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Controversies in the Management of Endometrial Cancer

Guest Editors: Enrique Hernandez, Andreas Obermair, Paul J. Hoskins, Javier F. Magrina, and Robert Mclellan

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Editorial Board

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Editorial

Controversies in the Management of Endometrial Cancer

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Endometrial cancer is the most common gynecologic malignancy among women in developed countries. Most are diagnosed at stage I and their probability of surviving the disease is excellent. Most women at diagnosis are older, obese, and have multiple comorbidities. These factors need to be considered when treating patients with this highly curable disease. When recurrences occur at the vaginal apex, almost 50% are salvaged with radiation therapy with or without surgical excision. However, treatment of nodal or distant recurrences or of advanced disease at diagnosis is more challenging.

One of the challenges faced by those treating this disease is how to identify those women who are at risk of having occult metastatic disease at initial diagnosis and to provide effective adjuvant therapy that would prevent recurrences in this select group of patients while minimizing therapy-induced morbidity.

In this special issue on endometrial cancer, the authors tackle some of these issues. The articles accurately and succinctly summarize the current approach to the treatment of this disease and looks at the future by discussing possible novel interventions for the treatment of advanced or recurrent disease. The controversies in the surgical management of endometrial cancer are discussed, as are the minimally invasive surgical techniques.

The international group of authors and editors provide a worldwide perspective about areas of agreement, topics of controversies, and issues that need yet to be clearly defined. Authors from The Netherlands discuss the controversies in evaluating women with postmenopausal bleeding. They weight the convenience, but possible decreased accuracy, of transvaginal ultrasound against the invasiveness of endometrial biopsy, hysteroscopy, and D&C. Another group from The Netherlands, using their national pathology database, demonstrates the prevalence of synchronous ovarian and endometrial adenocarcinomas.Authors from Indonesia thoroughly discuss the genetics of endometrial cancer, while authors from Bologna, Italy address controversies in the surgical treatment of endometrial carcinoma to include the laparoscopic and robotic-assisted approaches. The group from the University of Toyama, Japan presents a retrospective analysis of 83 women with endometrial carcinoma who by pre- and intraoperative assessment was considered to be at low risk for recurrence. These women underwent a total abdominal hysterectomy and bilateral salpingo-oophorectomy without lymphadenectomy. The authors report a 98% 5-year survival. The authors from China present a succinct but comprehensive review of endometrial carcinoma, as do the group from the Catholic University of Sacred Heart in Rome and Temple University in Philadelphia. The authors from the University of Texas in San Antonio discuss the differences in the molecular profile of type I and type II endometrial carcinoma, as well as the molecular changes observed in endometrial sarcomas. The authors from Oita University, Japan; Utrecht, The Netherlands; and the University of Florence, Italy discuss

possible novel approaches to the treatment of advanced or recurrent endometrial adenocarcinoma. And finally, authors from Greece and the United Kingdom summarize the evidence for adjuvant and molecularly targeted therapy of endometrial cancer.

In this special issue of *Obstetrics and Gynecology International*, the reader will conveniently find a comprehensive summary of the state-of-the-art diagnostic strategies, biology, and evidence-based treatment of endometrial cancer from an international perspective.

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Review Article

Diagnostic Strategies for Postmenopausal Bleeding

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Postmenopausal bleeding (PMB) is a common clinical problem. Patients with PMB have 10%–15% chance of having endometrial carcinoma and therefore the diagnostic workup is aimed at excluding malignancy. Patient characteristics can alter the probability of having endometrial carcinoma in patients with PMB; in certain groups of patients the incidence has been reported to be as high as 29%. Transvaginal sonography (TVS) is used as a first step in the diagnostic workup, but different authors have come to different conclusions assessing the accuracy of TVS for excluding endometrial carcinoma. Diagnostic procedures obtaining material for histological assessment (e.g., dilatation and curettage, hysteroscopy, and endometrial biopsy) can be more accurate but are also more invasive. The best diagnostic strategy for diagnosing endometrial carcinoma in patients with PMB still remains controversial. Future research should be focussed on achieving a higher accuracy of different diagnostic strategies.

1. Introduction

Postmenopausal bleeding (PMB) can be defined as uterine bleeding occurring at least one year after menopause. PMB is a common clinical problem in both general and hospital settings [1, 2]. The incidence of spontaneously occurring PMB in the general population can be as high as 10% immediately after menopause [3].

PMB is often caused by abnormalities of the endometrium, whether they are benign or malignant. Of postmenopausal women with vaginal bleeding, 10%–15% have endometrial carcinoma [4–8]. In contrast, the prevalence of endometrial polyps in patients with PMB and an increased endometrial thickness measured with transvaginal sonography (TVS) is estimated to be around 40% [9, 10].

Endometrial cancer is the most common malignancy of the female genital tract in developed countries [11]. Unlike other malignancies, endometrial cancer often presents at an early stage when there is a possibility of curative treatment by hysterectomy. Survival decreases with increased staging and lower histological differentiation, thus accurate and timely diagnosis is important and should preferably be carried out by a safe, simple and minimally invasive method. Guidelines addressing PMB are therefore aimed at excluding cervical cancer, endometrial carcinoma or precancerous lesions of the endometrium [12–15].

2. Diagnosis of Endometrial Carcinoma

2.1. Accuracy of Transvaginal Ultrasonography for Diagnosing Endometrial Carcinoma. Since two decades TVS has become widely used in the evaluation of women with PMB. Before TVS was introduced in the early 1990s, women with PMB were scheduled for dilatation and curettage (D&C). The goal of TVS assessment of the endometrium is to exclude endometrial carcinoma. The probability of endometrial pathology is strongly reduced in the presence of an endometrial ultrasound with an endometrial thickness $\leq$4 mm. Endometrial sampling is not recommended below this cutoff value [16–18].

Guidelines [12–15] almost always refer to a meta-analysis performed by Smith-Bindman et al. [17]. Although this is the

most cited publication, there are three meta-analyses on this subject which have used different methods and have come to different conclusions [16–18].

The meta-analysis of Smith-Bindman et al. [17] combined published data from different studies. Using the reported data, 2×2 tables per included study were constructed that compared endometrial thickness measured at TVS to presence or absence of endometrial carcinoma. Results across studies were combined in a summary Receiver Operator Characteristics (ROC) Curve. At a 5 mm cutoff the sensitivity for detecting endometrial cancer was 96% for a 39% false-positive rate. Such a combination of sensitivity and specificity would reduce a pretest probability of 10% for endometrial cancer to a posttest probability of 1% [17]. Based on this posttest probability, expectant management is at present recommended to these women.

Gupta et al. [16] conducted a comprehensive systematic review in which they focused on the study quality assessment of each study. Only four studies were identified as best-quality studies [19–22]. For each paper a 2×2 table was constructed and likelihood ratios (LR) were calculated. Pooling of the results of these four studies for endometrial thickness $\leq$5 mm resulted in a LR of a negative test of 0.16. In a patient with a negative test result, the posttest probability was 2.5% [16].

Tabor et al. [18] included only studies from which they were able to get the original data from the authors. For each study they calculated median endometrial thickness per centre and used multiples of the median for endometrial thickness to pool data. They reported a sensitivity of 96% for a specificity of 50% and concluded that such a sensitivity with a 4% false-negative rate was too high. Therefore, in their opinion endometrial thickness measurement does not reduce the need for invasive diagnostic testing [18].

Besides the test accuracy, the pretest probability (before any test is done) influences the performance of a diagnostic test in clinical practice. The pretest probability is approximately 10% for the whole population of patients with PMB, but various clinical characteristics can alter this pretest probability. The probability of endometrial carcinoma in women with PMB rises from 1% in women younger than 50 years to 23.8% in women older than 80 years and the incidence of malignancy is, regardless of age, higher in women with PMB and obesity (18%) or diabetes (21%) as compared to women without one of these risk factors (8.0%) [23]. In obese women with diabetes the incidence is reported to be as high as 29% [23]. As the pretest probability for malignancy is higher, the potential of the test to reduce the posttest probability to below 5% can be limited.

2.2. Accuracy of Invasive Endometrial Assessment Methods. Patients with an increased endometrial thickness should undergo more invasive testing, that is, office endometrial sampling, hysteroscopy or dilation and curettage (D&C), to exclude endometrial pathology.

D&C was traditionally the method of choice for investigating patients with postmenopausal bleeding. However, in approximately 60% of the D&C procedures less than half of the uterine cavity is curetted. Another drawback of D&C is that this procedure is performed under general anaesthesia in an inpatient setting [24]. D&C is now considered to be outdated practice and is replaced by less invasive outpatient evaluation using endometrial biopsy devices and outpatient hysteroscopy guided biopsies [25].

