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Endometrial Adenocarcinoma: A Genetic Focus Review

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Abstract

Endometrial Carcinoma (EC) is the abnormal proliferation of endometrial tissue and constitutes more than half of all gynecological cancer diagnosis in USA. In Mexico, is also the second most common carcinoma? Pathological classification is a relevant element of disease management. EC is classified into two types: Type I, is known as endometrioid carcinoma and comprise 90% of adenocarcinomas. Type II, known as non endometrioid carcinoma, conforms 10% of the adenocarcinomas and is poorly differentiated.

Objective: The purpose of this review is to introduce the role of genetics in this type of adenocarcinomas, as well as update the current information regarding EC. In Type I, the most relevant genetic alterations are the inactivation of *PTEN* gene, the altered expression of *PAX-2*, the mutation in β-catenin/*CTNNB1* and the microsatellites instability. Due to the fact that Type I adenocarcinoma is the most frequent type of endometrial carcinoma, we focus on the genetic alterations on *PTEN* and *PAX-2*.

Methods: To make this review, we used the research engines PubMed, OVID, MEDLINE and SciELO with the following keywords: Endometrial carcinoma, genetics, molecular classification, *PTEN*, *PAX2*, *P53* and mutations.

Keywords: Endometrial carcinoma; Genetics; *PTEN*; *PAX2*; *P53*

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Introduction

Endometrial adenocarcinoma is the irregular proliferation of endometrial tissue, which can cause expansion and infiltration into neighboring tissues and/or invasion of distant tissues through different routes. It is classified into two types. Type I, known as endometrioid carcinoma, usually appears close to menopause, in addition to being accompanied by obesity, nulliparity, and hyperestrogenism. This neoplasm has a history of precursor endometrial lesions. On the other hand, Type II or non-endometrioid carcinoma appears at older ages in multiparous patients, presenting endometrial atrophy [1]. To carry out this review, a query was carried out with search engines such as PubMed, OVID, MEDLINE and SciELO using the keywords: endometrial carcinoma, genetics, *PTEN*, *PAX2*, *P53*, molecular classification and mutations. The search results were filtered to use only original publishable articles from 2012 to 2020.

International epidemiology

Endometrial Cancer (EC) occurs worldwide with 36,000 new cases and 6,000 deaths per year. Survival in the early clinical stages is 80%, while patients with an advanced disease have a long-term survival of less than 50%. Endometrial adenocarcinoma occurs in patients older than 50, showing an elevation between 70 years and 74 years and only 3% to 5% of cases occur before the age of 40. The countries with the lowest incidence of this type of cancer are China, which has approximately 2 cases per 100,000 inhabitants, and India with 1.7 cases [2].

The incidence of endometrial adenocarcinoma is six times higher in developed countries compared to under developed countries. The mean age of the patients is 63 years [3,4].

National epidemiology

It is known that the incidence of cervical cancer in Mexico is 7,800 new cases per year. According to the Histopathological Registry of Malignant Neoplasms, endometrial carcinoma ranks second among gynecological cancers, after cervical cancer.

Risk factors

According to the cytogenetics of endometrial carcinomas [5]:

- Type I

1. Most of the time it is well differentiated, clinical presentation occurs in premenopause, obesity, nulliparity, endogenous or exogenous hyperestrogenism, diabetes mellitus and hypertension are also associated.

- Type II

1. Poorly differentiated, it occurs in older ages or in post-menopause, the most frequent histologies are papillary serous or clear cells; they are more aggressive, patients are generally multiparous, and do not have an association with obesity, hypertension or diabetes.

Other risk factors that are particularly present are the use of tamoxifen (as hormone blocking therapy in estrogen-dependent breast cancer) and polycystic ovary in some patients. Obesity, with a body mass index greater than or equal to 40, represents an important factor because it causes the peripheral change from androstenedione to estrone [6-9].

On the other hand, the prolonged use of oral hormonal contraceptives has been related to a decrease in the risk of suffering from this type of carcinoma, the risk decreases proportionally to the time of use of the contraceptives [10].

