrial thickness greater than 4 mm warrants endometrial biopsy [18]. Preoperative endometrial sampling by office Pipelle or curettage remains the cornerstone in diagnosing endometrial carcinoma . Nowadays, office-based blind biopsy techniques- Novak curette, suction samplers (Pipelle, Vabra) and brush- are increasingly being used instead of dilation and curettage. These office procedures are anesthesia free. The diagnostic accuracy of office endometrial sampling is 85%-98% with regard to dilation and curettage.

However, there is a discrepancy in histologic subtype and grade between the pre- and postoperative specimens.

Histological subtype

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 [19]. 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 neosinophilic. Also, their nuclear polarity is unchanged. Moreover, the glandular lumen may contain some solid growthnwhose cells resemble those lining the lumen. Endometrioid carcinoma containing malignant cells withnsquamous differentiation is the most common variant.

Then squamous element should not be regarded as part of the solid component that upgrades endometrial carcinoma.

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

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

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 [20].

Villoglandular endometrioid carcinomas exhibit long, slender, smooth finger-like papillary growths and a fibrovascular core. They are lined by columnar epithelial cells with minimal or absent cytological atypia. The nuclei are aligned perpendicular to the basement membrane [21]. Secretory endometrioid adenocarcinoma is lined by epithelium that bear sub-nuclear, glycogen vacuoles that resemble the early secretory endometrium. 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 . 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. 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. They are also pleomorphic and often contain psammoma bodies. [22].

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.

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. Similar to the histological subtype, grade is also determined from the preoperative biopsy specimen. 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. **Table 3** below shows the characteristics of architecture grading [23].

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 nucleargrade 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 [24]. 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. 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 ifthe 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 [25]. 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. Matsuo et al explained that the inaccuracybetween the biopsy sample and hysterectomy specimen is theresult of sample error. The surgeon fails to biopsy or curettage an underlying high grade tumor [26].

Stage

The International Federation of Obstetrics and Gynecology was first set up in 1958 to stage gynecologic cancers [27]. Endometrial cancer was clinically staged until 1988 when the surgical staging system was adopted. Surgical staging differsfrom clinical staging in that it is based on the surgicopathologic findings of the hysterectomy specimen [28]. FIGO staging for endometrial cancer has been lastly refined in 2009 and three major modifications had been made to the 1988 staging system. 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 hasinvaded 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 [29]. 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. 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 [30]. Based on clinical stage, treatment is tailored to avoid extensive surgery in lowrisk disease. 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 [31]. High dose progestin is recommended in these women with clinical stage IA and grade 1 disease. They are followed by repeated D&C, and hysterectomy is indicated in the event of failure to conservative treatment. Furthermore, endometrial carcinoma is generally linkedto 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 [32]. 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 [33]. 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 [34]. 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 [35]. Peritumoral inflammation may also lead to overestimation of the depth of myometrial invasion [36]. On the contrary leiomyomas and adenomyosis decrease the accuracy MRI. 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 MRIvisible tumors [37]. 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 [38].

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 noncommunicable 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.

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 histologicsubtypes: the NIH-AARP Diet and Health Study. Am J Epidemiol177: 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 typicalendometrial 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.