Guidelines advocate office endometrial sampling to rule out endometrial carcinoma in women with PMB and an increased endometrial thickness, measured with TVS. Dijkhuizen et al. [26] performed a meta-analysis comparing different minimally invasive endometrial biopsy devices. In postmenopausal women endometrial sampling with both the Pipelle device (Pipelle de Cornier, Paris, France) and the Vabra device (Berkeley Medevices, Inc., Richmond, Calif, USA) are very sensitive techniques for the detection of endometrial carcinoma, with detection rates of 99.6% and 97.1%, respectively, [26]. Despite these reassuring features, the amount of tissue obtained by office sampling varies considerably and is sometimes insufficient for a reliable histological diagnosis. In case the material is classified as insufficient, the clinician is in doubt whether or not to proceed with more invasive testing or to rely on the negative biopsy. In a prospective study performed by Van Doorn et al. four (6%) out of 66 patients with insufficient tissue at office endometrial sample were subsequently diagnosed with endometrial cancer ($n = 3$) or atypical hyperplasia ($n = 1$). This finding implicates that women with an insufficient sample and an endometrial thickness of 5 mm or more should not be reassured [27].

Compared with traditional methods such as curettage, hysteroscopy offers the possibility of visualizing macroscopic or focal abnormalities and taking directed biopsies [28, 29]. With the development of smaller diameter hysteroscopic systems and the introduction of a "vaginoscopic" approach to hysteroscopy (without the use of a speculum or tenaculum), patient acceptance has improved considerably and hysteroscopy nowadays can be performed in an outpatient setting without the use of anaesthesia [30, 31].

3. Diagnostic Strategies for Postmenopausal Bleeding

In clinical practice, tests are commonly combined in diagnostic sequences and disease probabilities are usually estimated in a hierarchical manner, first combining information from history and patient characteristics followed by information from additional testing. Test accuracy studies often do not take this clinical paradigm into account. They usually report on the status of a test disregarding history and patient characteristics. Assessing tests in isolation of other tests in the diagnostic sequence (including information from clinical history and patient characteristics) exaggerates the diagnostic information that test combinations can provide in practice.

To determine the most cost-effective testing strategy for diagnosing endometrial carcinoma in women with PMB, Clark et al. constructed a decision model and evaluated 12 different strategies for the initial investigation of PMB.

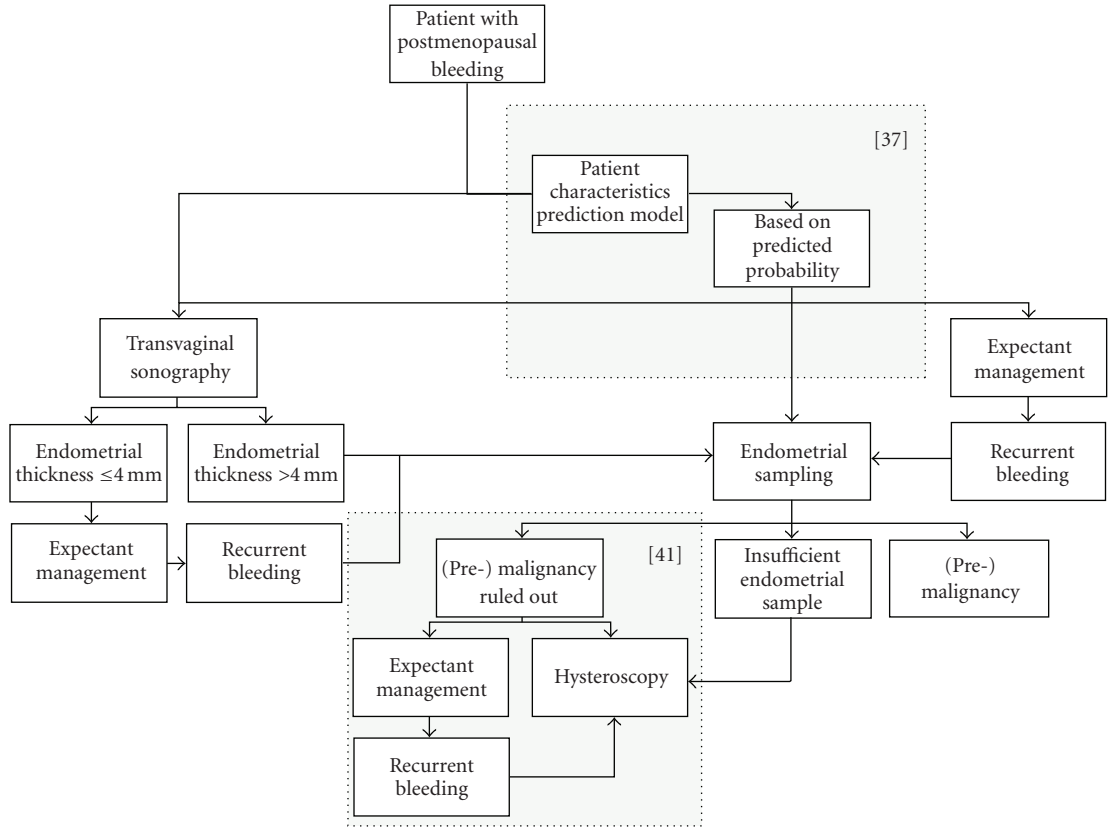

Figure 1: Possible diagnostic pathways for postmenopausal bleeding. The areas surrounded by a dotted square require futher research.

Depending on cancer prevalence (5% versus 10%, resp.), a strategy with TVS as initial investigation with a cut-off of 5 mm or 4 mm followed by endometrial biopsy was most cost effective [1].

There is considerable variability in the endometrial thickness and the likelihood of endometrial carcinoma across women. This variability has been associated with individual patient characteristics including age, time since menopause, obesity, hypertension, diabetes mellitus, and reproductive factors [23, 32–36]. However, guidelines currently used are mainly based on endometrial thickness only, and do not systematically take these additional characteristics into account [12–15].

Inclusion of these individual characteristics may allow for a more refined differentiation of women with the same endometrial thickness. This could result in a more individualised and possibly more accurate and efficient work-up strategy, in which a very high a priori chance of endometrial carcinoma warrants further histological testing, whereas women with a very low prior chance might be reassured even without TVS.

Multivariable models to predict endometrial carcinoma incorporating patient characteristics in the diagnostic work-up for patients with PMB have been developed [37–40]. Khan et al. proposed the use of individual patient data meta analysis in developing these multivariable models to calculate a posttest probability of disease for a different combination of test results (including patient characteristics and information from clinical history) [38].

Figure 1 shows an algorithm with *possible* diagnostic pathways for PMB. In this figure an evidence-based approach is combined with approaches requiring more research. Two areas require further research: (1) probability modelling to calculate the pretest probability of endometrial cancer based on patient characteristics [37] and the implementation of such a model in the diagnostic strategy and finally implementation into daily practice and (2) diagnostic approach to benign pathology. That is wether or not subsequent endometrial cavity evaluation for benign abnormalities should be performed after malignancy has been ruled out [41].

4. General Conclusions and Future Research

Sensitivity of TVS endometrial thickness measurement in women with PMB is still controversial. Future research should aim at achieving a higher accuracy of the diagnostic strategy applied. Such higher accuracy might be achieved by incorporation of patient's characteristics (e.g., age, presence of diabetes, Body Mass Index (BMI), presence of hypertension) in the diagnostic work-up. The incorporation of TVS with patient's characteristics in a diagnostic strategy has been studied and resulted in higher diagnostic accuracy

[37, 39, 40]. Statistical methods can be used to develop and further improve such models and incorporating patient's characteristics with diagnostic tests [38, 40]. Furthermore, by combining and analysing individual patient data from different studies (IPD meta analyses), larger databases can be obtained, in which previously described models can be externally validated [38, 42]. Such models could be incorporated in clinical prediction rules, where the individual probability for endometrial cancer is obtained for each individual woman, and a diagnostic algorithm is developed to maximize the diagnostic accuracy at an acceptable patient burden and health care costs. Such prediction rules are currently also available in reproductive medicine, and comparable to the risk of malignancy index in ovarian tumours [43, 44]. After developing such clinical prediction rules, diagnostic accuracy and clinical applicability should be tested in clinical practice in a prospective multicentre study. If indeed, such model; would lead to higher diagnostic accuracy than TVS alone, office endometrial sampling or office hysteroscopy could then be offered only to those women with a high probability of endometrial cancer and its precursors.