Clinical Presentation

Abnormal uterine bleeding is the most common finding in endometrial adenocarcinoma. Patients with advanced disease have a clinical presentation similar to that of ovarian cancer with abdominal-pelvic pain, abdominal distention, early satiety and changes in defecation habits, so it is important to make an adequate differential diagnosis [11].

Diagnostic Tools

The American College of Obstetrics and Gynecology and the Society of Radiologists recommend performing a transvaginal ultrasound and endometrial biopsy as the first diagnostic step in women with postmenopausal bleeding [12].

Transvaginal ultrasound

Transvaginal ultrasound allows the selection of patients who have postmenopausal uterine bleeding. In this study, the endometrial thickness is evaluated, the probability of cancer increases when the endometrial thickness approaches 20 mm.

Endometrial biopsy

The diagnosis is complete with the histological study of a fragment of endometrial tissue, achieved by uterine curettage, by endometrial cytology or by hysteroscopy [13].

Role of estrogens in endometrial adenocarcinoma

In premenopausal and postmenopausal women, polycystic ovary syndrome and obesity are related to anovulatory cycles, this results in the endometrium being exposed to the action of estrogens, which, in the absence of the regulatory action of progesterone, cause endometrial proliferation that can progress to hyperplasia over time.

Estrogens play a fundamental role in the appearance of endometrial cancer, since most are estrogen-dependent adenocarcinomas; however it has been proven that the use of tamoxifen has estrogenic activity in the uterus. Estrogens and Tamoxifen regulate the transcription of several sets of genes, some of which can be targeted by both estrogens and the drug. Of these, *PTEN* and *PAX2* increase their expression with both and are extremely relevant genes in the development of the disease [14,15].

Precursor lesions of endometrial adenocarcinoma

Ninety percent of endometrial adenocarcinomas are estrogen dependent so they are related to a situation of Hyperestrogenism, the predecessor lesions of endometrial cancer are endometrial hyperplasia's [16].

Relationship between endometrial hyperplasia and endometrial cancer

Endometrial hyperplasia is the growth of glands of irregular size with an increase in the gland-stroma ratio, and as it has been proven, endometrial hyperplasia is the predecessor of endometrial cancer.

Endometrial hyperplasia arises in most cases as a result of excessive estrogenic stimulation coupled with low levels of progesterone which cause a remodeling of the epithelial glands that lead to hyper proliferation.

The most frequently used classification is the one proposed by the WHO in 1994, which categorizes it according to morphology and cytological atypia:

1. Simple hyperplasia
2. Complex hyperplasia
3. Simple hyperplasia with atypia
4. Complex hyperplasia with atypia.

The histopathological study of patients with endometrial hyperplasia has found that, in patients with simple hyperplasia without treatment, 9% of the cases progressed to endometrial carcinoma. In patients with simple hyperplasia with atypia the same occurred in up to 30% of the patients.

Due to the fact that this classification had low consistency in diagnosis in 2014, this classification was updated by the WHO to include only 2 categories: hyperplasia with or without atypia [17].

Endometrial Carcinoma Classification

Bokhman's Clinical, epidemiological and morphological classification

This duality, proposed in 1983, has been the classic classification of adenocarcinomas (Table 1); however, it has been challenged by the new definition and characterization of genetic mutations in the types of adenocarcinoma.

Type I: The endometrioid-type endometrial adenocarcinoma makes up 90% of adenocarcinomas, and patients have a good prognosis. It is related to the extensive estrogen drive of the endometrial mucosa and late menopause. It is of low histological grade, little myometrial invasion, and it has been related to a previous endometrial hyperplasia.

Type II: These are the non-endometrioid variables: Clear cells carcinoma and papillary carcinoma, they are less frequent, not related to the estrogenic manifestation and form a more aggressive biological behavior [18].

Table 1: Bokhman classification*.