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Review Article

Genetics of Endometrial Cancers

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Endometrial cancers exhibit a different mechanism of tumorigenesis and progression depending on histopathological and clinical types. The most frequently altered gene in estrogen-dependent endometrioid endometrial carcinoma tumors is *PTEN*. Microsatellite instability is another important genetic event in this type of tumor. In contrast, *p53* mutations or Her2/neu overexpression are more frequent in non-endometrioid tumors. On the other hand, it is possible that the clear cell type may arise from a unique pathway which appears similar to the ovarian clear cell carcinoma. *K-ras* mutations are detected in approximately 15%–30% of endometrioid carcinomas, are unrelated to the existence of endometrial hyperplasia. A *β-catenin* mutation was detected in about 20% of endometrioid carcinomas, but is rare in serous carcinoma. Telomere shortening is another important type of genomic instability observed in endometrial cancer. Only non-endometrioid endometrial carcinoma tumors were significantly associated with critical telomere shortening in the adjacent morphologically normal epithelium. Lynch syndrome, which is an autosomal dominantly inherited disorder of cancer susceptibility and is characterized by a MSH2/MSH6 protein complex deficiency, is associated with the development of non-endometrioid carcinomas.

1. Introduction

Endometrial cancer is the most common cancer of the female reproductive tract with 150,000 new cases diagnosed annually worldwide. Approximately 90% of endometrial cancers are sporadic, and the remaining 10% are hereditary. Bokhman have generally categorized endometrial cancer into two broad groups of tumors using both clinical and histopathological variables: estrogen-dependent endometrioid endometrial carcinomas (EECs), or type I, and non-endometrioid endometrial carcinomas (NEECs), or type II tumors (Table 1) [1]. It should be noted that this model is not strict, and only a minority of endometrial cancer may exhibit shared characteristics. For example, mixed serous and endometrioid tumors are being increasingly recognized. Approximately 70% to 80% of new cases are classified as EECs, and other 10% to 20% are designated as NEEC tumors [1]. EECs are strongly associated with the estrogen-related pathway and arise in association with unopposed estrogen stimulation [2]. In contrast, NEECs are unrelated to the estrogen pathways and arise in the background of atrophic endometrium [3]. EECs typically occur in premenopausal and younger postmenopausal women and are usually low-grade and have a favorable outcome, whereas NEECs occur in older postmenopausal women. In addition, NEECs tend to predict a high tumor grade and poor patient prognosis [4, 5]. The first pathway is associated with endometrioid histopathology, and the second is linked to the serous and clear cell subtypes. The precursors of these subtypes are known as atypical hyperplasia and endometrial intraepithelial carcinoma (EIC), respectively. Clear cell cancer, classified as an NEEC, is associated with atypical hyperplasia as well as EIC.

Recent reports suggest that histological differences may be associated with distinct molecular genetic alterations. Molecular genetic evidence indicates that endometrial

carcinomas are likely to develop as the result of a multistep process of oncogenic activation and tumor suppressor inactivation (Table 2) [6].

2. Gain-of-Function Genetic Events

The genes implicated in the gain-of-function events are oncogenes. The important genes related to endometrial oncogenesis or progressions are the *K-ras*,*B-raf, Her2/neu*, *β-catenin, AKT*, and *FGFR2* oncogenes.

2.1. K-ras and B-raf. *K-ras* proto-oncogene mutations are detected in approximately 10%–30% of endometrioid carcinomas [7]. *K-ras* mutations have been identified in endometrial hyperplasias, although at a lower frequency than in carcinomas [8–10]. According to these studies, the gain of the *K-ras* function may represent an early event in endometrioid-type tumorigenesis. During tumorigenesis, activated RAS is usually associated with enhanced proliferation, transformation, and cell survival. Conversely, *K-ras* mutations occur with equal frequency in tumors with and without hyperplasia, and the epidemiologic results seem to suggest that *K-ras* activation is associated with malignant progression of endometrial tumors without the need for transition via hyperplasia [11]. In contrast to endometrioid carcinomas, *K-ras* mutations are extremely rare among serous and clear cell carcinomas [12, 13].

A correlation between colon cancer development and Ras/Raf point mutations in the MAP kinase pathway drives the malignant transformation of colon cancer. In contrast, only a few reports have shown *B-raf* mutations in patients with endometrial cancer. Feng et al. identified a *B-raf* mutation in 21% of patients with endometrial cancers and suggest that the mutation correlated with decreased hMLH1 expression [14]. In contrast, Salevesen et al. described a *B-raf* mutation in only 2% of endometrial cancers; and Kawaguchi et al. and Mizumoto et al. reported no mutation in the patients with endometrial cancer [15–17]. Therefore, a consensus about the role of *B-raf* mutation in the development of endometrial cancer has not yet been developed.

2.2. Her2/neu. *Her2/neu (erbB2)* is an oncogene that encodes a transmembrane receptor tyrosine kinase involved in cell signaling. Either the overexpression or gene amplification of *Her2/neu* proto-oncogene activates receptor and soluble tyrosine kinases. Her2/neu overexpression is detected in about 10%–20% of Grades 2 and 3 endometrioid carcinoma [9, 18, 19]. These studies suggest that Her2/neu overexpression in endometrioid carcinoma characterizes late progression and differentiation events. *Her2/neu* overexpression is detected in approximately 9%–30% of serous carcinomas [20]. Elucidation of the role of Her2/neu in these pathogenic tumor types, therefore, requires further study.

2.3. β-Catenin. *β-catenin*, a component of the E-cadherin family of proteins, is essential for cell differentiation and maintenance of normal tissue architecture, and plays an important role in signal transduction. *β-catenin* also acts as a downstream transcriptional activator in the Wnt signal transduction pathway. A *β-catenin* mutation results in the stabilization of proteins that are degradation resistant, thus resulting in cytoplasmic and nuclear β-catenin accumulation and constitutive target gene activity. The accumulation of *β-catenin* is demonstrated by immunohistochemistry. Several studies have analyzed endometrial cancers, showing that nuclear accumulation of β-catenin is significantly more common in endometrioid lesions (31% to 47%) compared to nonendometrioid histologies (0% to 3%) [21]. In another report, β-catenin nuclear accumulation was more frequent in endometrial hyperplasias than in endometrial carcinoma samples, suggesting a β-catenin role in the early development of this tumor type [22]. In fact, alterations in β-catenin have been described in endometrial hyperplasia that contains squamous metaplasia or morules. Koul et al. found that all *β-catenin* mutated tumors were estrogen-receptor (ESR) positive and most were progesterone-receptor (PgR) positive, thus suggesting a dependence on estrogen stimulation during endometrial carcinogenesis [11]. In contrast, there is no correlation between *β-catenin* mutations and Microsatellite Instability (MI) or *K-ras* or *PTEN* mutations.

2.4. AKT. The phosphatidylinositol 3-kinase (PI3K) AKT pathway is activated in many human cancers and plays a key role in cell proliferation and survival. *PIK3CA* mutations frequently occur with other genetic alterations such as *Her2/neu*, *K-ras,* and *PTEN* in several types of tumors. Endometrial cancer is known to possess various genes alterations which activate the PI3K-AKT pathway. The frequency of mutations for *PIK3CA* in endometrial cancer is reported to be 28% [23]. However, Shoji et al. reported that *AKT1* (E17K) mutations were detected in 2 out of 89 tissue samples and 0 out of 12 cell lines [24]. They suggested that *AKT1* mutations might be mutually exclusive from other PI3K-AKT activating alterations, although *PIK3CA* mutations frequently coexist with other gene aberrations. Additional mutations in AKT family members in endometrial cancers were reported in *AKT2* (D399N, 426T, and 141T) and in *AKT3* (E438D) [25]. Taken together, studies found that 5 out of 41 endometrial cancers have mutations in AKT family members at a frequency of approximately 12%.

2.5. FGFR2. Alterations in the fibroblast growth factor receptor 2 *(FGFR2)* gene causes the receptors to become active, leading to cell proliferation. Byron et al. reported mutations in FGFR2 in 10% of primary uterine tumor samples [26]. Mutations were observed in 16% of the endometrioid histology subtype tumors. In primary endometrioid endometrial cancers, *FGFR2* and *K-ras* mutations were mutually exclusive. Conversely, *FGFR2* mutations were seen together with *PTEN* loss-of-function mutations. The authors also showed that endometrial cancer cell lines with activating *FGFR2* mutations are selectively sensitive to the pan-FGFR inhibitor, PD173074 [27]. In addition, upregulation of FGF2 mRNA expression was observed in endometrial cancer specimens [28]. These data suggest that investigation of these

Table 1: Clinical and pathological features of endometrial carcinoma.