Bokhman Classification		
	Type I	**Type II**
Percentage of cases	60% to 70%	30% to 40%
Reproductive capacity	Diminished	Not affected
Menopause	>50 years	<50 years
Endometrial comorbilities	Hyperplasia	Atrophy
Estrogen association	Yes	No
Association with obesity, hyperlipidemia and hypertension	Yes	No
Tumoral grade	Low (G1-2)	High G3
Miometrial invasion	Superficial	Deep
Linfatic dissemination potential	Low	High
Prognosis	Good	Bad
Progestagen sensibility	High	Low
5 years overall survival	86%	59%

*This classification catalogues endometrial cancer in 2 types, based on their clinical, epidemiological and histological characteristics

Molecular and histological classification of endometrial adenocarcinomas

Recent analyzes of "The cancer genome Atlas Research Network (TCGA)" in transcriptomics, genomics and proteomics have allowed the creation of a new molecular classification in endometrial cancer (Table 2) [19,20] based on:

- POLE ultra-mutated
- Microsatellite Instability-Hypermutated (IMS-H)
- Copy number-low
- Copy number-high

The World Health Organization (WHO) [21] classification histologically divides endometrial adenocarcinoma into:

- Endometrioid adenocarcinoma represents 75% of the lesions, with a survival rate of 60% to 80% at five years.
- Mucinous adenocarcinoma: Rare.
- Clear cell adenocarcinoma: Represents 5% of the lesions. Considered to have a worse prognosis, it shows itself in advanced stages with a survival rate of 6% to 44% in five years.
- Serous adenocarcinoma: Constitutes 1% to 10% of lesions. Associated with a serious prognosis, it presents itself in an invasive stage, with a survival rate of 4.7% to 68% in five years.
- Squamous cell carcinoma: Very infrequent. It constitutes 0.1% of the lesions, with a survival rate of 6.9% to 53% in five years.
- Undifferentiated carcinoma: Constitutes 1% to 2% of the lesions. There are 2 subtypes: Large cells and small cells, which have a poor prognosis.
- Mixed Carcinoma: Made of up of two or more subtypes of carcinomas.

FIGO classification

Over the years, clinical staging of endometrial cancer has been replaced by surgical staging bye FIGO Committee. During staging it is required a histologic verification measuring distance from tumor to serosa, myometrial invasion, lymphovascular space invasion and presence of metastases to assess the prognosis (Table 3) [22].

Genetic Alterations in the Development of Endometrial Cancer

PTEN

One of the genes that is most frequently altered is *PTEN*. When this happens it can lead to the development of adenocarcinoma since its function is to be a tumor suppressor. This gene codes for a protein with a tyrosine-kinase function and also has lipid-phosphatase and protein-phosphatase activity. It plays an important role in the PI3K-PTEN-AKT-mTOR pathway which regulates cell growth, cell survival, and protein synthesis. Therefore, if *PTEN* is lost or altered, aberrant cell growth will result. Inactivation of *PTEN* can be caused by a mutation leading to a loss of expression or loss of heterozygosity. *PTEN* usually antagonizes the activation of the PI3K pathway (Figure 1), mutations in this tumor suppressor gene can be found in up to 69% to 80% of endometrial tumors [23].

It has been observed that *PTEN* mutation is not enough for endometrial cancer to develop. Other genes participating in this alteration are *KRAS* (15% to 30%), β-catenin/*CTNNB1* (14% to 44%),

Table 2: New molecular classification.

	POLE (ultramutated)	**IMS-H (hypermutated)**	**Copy number-low (endometrioid)**	**Copy number-high (serous)**
Frequent genetic mutations	*POLE* (100%)	*PTEN* (88%)	*PTEN* (77%)	*TP53* (92%)
	PTEN (94%)	*PRPL22* (37%)	*CTNNB1* (52%)	*PPP2R1A* (22%)
	PIK3CA (71%)	*KRAS* (35%)	*PIK3CA* (53%)	*PIK3CA* (47%)
	PIK3R1 (65%)	*PIK3CA* (54%)	*PIK3R1* (33%)	
	FBXW7 (82%)	*PIK3R1* (40%)	*ARID1A* (42%)	
	ARID1A (76%)	*ARID1A* (37%)		
	KRAS (53%)			
	ARID5B (47%)			
Mutation rate Histological type	Very high	High	Low	Low
	Endometrioid	Endometrioid	Endometrioid	Serous, endometrioid and mixed
Tumoral grade Disease free progression	Mixed (G1-3)	Mixed (G1-2)	G 1-2	G3
	Good	Medium	Medium	Bad