	Type I (EEC)	Type II (NEEC)
Age	Pre- and perimenopausal	Postmenopausal
Behavior	Stable	Progressive
Grade	Low	High
Hyperplasia-precursor	Present	Absent
Unopposed estrogen	Present	Absent
Myometrial invasion	Minimal	Deep
Specific Subtypes	Endometrioid carcinoma	Non-endometrioid carcinoma
Prevalence	70–80%	10–20%
Risk factors	Obesity, anovulation, nulliparity and exogenous estrogen exposure	In atropic endometrium

Table 2: Genetics features of endometrial carcinoma.

	EEC	NEEC
Gain-of Function		
K-ras	15–30%	0–5%
Her2/neu	10–20%	9–30%
β-Catenin	31–47%	0–3%
Loss-of Function		
PTEN	35–50%	10%
P53	10–20%	90%
Genomic instability (microsatellite)	20–40%	0-5%

agents may be therapeutically beneficial for endometrial cancer patients.

3. Loss-of-Function Genetic Events

3.1. PTEN. Endometrial carcinomas are characterized by a variety of genetic alterations, but the most frequent alteration is in the *PTEN* gene. *PTEN*, located at chromosome 10q23, encodes a protein and lipid phosphatase which behaves as a tumor suppressor gene. *PTEN* inactivation is induced by mutations that lead to a loss of expression and is induced to a lesser extent by a loss of heterozygosity. The PTEN protein has both lipid and protein phosphatase activities, with each serving different functions. The lipid phosphatase activity of *PTEN* induces cell cycle arrest at the G_1/S checkpoint. In addition, the upregulation of proapoptotic mechanisms involving AKT-dependent mechanisms is mediated through *PTEN*, as is the downregulation of anti-apoptotic mechanisms through Bcl-2 [29–31]. *PTEN* further acts in opposition to PI3K to control levels of phosphorylated AKT [23, 32]. A PI3K mutation is seen in 36% of endometrioid endometrial cancers and is common in tumors that also carry the *PTEN* mutation. The protein phosphatase activity of *PTEN* is involved in the inhibition of focal adhesion formation, cell spread, and migration, as well as the inhibition of growth-factor-stimulated MAPK signaling [33]. The *PTEN* gene, which acts as a tumor suppressor gene, is present in individuals and causes increased cancer susceptibility, including those with Cowden's syndrome. *PTEN* mutations are the most frequent genetic lesions in endometrial adenocarcinomas of the endometrioid subtype. *PTEN* mutations are reported in 25%–83% of tumors, more frequently in endometrioid carcinomas and microsatellite unstable tumors, and are, thus, the most frequent genetic alteration reported in cancers [34]. *PTEN* gene alterations are associated with metastatic behavior and advanced stage in other cancer types. In contrast, the loss of PTEN function is an early event in endometrial tumorigenesis. Several groups have described a concordance between MI status and *PTEN* mutations; the mutations occur in 60%–86% of MI-positive endometrial carcinoma EEC cases, but only occur in 24%–35% of MI-negative tumors. Genetic alterations that account for *PTEN* protein inactivation include various mutations, a loss of heterozygosity (LOH), or promoter hypermethylation, with mutations occurring the most frequently [30]. *PTEN* promoter methylation is observed in 19% of cancers and is significantly associated with metastatic disease [35]. Kim et al. reported that *PTEN* and *K-ras* double-mutant mice ($Pten^{d/d}K\text{-}ras^{G12D}$) exhibited dramatically accelerated endometrial cancer development compared to cancers formed from a single *PTEN* or *K-ras* gene mutation [36]. These results suggest a synergistic effect of dysregulation of the *PTEN* and *K-ras* signaling pathways during endometrial tumorigenesis.

3.2. P53. The *p53* gene is located on chromosome 17 and is important in preventing the propagation of cells with damaged DNA. *p53* mutations or TP53 overexpression is twice as frequent in tumors without hyperplasia (estrogen unrelated) than in those with hyperplasia (estrogen related) [11, 37]. This is consistent with other data in which the most striking genetic alteration, present in about 90% of serous carcinomas (estrogen-unrelated NEEC), is a *p53* mutation [38]. In other reports, statistically significant correlations were observed

between *p53* alterations and non-endometrioid histology type, high-grade tumors, and the absence of the progesterone receptor [39]. On the other hand, *p53* genetic alterations were observed in 17% of endometrioid carcinomas, which were primarily Grade 3 [40]. The exact mechanisms causing this mutation are still not well characterized. In response to DNA damage, nuclear *P53* accumulates and causes cell cycle arrest by inhibiting Cyclin D1 phosphorylation of the Rb gene and thereby promotes apoptosis. Therefore, mutated *P53* results in a nonfunctional protein that accumulates in the cell and acts as a dominant negative inhibitor of wild-type *P53*, leading to propagation of aberrant cells. *p53* mutations in endometrioid carcinoma are a late event during progression or differentiation. *P53* alterations play a relatively minor role in clear cell type endometrial carcinoma in comparison to the serous type [41]. *p53* mutations are also rarely observed in ovarian clear cell adenocarcinomas in comparison to endometrioid adenocarcinomas [42]. As a result, it is possible that the pathogenesis of clear cell carcinoma in the female genital tract arises from a unique pathway [43].

4. Genomic Instability

The most important types of genomic instability in endometrial cancers are MI and chromosomal aneuploidy. DNA mismatch repair (MMR) deficiency, detected as MI, is the most common molecular phenotype in endometrioid cancer, as *PTEN* tumor suppressor gene mutations. MI is seen in cancers (colonic, endometrial, and others) of patients with hereditary nonpolyposis colon cancer (HNPCC) and is also present in 28% of sporadic endometrioid cancers but is not present in serous cancers [40]. MI is distributed almost equally among the three histopathological tumor grades of endometrioid cancers. However, MI is rare in the clear cell type [44]. HNPCC patients with endometrial cancers have an inherited germline mutation in *MLH-1*, *MSH-2*, *MSH-6*, or *PMS-2*, but endometrial cancer only develops after the instauration of a deletion or mutation in the contralateral *MLH-1*, *MSH-2*, *MSH-6*, or *PMS-2* allele. Following this, the deficient MMR (MLH-1, MSH-2, MSH-6, or PMS-2) causes the acquisition of MI and the development of the tumor. Inactivation of the mismatch repair gene *MLH1* by methylation of the promoter seems to be the most frequent cause of MI in sporadic endometrioid carcinomas, followed by a loss of the expression of other two mismatch repair genes, the *MSH2* and *MSH6* genes. The mechanism for the inactivation of *MSH2* is still not clear, as promoter methylation and mutations are rare. *MSH6* inactivation is usually caused by a mutation.

Aneuploidy is frequent in serous cancers, and is uncommon in endometrioid cancer. When present, aneuploidy is exhibited predominantly by Grade 3 tumors [45, 46]. These data suggest that a different type of genomic instability is associated with the different histopathological-type tumors. However, in some reports, no significant correlations were found to exist with either the *K-ras* or *p53* mutations [7, 11, 47].

Telomeric attrition triggers genomic instability in certain cancer types. Both EEC and NEEC cells have short telomeres in endometrial cancer. However, only NEECs are significantly associated with critical telomere shortening compared to adjacent morphologically normal epithelium, thus suggesting that telomere shortening contributes to the initiation of NEECs but not EECs [48]. The authors also proposed a model in which telomere attrition gives rise to the initiation of NEECs and the progression of EECs.

5. Genetics Events outside the Cancer Pathway

Genetic variation acting either within or outside of the cancer cell may determine the outcome of interaction with exogenous or endogenous carcinogens. Endometrial stimulation by estrogens without the differentiating effects of the progestins is a primary etiologic factor associated with the development of endometrial hyperplasia and carcinoma [3]. There is evidence that estrogens and some of their metabolites are involved in the endometrial cancer pathogenesis. Estrogens and some of their derivatives are genotoxic and induce DNA damage, which if not removed could, thus, contribute to an increased risk of malignancy. Defects in the estrogen metabolism can result in defective apoptosis, DNA repair, and proliferation [49, 50]. Estrogens mediate their effects via the estrogen receptors (ESRs), estrogen receptor alpha (ESR1) and estrogen receptor beta (ESR2), which activate its metabolic pathways. The polymorphisms of ESR1 and ESR2 suggest an association with an increasing risk of developing endometrial cancer [51]. Cytochrome P450 1B1 CYP1B1 is a constitutively expressed and inducible enzyme with a central role in the oxidative metabolism of a wide range of endogenous and exogenous compounds including many carcinogens [52, 53]. Saini et al. reported that *CYP1B1* depletion in endometrial cancer cells leads to decreased cellular proliferation and induced G0-G1 cell cycle arrest, thus suggesting that CYP1B1 inhibition in endometrial cancer cells could be a useful therapeutic approach [54]. Progesterone or its synthetic form has been used as a primary treatment or palliative treatment of advanced and recurrence endometrial cancer, because progesterone inhibits estrogen-induced endometrial proliferation. In addition, the loss of progesterone-mediated Wnt signaling inhibition in the endometrium plays a rate-limiting role in tumor onset and progression [55].