These are the four major genomically defined types of tumor on base of main genetic mutations of endometrial cancer. They correlated with progression-free survival: those with copy number high had very poor prognosis, while IMS-H and copy number low groups had intermediate prognosis

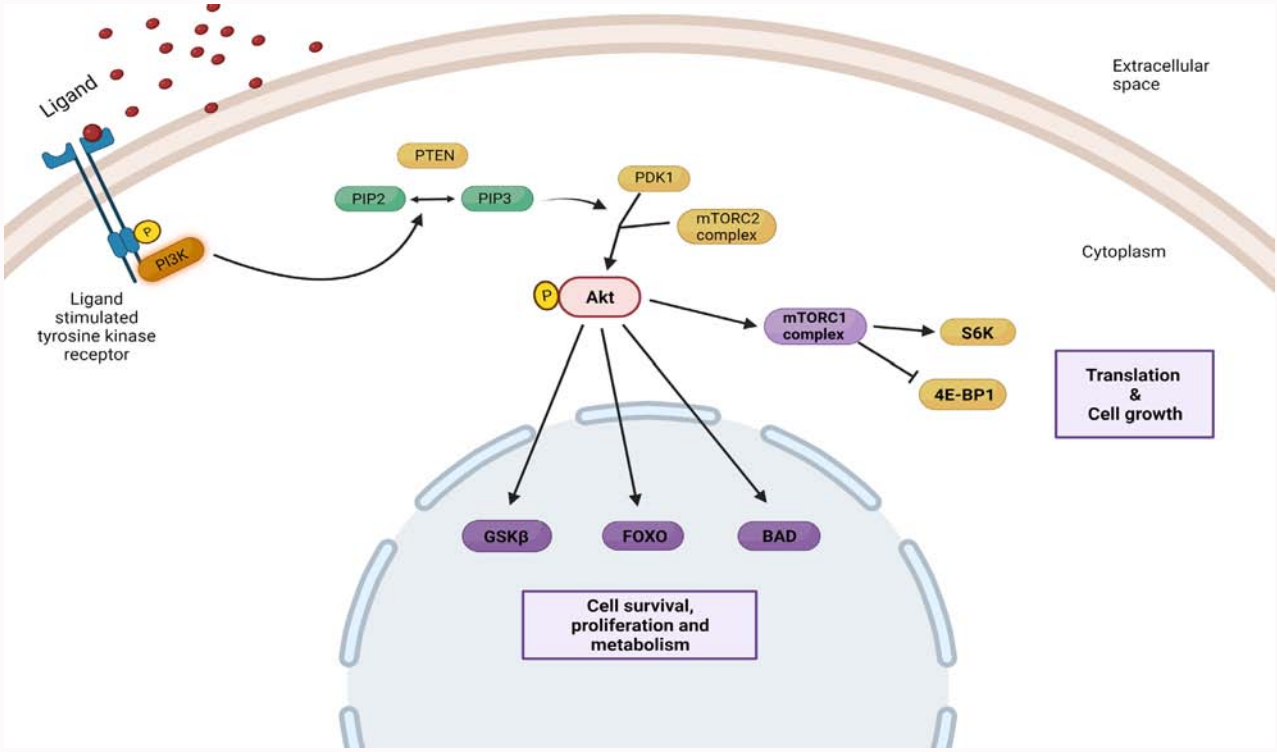

Figure 1: The PI3K-Akt pathway.
PI3K catalyzes the conversion of PIP2 to PIP3; this protein phosphorylates AKT, which activates the mTORC1 complex promoting cell growth and translation *via* 4E-BP1 and S6K. Akt also promotes cell survival, proliferation and metabolism *via GSK3β*, *FOXO* and *BAD*. The *PTEN* tumor suppressor negatively regulates this pathway by converting PIP3 to PIP2.

PIK3CA (26% to 36%), *PAX 2* (77%) and microsatellite repair factors (20% to 45%) [24].

Mutter et al. [25] conducted a series of studies at Brigham and Women's Hospital (Boston, MA) where endometrial samples were taken from women between 30 years and 90 years separated in 28 days and 1280 days, to study the fate and clonal continuity of glands with *PTEN* mutations. Samples from patients with high risk of endometrial adenocarcinoma and samples from patients with low risk were compared in paired samples [25]. *PTEN* immunohistochemistry was successfully performed in paired endometrial samples from 45 high-risk and 167 low-risk patients. High-risk patients had findings of adenocarcinoma while benign samples were in the samples of low-risk patients. The most frequent result was the demonstration of independent somatic mutations of *PTEN* in glands deficient of the *PTEN* protein sampled at different points, 47% of these were high risk and 38% were low risk. These results demonstrated the rotation of clones over time, with a mutant clone in the process of involution that later will be replaced by a new one.

This study confirms that there is a high prevalence of latent precursors of cancer both in women who progress to endometrial cancer and in those who remain cancer-free. This frequency indicates that the finding of pre-malignant lesions in a normal-appearing tissue has little or no specific predictive value at all. The prognosis that the patient will develop cancer or not, requires in addition to this fact, a progression from histological normality to an abnormal progression that includes cytological and anatomical alterations, as a result of IEN (Intraepithelial Endometrial Neoplasia).

PIK3CA and *PIK3R1*

PIK3CA and *PIK3R1* mutations are usually co found with *PTEN* abnormalities, these genes encode for the catalytic and regulatory subunits of *PI3K*. It has been suggested that these mutations have synergistic or additive effects to the alterations of *PTEN* [26,27].

PAX-2

The embryonic *PAX-2* is essential for the development of the kidneys, ureters, uterus and oviducts in women, whereas in men it produces the development of the epididymis and the vas deferens. Since *PAX-2* is a tumor suppressor, loss of *PAX-2* has been also linked to the development of endometrial carcinogenesis and to the *PTEN* gene [28,29]. Studies of RNA expression of *PAX-2* in human endometrial resulted in high levels of expression in benign proliferative endometrium with a two times reduction in women using tamoxifen therapy, and a five times reduction in the cancers.

Monte and colleagues carried out a series of studies at Brigham and Women's Hospital using a collection of samples where the loss of the expression of *PAX-2* and *PTEN* in EIN and cancer samples caused a clonal distribution, which affected most of the patients' neoplastic glands. When there was a loss of the protein products of both genes, there was a scattered or complete overlap of the loss of *PAX-2* and *PTEN*. The clonal form of loss of the proteins *PTEN* (68%) and *PAX-2* (77%) in endometrial cancer is a huge evidence for a fundamental role of these two genes during endometrial carcinogenesis. The proportion of glands with loss of *PAX-2*, *PTEN* or both in samples of normal proliferative endometria was very low: 0.46%, 1.34% and 0.01% respectively.

The hypothesis is that the accumulation of increased genetic damage in the sequence of normal to premalignant tissues and from premalignant to malignant shows that there is a gradual change in the loss of protein expression. However, this occurred at different

Table 3: FIGO classification.