6. Inherited Predisposition

6.1. Lynch Syndrome. Lynch syndrome, or hereditary nonpolyposis colorectal cancer (HNPCC), is characterized by an increased risk for colorectal cancer. Endometrial cancer is the most common malignancy in patients with Lynch syndrome or HNPCC [56]. Lynch syndrome is caused by an inherited mutation in the MMR gene family, such as *MLH1*, *MSH2*, *MSH6*, *PMS1,* or *PMS2* [57]. The age at diagnosis of Lynch syndrome associated endometrial cancer is approximately 2 decades younger than that for sporadic endometrial cancers [58]. Parc et al. demonstrated that 34% of young patients

with endometrial cancer (median age 46) were associated with MI, 57% of the MI positive group showed an absence of *hMLH1* expression, 19% showed an absence of *hMLH2* expression, and 23.8% demonstrated a normal expression of both proteins, while 9.5% of all patients were diagnosed with Lynch syndrome [59]. In another report, the development of the latter tumors of Lynch syndrome is significantly associated with MSH2/MSH6 protein complex deficiency [60].

6.2. Familial Site-Specific Endometrial Carcinoma. The clustering of endometrial carcinoma alone, termed as familial site-specific endometrial carcinoma, may constitute a separate entity. Eight percent of this group have been reported to have germline MMR mutations [61]. This mutation rate is lower than that of Lynch syndrome with endometrial cancer patients, of whom 15% show MMR mutations [62]. The difference in MMR, mutations, therefore suggests the existence of different genetic alteration pathways in familial site-specific endometrial carcinoma.

7. Malignant Mixed Mullerian Tumors (MMMTs)

Carcinosarcomas (malignant mixed mullerian tumors, or MMMTs) are currently excluded from uterine sarcoma and classified as metaplastic carcinoma, and many studies include these as NEECs [63]. However, endometrial carcinoma and MMMTs develop along distinctive molecular genetic pathways and exhibit different biological features. In MMMT, *p53* alterations occur early, during progression, just prior to clonal expansion and acquisition of genetic diversity [64]. In addition, changes in the AKT/β-catenin pathway may be essential for both the establishment and maintenance of phenotypic characteristics of MMMTs, playing key roles in the regulation of E-cadherin through transactivation of the *Slug* E-cadherin repressor gene [65]. Vaidya et al. reported that according to the discrepancy in survival the patients of MMMT should not be included in studies of endometrial cancers [66]. From this viewpoint, future studies will identify factors to classify these diseases.

8. De-Differentiation of Endometrioid Tumors

Mixed serous and endometrioid tumors have serous components that may be related to the "de-differentiation" of endometrioid tumors. This concept would explain the presence of overlapping EEC and NEEC features, both morphological and molecular in some tumors [67].

9. Epigenetic Changes

Aberrant CpG island hypermethylation in promoter regions occurs in many cancer-related genes, including those associated with cell cycle control, apoptosis, and DNA repair. Usually, unmethylated CpG islands become methylated, causing transcriptional silencing in cancer cells. Banno et al. reported that the frequencies of aberrant hypermethylation were 40.4% in *hMLH1*, 22% in *APC*, 14% in *E-cadherin*, and 2.3% in *RAR-*β in endometrial cancer specimens [68]. However, no aberrant DNA methylation was found in the *p16* gene. Other genes inactivated by promoter hypermethylation in endometrial cancer include PgR [69], the cell cycle control genes 14-3-3 sigma [70], homeobox gene HOXA11, thrombospondin-2 gene (THBS2) [71], paternally expressed gene 3 (PEG3) [72], as well as the detoxifying enzyme glutathione S-transferase P1 (GSTP1) [73]. The impact of methylation on these genes in endometrial cancer development has not been well established. In endometrial cancers, differential DNA methylation patterns are detected in EICs and NEECs, suggesting divergent epigenetic backgrounds and unique tumorigenic pathways [74]. Promoter hypermethylation is a frequent event in EIC but not NEECs [75]. Many of the tumor suppressor pathways that are mutated in EIC can also be inactivated by hypermethylation.

10. The Future

The goal of screening endometrial cancers is to identify all patients who have a risk for developing this disease. Therefore clarification of the molecular and genetic mechanisms of development or progression of this disease is required. Understanding the genetic changes underlying cancer development or progression in the different histological subtypes is important for discovery of new targets for both diagnosis and therapy for individual patients.

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Research Article

The Association between Primary Endometrioid Carcinoma of the Ovary and Synchronous Malignancy of the Endometrium

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Objective. Ovarian and endometrial cancers coincide rather frequently in the same patient. Few data are available on the involvement of the specific morphological subtypes. To identify histological pathways in the synchronous occurrence, a population-based study was performed in The Netherlands. *Methods*. Using the national pathology database (PALGA) information of ovarian cancers and of earlier or later cancer in the endometrium was obtained. 5366 Patients were identified with primary malignant epithelial or borderline malignancy. *Results*. In 157 cases (2.9%) a new primary malignancy in the endometrium was diagnosed (146 within 1 year). The ratio of observed versus expected number of synchronous malignancy in the endometrium was estimated at 3.6 (95% CI: 2.7–4.7). Among 460 ovarian endometrioid carcinoma patients 53 cases showed a second primary endometrial cancer; 40 out of these 53 cases (75.5%) showed at both organ sites an endometrioid adenocarcinoma. *Conclusion*. These findings suggest an important role for the endometrioid subtype and prompt to mechanism-based studies incorporating molecular techniques.

1. Introduction

Approximately 10% of all patients with ovarian cancer appear to have endometrial cancer synchronously, and 5% the other way around [1]. However, it is often unclear whether this confers to primary tumors or to metastasis from the ovary to the endometrial tumor or vice versa [2, 3]. As described by Herrinton et al., both of these tumors are probably mechanistically linked to reproductive hormones. But it is also possible that the joint presence of these two tumors in different organ sites indicates to etiologically distinct and until now unknown conditions [4].

According to the sparse literature, and which mainly consists of case series, the simultaneous presence of primary cancers in the ovary and the endometrium is not well documented. A strong association has first been quantified by Sheu et al. [5]. More recently, Van Niekerk et al. [6] calculated for ovary cancer the observed versus expected numbers of cancer in the endometrium to be a ratio of 62.3. This strong relationship prompted us to further evaluate the risk by histological subtype of the epithelial ovarian tumors.

Most ovarian tumors are adenocarcinomas of different histological subtypes, derived from the surface epithelium of the ovary [7]. They manifest in various morphological forms as (cyst)adenocarcinomas with serous, mucinous, clearcell, or endometrioid differentiations. Further to that it is known that primary endometrial neoplasms include the same subtypes [8].

2. Material and Methods

2.1. Design and Patients. We examined the association of the various histopathological subtypes of ovarian epithelial cancer in relation to second primary endometrial cancers using two random samples of the nationwide pathology database "PALGA" in The Netherlands. Every record in the

PALGA database contains a summary of the full pathology report and diagnostic codes similar to the Systematized Nomenclature of Medicine (SNOMED) classification of the College of American Pathologists. From the first sample of the years 1987–1993 we investigated 4577 patients and from a second sample of the years 1996–2003, a number of 789 cases [6]. Of these 5366 patients with a new malignant or borderline malignant epithelial ovarian cancer diagnosis we also obtained all the other histopathologically confirmed diagnoses of primary invasive malignancies in the endometrium if present, and earlier than, concurrently or after the ovarian tumor was diagnosed.

The scientific committee of PALGA approved the study protocol beforehand.

2.2. Measurements. Erroneous coding of the pathologist can hamper the interpretation of diagnostic codes. Therefore, we also studied a second more recent and smaller PALGA dataset. The diagnostic codes in the PALGA database were reviewed, and the corresponding pathology conclusions, that is, PALGA codes and PALGA conclusions, as well. Two experienced pathologists (GPV, JB) reviewed all reports.