International Federation of Gynecology and Obstetrics classification (FIGO) [21]	
FIGO Stage	
I*	Tumor confined to the corpus uteri
IA*	None or less than half myometrial invasion
IB*	Invasion equal to or more than half of the myometrium
II	Tumor invades cervical stroma, but does not extend beyond the uterus
III	Local and/or regional spread of the tumor
IIIA*	Tumor invades the serosa of the corpus uteri and/or annex
IIIB*	Vaginal involvement and/or parametrial involvement
IIIC*	Metastases to pelvic and/or para-aortic lymph nodes
IIIC1*	positive pelvic nodes
IIIC2*	Positive para-aortic nodes with or without positive pelvic lymph nodes
IV	Tumor invades bladder and/or bowel mucosa, and/or distant metastases
IVA*	Tumor invasion of bladder and/or bowel mucosa
IVB*	Distant metastases, including intra-abdominal metastases and/or inguinal nodes
*Either G1, G2 or G3	

The FIGO classification grades endometrial cancer into 4 stages based on the surgical and histological findings

times for both genes: The *PAX2* gene was in transition from normal to premalignant and with the *PTEN* gene it occurred in the transition from Intraepithelial Endometrial Neoplasia (EIN) to cancer. Ninety percent of carcinomas lacked proteins from one or both genes.

It has also been noted that endometrial adenocarcinomas have an expression profile similar to that of the proliferative endometrium stimulated by estrogens. This explains the way how is eliminated the loss of expression of *PTEN* by using progesterone to avoid the formation of adenocarcinoma.

PAX-2 is a relevant transcription factor that acts by feeding back other genes. Several examples of this can be given, such as how the expression of *PAX-2* increases the endogenous gene expression of the *WT1* tumor suppressor gene in urogenital tissues. The most common phenotype related to the loss of both *PTEN* and *PAX-2* is EIN or Endometrial Carcinoma [30].

β-Catenine

Encoded by the *CTNNB1* gene, it helps in cell adhesion with Cadherin-E; it also acts in the nucleus as an activator in the transcription of Wnt signals, which is related to embryogenesis and carcinogenesis. Therefore, both the accumulation of cytosolic β-Catenin, as well as its inadequate function, can produce an increase in cell proliferation and loss of adhesion, together with tumor dissemination [31-33].

If an increase in β-Catenin is detected in the nucleus, it is related to a poor prognosis of the disease and the probability of survival decreases. β-Catenin mutations can be seen in 14% to 44% of endometrial cancers, being one of the most important characteristics of Type I or endometrioid tumors [34,35].

Microsatellite instability (IMS)

Microsatellites are short sequences of polymorphic DNA. When errors occur in microsatellite repair, it leads to wrong base pairing, thus forming microsatellite instability. In endometrioid adenocarcinomas, IMS has been found in up to 45% of cases. Hypermethylation of the MLH1 promoter has been the most frequent cause of this instability, being considered a premature event in the development of cancer, since it is even found in hyperplasia [36-39].

p53 mutations

This gene is a tumor suppressor found on chromosome 17. The function of this gene is to code for a protein that stops the cell cycle in the event of cell damage being detected. It has been found that non-synonymous missense mutations in *TP53* results in a protein that resists degradation, the resultant protein accumulates in tumor cell nuclei and may be a good biomarker for endometrial carcinoma [40,41].

The *p53* mutation is found mainly in Type II adenocarcinomas (up to 90% of cases). In a study by Samani et al. [37] performed in 94 endometrial samples (48 samples with carcinoma, 21 with hyperplasia and 25 healthy samples) it was found that the *p53* gene was overexpressed in 77% of the samples studied with endometrial carcinoma, however, this gene was not found overexpressed in hyperplastic or healthy cells, nor does it correlate with the clinical stage [42].

HER-2/neu amplification in type II endometrial carcinoma

The *HER-2/neu* gene is an oncogene predominantly expressed in the embryo of neuroblastoma cells, although it can also be normally found in some adult tissues. This gene encodes a protein similar to the epidermoid growth factor receptor and its overexpression can cause abnormal cell proliferation and consequently malignant transformation. *HER-2/neu* amplification is associated with high-grade endometrial carcinomas, rapid progression and poor prognosis, especially in Type II endometrial carcinomas [43,44].

Genetic alterations in type I and type II tumors

The official journal of the Spanish society of gynecology and obstetrics presents a table showing the most frequent genetic alterations in endometrial cancer. For Type I they are *PTEN*, *PIK3CA*, and *ARID1*. Regarding type two tumors, they are: *TP53*, *HER2* and *PIK3CA* amplification.

Lynch syndrome

Lynch syndrome is a genetic pathology with autosomal dominant inheritance where errors are found in DNA repair, which leads to

abnormal base pairing, generating microsatellite instability. The genes associated with Lynch syndrome are *MLH1*, *MSH2*, *MSH6*, and *PMS2*. These genes are responsible for repairing errors in DNA, so their mutations prevent this process from being carried out properly.

Lynch syndrome confers a high risk for developing colorectal cancer, endometrial carcinoma, ovarian carcinoma, gastric cancer, cancer of the bile ducts and small intestine [45,46].

Endometrial Carcinoma Treatment

Surgical treatment

Based on extensive research, treatment of patients with stage I endometrial adenocarcinoma is less expensive and shorter with a total hysterectomy with bilateral salpingo-oophorectomy and therapeutic lymphadenectomy, as pelvic lymph node metastasis occurs in approximately 10% of patients with endometrial adenocarcinoma. In addition, the treatment is accompanied by peritoneal lavage and/or omentectomy, as previously determined.

In endometrioid histologies, the staging surgery can be open or laparoscopic and it consists of [47,48]:

- Total hysterectomy
- -Bilateral salpingo-oophorectomy (in some cases of young women with unsatisfied parity it can be modified).
- Bilateral pelvic sampling or bilateral pelvic lymphadenectomy.
- Peritoneal lavage for cytology
- For histological types with a poor prognosis, the best course is to perform an infracolic omentectomy and appendectomy in addition to the above.

Brachytherapy

Isolated vaginal brachytherapy helps as adjunctive treatment to reduce the risk of local recurrence (which is the most common) and reduce toxicity compared to external radiotherapy. However, an increase in overall survival has not been reported with the use of this therapy. In early stages, the adjuvant brachitherpia treatment is implemented in 1AG1. In stages 1AG2 or higher, brachytherapy is recommended as part of local control, according to the NCCN guidelines. For the case of histologies with bad prognosis such as papillary serous and clear cells, adjuvant treatment with brachytherapy should be used with doses from 1500 cGy to 2000 cGy in 3 to 4 fractions.

Hormonal treatment

Progesterone eliminates the null endometrial glands with *PTEN* in the normal endometrium. This hormone is not the only one that can be used to prevent the genesis of cancer in the endometrium. Other interventions such as treatment with oral contraceptives or the placement of the Levonorgestrel-releasing Intrauterine Device (IUD) are used and recommended for inoperable patients as a reinforcement of the primary radiotherapy treatment. It is currently given as palliative therapy to patients with advanced adenocarcinoma or at an advanced age.

Conclusion

Internationally, endometrial cancer is one of the most frequent malignant diseases in the female gender. Being an estrogen-dependent carcinoma, those factors that increase the concentration of this hormone also increase the risk of developing this disease. There are three different ways of classifying this illness that complement each other: Pathological description (Bokhman Classification), histopathological and molecular classification. The recent study by the TCGA group has described multiple mutations that correlate with the pathogenesis of the disease. Amongst the most linked genetic mutations to this tumor are: *PTEN*, *PAX-2*, *PIK3CA* and *TP53*. On the other hand, four genomically identified tumor classes have been identified (*POLE* ultramutations, MSI-H, with decreased copy number and increased copy number). With the advancement of genomic technologies, the increase in the knowledge of this pathology has seen an important growth.

The challenge for the future is to determine the specific molecular characteristics for each subtype of endometrial cancer, and based on that to develop new particular therapeutic strategies to improve efficacy of treatment. Still with the high prevalence of mutations in the genes involved in the pathophysiology of this malignancy, there is no recommended single marker to identify a specific histotype. In the future, a panel of biomarkers with *PTEN*, *P53*, *ARID1*, etc. may be essential in order to know the prognosis of such patients.

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