The criteria of Young and Scully [8] were used for interpretation of synchronous primary tumors of both organs or of metastasis from one organ to the other. The diagnosis of independent primary tumors could be made in most cases. Histological dissimilarity of the tumors at both organ sites makes two independent synchronous tumors highly probable. In addition, if the codes and conclusions report no or only superficial myometrial invasion of the endometrial tumor and/or both tumors were confined to the ovary and uterus, the diagnosis of two independent primary tumors could be reliably made.

If it was doubtful whether or not we were dealing with a metastasis or recurrence of the primary malignant tumor of the ovary or a new secondary type of tumor, these uncertain diagnosis and difficult cases were excluded.

2.3. Data Analysis. Descriptive analysis was applied to the ovarian epithelial cancers for histopathological subtypes. For the major histological subtypes the number of patients observed with a second primary endometrial cancer was contrasted to the expected number. Expected numbers were calculated from the 5-year age specific rates of 2nd primaries in the total ovary cancer group. The observed versus expected ratio and its 95% confidence interval (CI) were calculated according to the method of Byar [9].

3. Results

157 (2.9%) cases of the reviewed 5366 patients with ovarian epithelial cancer appeared to have a second primary malignant tumor in the endometrium (146 within 1 year). In both samples this percentage was identical (2.9%). The mean age at diagnosis of all patients with ovarian cancer was 59.6 years; the 157 cases aged 58.6 years on average. The histological subtypes and age results are shown in Table 1. In general, three quarters of all patients aged 50 years and over, except for patients with a mucinous tumor, of whom almost half of them are under the age of 50.

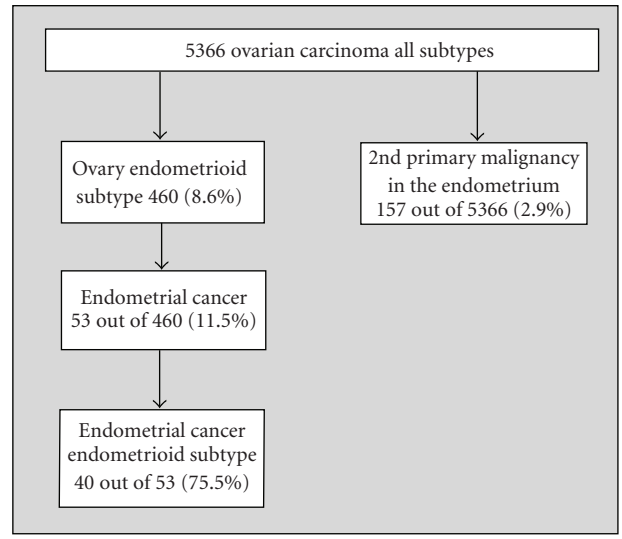

Figure 1: Number of second primary tumors in the endometrium in 460 patients with endometrioid ovary cancer.

If a second primary cancer is present in the endometrium, the endometrioid carcinoma subtype in the ovary is found to be more frequent in the younger age-group (<50), while mucinous and serous cancer are less frequent.

As can be derived from Figure 1, the relative frequency of endometrioid carcinoma is 8.6%, and also highly prevalent if a second primary is present in the endometrium ($n = 53$, 11.5%). We observed that 40 out of these 53 cases (75.5 %) had an endometrioid adenocarcinoma in the ovary as well as in the endometrium.

In Table 2, the observed versus expected numbers of cancer of specific histology are presented among the 157 cases, having both ovary cancer and a second primary cancer of the endometrium. For the 53 (33.8%) cases with endometrioid cancer in the ovary the observed versus expected ratio was calculated to be 3.6 (95% CI: 2.7–4.7), implicating a more than threefold risk of second primary in the endometrium. The other histological subtypes did not reveal such an excess risk, but a lower finding (mucinous and serous carcinoma).

4. Discussion

The present study with data from the PALGA nation-wide pathology archives in The Netherlands reports a strong association between the occurrence of epithelial malignancy in the ovary of the endometrioid histological subtype and a second primary malignancy in the endometrium. The study period was comparable with the study of Vernooij et al., also from The Netherlands [10]. The latter nationwide study focused on survival of patients with ovarian cancer and hospital type. The percentages for the different histological subtypes of ovarian carcinomas (Table 1) are very much

Table 1

(a) All epithelial ovarian cancers according to histological type and age at diagnosis.

Histological type of ovarian cancers	Patients *n*	%	Range	Median	Mean	% <50 years	% ≥ 50 years
Adenocarcinoma	1456	27.1	18–97	64	62.5	16.3	83.7
Clearcell carcinoma	236	4.4	28–88	58	59.2	23.7	76.3
Endometrioid carcinoma	460	8.6	20–86	59	58.8	25.4	74.6
Mucinous carcinoma*	733	13.7	14–92	52	52.1	44.9	55.1
Serous carcinoma*	1801	33.6	16–100	62	59.9	22.9	77.1
Others*[a]	680	12.7	16–100	62	61.5	20.9	81.2
Total	5366	100	14–100	61	59.6	24.2	75.8

(b) Subset of epithelial ovarian cancers with malignancy in the endometrium.

Histological type of ovarian cancers	Patients *n*	%	Range	Median	Mean	% <50 years	% ≥ 50 years
Adenocarcinoma	49	31.2	34–85	59	59.8	22.5	87.5
Clearcell carcinoma	3	1.9	53–78	71	67.3	0.0	100.0
Endometrioid carcinoma	53	33.8	36–80	53	54.9	32.1	67.9
Mucinous carcinoma	7	4.5	49–73	57	59.7	14.3	85.7
Serous carcinoma*	27	17.2	31–78	68	64.1	11.1	88.9
Others[a]	18	11.5	46–78	55	57.9	22.2	79.8
Total	157	100	31–85	57	58.6	22.9	77.1

*borderline malignancies included.
[a]including mixed carcinomas, anaplastic carcinoma, malignant Brenner tumor, carcinosarcoma, adenosquamous carcinoma, squameus cell carcinoma etc.

Table 2: Association among 157 cases between subtype of epithelial ovarian cancer and second endometrial cancer.

Histology of ovarian tumors	Observed	Expected	O/E**	95%-CI
Adenocarcinoma	49	42.82	1.14	(0.85–1.51)
Clearcell carcinoma	3	7.57	0.40	(0.08–1.16)
Endometrioid carcinoma	53	14.93	3.55	(2.66–4.64)
Mucinous carcinoma*	7	19.30	0.36	(0.15–0.75)
Serous carcinoma*	27	52.62	0.51	(0.34–0.75)
Others	18	19.75	0.91	(0.54–1.44)

*including borderline malignancies.
**Observed versus Expected number of cases of synchronous endometrial cancer.

concordant across both study groups [10]. Only a slight difference in the "other" and "adenocarcinoma" categories was noticed. Precise percentages about the histological subtypes of ovarian carcinomas are hardly found in the international literature and gynaecopathological leading handbooks. The reason is that most referred studies are often small, have incomplete data, and are difficult to compare. Moreover, if histological subtypes are given, the percentages in literature and overviews mostly also include benign ovarian neoplasm's [11].

We found in both databases, 1987–1993 and 1996–2003, a similar 2.9% incidence of synchronous primary ovarian and endometrial cancer. This is in accordance with the study of Chiang et al. [1] and Williams et al. [12]. The objective of their study was to clarify the potential factors that influence the survival of patients with simultaneous primary malignancies in the endometrium and ovary. The group of Chiang [1] retrospectively reviewed the medical records and pathologic reports from the National Taiwan University Hospital Cancer Registry from the period 1997–2005. They detected 27 cases out of 1004 (2.7%) ovarian carcinoma patients with a malignancy of the endometrium as well. Williams et al., [12] identified 1.355 synchronous ovarian and endometrial cancer cases in a total of 56.986 primary ovarian cases (2.4%) diagnosed in the period 1973–2005. They used the SEER definition of synchronous cancers, that is, cancer of the endometrium (C54.1) and ovary (C56.9). Women were excluded from analysis if they were diagnosed with other primary cancers (e.g., from breast, colon, or cervix).

Recently, the simultaneous presence of primary cancers in the ovary and the endometrium has been quantified

by Soliman et al. [2], and by Hemminki et al. [7, 13]. They also specified the relation to the histological subtype of the ovarian tumor. The median age in our study and in Soliman's study was almost similar at 53 and 50 year, respectively, for the endometrioid carcinomas. In our study 53 (33.8%) out of 157 patients having a second malignancy in the endometrium had an endometrioid malignancy in the ovary, while 40 (75.5%) out of those 53 cases also showed an endometrioid subtype in the endometrium. The study of Soliman reported 57 (68%) individuals with endometrioid malignancy in the ovary and endometrium out of 84 cases having indepent primary cancers in both of these organs. It remains unclear, however, from how many patients with ovarian malignancy these 84 women originated.

Hemminki et al. [7] reported an age-standardized incidence ratio of SIR = 86.7, (95% CI: 46.0–148.6) for ovarian endometrioid cancers and simultaneous primary endometrial carcinoma (13 cases). The difference in outcome with our investigation may be due to the character of their database, the Swedish Family Cancer-Database, which differs from our national pathology database of all cancers and not discerning family background.

In a different study Hemminki and Granström [13] describe a strong link of familial ovarian and endometrial cancers, which appears to be specific for the endometrioid morphology. They calculated an SIR = 3.40, (95% CI: 1.80–5.83), implicating a 3.4-fold risk of endometrioid ovarian cancer among daughters of mothers presenting endometrial cancer. Unfortunately, our database did not contain family background information.

Endometrioid adenocarcinoma is the most common type of endometrial adenocarcinonomas occurring in more than three-quarter of all cases [14]. Hyperestrogenic status plays an essential part in the origin of this subtype of endometrial carcinoma, as most of these patients have complaints of irregular menses, infertility, obesity, and polycystic ovary disease. As described by Chiang et al., [1] the pathogenesis of synchronous endometrial and ovarian cancer is unclear. The theory of a secondary Müllerian system says that the epithelium of cervix, uterus, fallopian tubes, ovaries, and peritoneal surface have shared molecular receptors responding to carcinogenic stimulus leading to the development of multiple primary malignancies synchronously. They further describe that the hypothesis provides an explanation for synchronous malignancies of similar histology. This may not be the case in synchronous cancers of dissimilar histology, and there a different mechanism underlying this interesting phenomenon should be operating. Further studies are needed to disclose the pathogenesis of synchronous ovarian and endometrial cancer.

Halperin et al. [15] compared 16 cases of simultaneous independent primaries of endometrium and ovary, presenting the same histological subtype, and 12 cases of primary endometrial cancer demonstrating ovarian metastases. The only clinical parameter differentiating significantly between the groups was the prevalence of familial cancer, being more frequent in the group of metastatic tumors. They further notified that the application of immunohistochemical analysis of estrogen and progesterone receptors is of value in the differentiation between cases of simultaneous independent carcinomas of endometrium and ovary versus cases of endometrial carcinoma with ovarian metastasis. We believe that immunohistochemical protein analysis will probably not discriminate for the same primary epithelial morphological subtypes arising in different organs. It is expected that concomitant tumors with exactly the same morphology arising in ovary and endometrium, especially the endometrioid carcinoma, will show the same immunohistochemical expression patterns.

Molecular markers emerging as mutation from PTEN and LOH analysis as described by Ricci et al. [16] may be more suitable to establish a correct final diagnosis in distinguishing between metastasis from primary synchronous carcinomas of the endometrioid subtype of the ovary and endometrium . The potential of these molecular markers has to be evaluated in larger series, because so far this has been done in only few patients [16, 17].

In the study of Soliman et al., 7 (7%) out of 102 women with synchronous endometrial and ovarian cancer had either clinical or molecular criteria suggestive for Lynch syndrome [18]. They believe that genetic evaluation of women with synchronous ovarian and endometrial cancer who had a prior history of at least one first-degree relative with an HNPCC-associated cancer may appropriately be identified as women with Lynch syndrome.

In summary, our results indicate that in 2.9% of patients diagnosed with epithelial ovarian malignancy a second new primary malignant tumor is occurring in the endometrium, especially in women diagnosed with an endometrioid histological subtype (33.8%). This histological tumor subtype is most prevalent in the age category of 50–54 years (30.2%) and shows a ratio of observed versus expected number of cases with a for endometrium malignancy being 3.6 (95% CI: 2.7–4.7).

Endometrioid adenocarcinoma at both organs sites is by far out the most prevalent subtype (75.5%). The other histological subtypes do not reveal such excess risks. These findings should stimulate further molecular studies into the possibly carcinogenic pathways.

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Review Article

Controversies in Surgical Staging of Endometrial Cancer

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Endometrial cancer is the most common gynaecological malignancy and its incidence is increasing. In 1998, international federation of gynaecologists and obstetricians (FIGO) required a change from clinical to surgical staging in endometrial cancer, introducing pelvic and paraaortic lymphadenectomy. This staging requirement raised controversies around the importance of determining nodal status and impact of lymphadenectomy on outcomes. There is agreement about the prognostic value of lymphadenectomy, but its extent, therapeutic value, and benefits in terms of survival are still matter of debate, especially in early stages. Accurate preoperative risk stratification can guide to the appropriate type of surgery by selecting patients who benefit of lymphadenectomy. However, available preoperative and intraoperative investigations are not highly accurate methods to detect lymph nodes and a complete surgical staging remains the most precise method to evaluate extrauterine spread of the disease. Laparotomy has always been considered the standard approach for endometrial cancer surgical staging. Traditional and robotic-assisted laparoscopic techniques seem to provide equivalent results in terms of disease-free survival and overall survival compared to laparotomy. These minimally invasive approaches demonstrated additional benefits as shorter hospital stay, less use of pain killers, lower rate of complications and improved quality of life.

1. Introduction

Endometrial cancer is one of the most common gynaecological malignancies in developed countries and, unfortunately, the incidence of endometrial cancer is rising. This may be attributed to risk factors, like increased life expectancy, obesity, diabetes, late menopause, and use of Tamoxifen [1–3]. Endometrial cancer spreads towards myometrial wall, cervix, and lymphatic stations of pelvic and paraaortic lymph nodes [4]. Prognosis of this malignancy depends on various factors: histological type of the tumour, the depth of invasion into the myometrium, and lymph node involvement [1–4].

Surgical management of endometrial cancer is a challenge. It is important to balance risks and benefits of each surgical option, avoiding both over- and undertreatment.

The Gynaecologic Oncology Group (GOG) trial published in 1987, lead to a crucial change from clinical to surgical staging. By this study, pelvic and paraaortic lymphadenectomy have been introduced in the oncological practice of endometrial cancer on the basis of the international federation of gynaecologists and obstetricians (FIGO) criteria [5]. The new FIGO classification addressed new information about prognostic predictors. However, the extent of surgical staging, the definition of high-risk patients who benefit from complete staging, numbers of lymph nodes, and anatomical limits in paraaortic area still lack standardisation [6–10].

In the present manuscript, we sought to review the available evidences and to discuss controversies in surgical management of endometrial cancer, considering the following items:

(1) Complete surgical staging: Role of lymphadenectomy in endometrial cancer;

(2) Preoperative evaluation: Predictors of lymph node metastasis;

(3) Intraoperative detection of lymph node metastasis;

(4) Extent of lymphadenectomy;

(5) Surgical approach for staging of endometrial cancer.

2. Complete Surgical Staging: Role of Lymphadenectomy in Endometrial Cancer

A complete surgical staging, including lymphadenectomy is the gold standard to evaluate lymph node involvement, the most common site of extrauterine spread of endometrial cancer. However, the exact role, indications, and extent of lymphadenectomy in endometrial cancer patients remain controversial [4, 6, 11–13]. A recent Cochrane protocol confirmed the prognostic role of lymphadenectomy, while its therapeutic role, the advantages in terms of survival, and extent of anatomical standardization are under debate [4]. Lymph node metastasis has been described, as well as one of the strongest predictors of disease recurrence and as a guide for subsequent adjuvant therapy in patients with positive lymph nodes. Patients with stage I disease have more than 90% 5-year survival rate compared to those with nodal metastasis who have survival rates ranging from 38% to 75% [14].

In a retrospective study, Bernardini et al. verified that a substantial number of patients with grade 1 endometrial cancer, based on preoperative and intra operative assessment, had higher grade disease on final pathology. Lymphadenectomy did not affect survival in these patients; however, it could identify patients with advanced disease and assist in tailoring adjuvant therapy for those with adverse risk factors [15].

Nevertheless, the exact therapeutic benefit in terms of survival associated with lymphadenectomy is difficult to define, especially in early stages.

Recently, a multicentric randomized controlled trial (ASTEC) demonstrated no evidence of benefit for systematic lymphadenectomy in terms of overall, disease-specific, and recurrence-free survival in women with endometrial cancer. A total of 1408 women, with a preoperative diagnosis of endometrial cancer confined to the corpus uteri were randomized to standard surgery or standard surgery plus pelvic lymphadenectomy. A similar proportion of women in both groups received postoperative radiotherapy. After a median follow up of 37 months, there was no difference in overall survival between two groups and the analysis of disease or treatment-related death was in favour of the standard surgery group. Moreover, there was a significant benefit in recurrence-free survival for the standard surgery group, and surgical complication rates were higher in the lymphadenectomy group [16]. The results of the ASTEC trial, however, have been widely discussed. One important concern to limit the generalization of these results is the low number of lymph nodes (median of 12 lymph nodes) removed in the lymphadenectomy group. In the literature, excision of higher number of nodes was proved to have an effect on overall survival, especially in patients with high-risk and intermediate-risk endometrial cancer [13, 17–19]. In addition, the ASTEC study did not assess the paraaortic nodes, which can be involved in up to 67% of patients with pelvic lymph node metastasis as demonstrated by Mariani et al. [20]. Another issue to be considered is the high rate of low-risk patients (STAGE 1A-1B grade 1-2) included in lymphadenectomy group, and subsequently low rates of pelvic node metastasis. Finally, the follow up duration was considered too short for a survival study of a malignant disease.

Furthermore, complete staging was not found to improve overall survival and disease-free survival in another RCT that compared treatment of early stage endometrial carcinoma with and without systematic pelvic lymphadenectomy [21].

A retrospective database review considered 12,333 patients undergoing surgical staging by lymphadenectomy and stratified them in groups: a low-risk (Stage IA, all grades and Stage IB, grade 1 and 2) and a medium- to high-risk group (Stage IB, grade 3 and Stage IC-IV, all grades). In low-risk group, there was no significant benefit of nodal resection, while a multivariate analysis demonstrated that in the medium- to high-risk group a more extended nodal resection was associated with increased 5-year survival [13].

3. Preoperative Evaluation: Predictors of Lymph Node Metastasis

There is general agreement that definitive staging of endometrial cancer is based on pathological examination, but an accurate preoperative risk stratification guides to the appropriate type of surgery, avoiding the morbidity associated with unnecessary procedures [2, 6].

Both histopathological and clinical risk factors have been identified as predictors of lymph node involvement: histological type, grade of tumour, myometrial invasion, and cervical infiltration [2–6, 14, 22, 23].

3.1. Preoperative Endometrial Biopsy. Tumour histological grading remains the most important preoperative factor in identifying risk status. There is only poor correlation between histological grade of tumour based on endometrial biopsy or D&C and final pathology. Histological upgrading was demonstrated in 18% of endometrial cancer patients after definitive histological examination [2, 24, 25]. On the other hand, the identification of clear cell or papillary serous carcinoma was demonstrated to have increased risk of distant metastasis, even in case of endometrial confined lesions [26].

3.2. Imaging Modalities and Risk Stratification. As regards preoperative clinical staging, several studies proposed that identification of patients with deep myometrial invasions (more than 50%; FIGO stage IC) and preoperative knowledge of cervical stroma infiltration (FIGO stage IIb) are important determinants for surgical decision [27, 28]. Several techniques are used to evaluate the depth of myometrial invasion and cervical infiltration. In this context, Magnetic Resonance Imaging (MRI), Computed Tomography (CT), and Transvaginal Sonography (TVS) are the main diagnostic tools used. Comparing the diagnostic accuracy of these techniques, several studies demonstrated no significant differences in performance for both myometrial extent and cervical invasion [29, 30]. A recent prospective study compared the high-frequency (5.0–9.0 MHz) TVS and contrast-enhanced MRI in preoperative staging of endometrial cancer. Authors concluded that, in expert hands, TVS seems to be a

feasible and more economic imaging method with accuracy comparable with MRI and it can be proposed as first-line option for evaluation of myometrial invasions and cervical spread [31].

Some imaging modalities can also investigate the status of lymph nodes, but the results, to date, have been disappointing. MRI and CT/PET are statistically comparable, but have only a limited specificity in detecting pelvic and paraaortic node metastasis [29, 30].

4. Intraoperative Detection of Lymph Node Metastasis

There is currently no validated method for predicting lymph node metastasis. Accordingly, many authors support a comprehensive surgical staging for endometrial cancer. Although intraoperative evaluation methods for lymph node metastasis, as frozen section examination and node palpations, are often used in surgical oncological practice, there is scientific agreement that they are inaccurate.

4.1. Lymph Node Palpation. Girardi et al. found that 37% of nodal metastases were less than 2 mm and only 7% larger than 2 cm [32]. Several authors demonstrated the high false-negative rates for intraoperative lymph node palpation (26% by Eltabbakh and 36% by Arango et al.) [33, 34].

4.2. Frozen Section. The incidence of lymph node metastasis is related to the depth of invasion and tumor grade. Intraoperative frozen section might identify patients who are at risk for extrauterine spread and required complete surgical staging.

Frozen section may help to further stratify for the risk of final pathology but is not entirely accurate [35]. To date, available evidence does not clearly support modulating the extent of surgical staging according to the results of frozen section examination.

Case et al. evaluated in a prospective-blinded study the accuracy of frozen section in surgical management of endometrial cancer. There was a poor correlation between frozen and final section: only 67% for invasion depth and 58% for tumour grade. This study demonstrated a clinically relevant upstaging in 18% of patient who underwent lymphadenectomy [36]. Another study by Frumovitz et al. verified that the combination of intraoperative frozen section analysis for histological grade and depth of myometrial invasion correlates poorly with final pathologic grade and stage in patients with apparent grade I and II tumor [37].

The finding of negative pelvic nodes at intraoperative frozen section has been proposed to guide further surgical management during surgical staging of endometrial cancer. A recent study by Papadia et al. confirmed that frozen section underestimated the risk of lymph node involvement in 16% of cases when compared with final section pathology [38]. Another trial by Pristauz et al. verified that intraoperative frozen section of pelvic nodes is not accurate to tailor the extent of lymphadenectomy. In this study, examination of pelvic nodes had a sensitivity of 41% and a false negative rate of 59% [39].

4.3. Sentinel Lymph Node Examination. In an effort to decrease the morbidity resulting from lymphadenectomy, several authors proposed the sentinel lymph node (SN) detection approach. Although it is still under investigation, this technique has several potential benefits in surgical management of endometrial cancer. Data on feasibility and utility are rapidly increasing. However, few studies have concluded the feasibility of SN in endometrial cancer [40–50]. It has been verified by many authors that SN detection may help to evaluate regional lymphatic status and to select the group of patients that must be submitted to a complete lymphadenectomy, avoiding surgical invasiveness in early stage cancer [49, 50]. Most investigators performed intramyometrial or intracervical punctures [40–50]. The identification rates were 61.5% to 67%, when blue dye was injected into the subserosal myometrium of the fundus, and 83% by additional injections of blue dye into the cervix [40]. The modern trend in lymphatic mapping for endometrial cancer is through subendometrial hysteroscopic injection. Delaloye et al. published a study evaluating hysteroscopic injection of patent blue dye and radioactive tracer beneath the tumour of 60 patients with endometrial carcinoma, sentinel nodes were identified in 49 of 60 patients (82%) [50].

5. Extent of Lymphadenectomy

Actually, the extent and anatomical limits of lymphadenectomy in endometrial cancer is another topic of scientific debate. The GOG (Gynaecologic Oncology Group) has standardized the surgical limits of pelvic and paraaortic lymphadenectomy including the genitofemoral nerve laterally, the hypogastric artery medially, the obturator nerve posteriorly, the circumflex iliac vein caudally, and inferior mesenteric artery (IMA) as cranial limit when performing paraaortic lymphadenectomy [51].

5.1. Paraaortic Lymphadenectomy: To Do or Not To Do? Retroperitoneal lymph node metastasis is a significant prognostic factor for patients with endometrial cancer. The risk of paraaortic nodal metastasis can be related to the presence of adnexal metastasis and/or pelvic lymph nodes metastasis: paraaortic lymph nodes are positive in 38%–52% of cases with positive pelvic lymph nodes, in 20%–57% with adnexal metastasis, and in only 2% with negative pelvic nodes [52]. In other trials, a range from 28.6% to 66.7% of patients with pelvic metastasis had concomitant positive paraaortic nodes [5, 52–54].

Mariani et al. demonstrated that 47% of patients with pelvic lymph nodes metastasis also have positive paraaortic lymph nodes or will submit a relapse in paraaortic region [20]. Furthermore there are reports in literature showing that increasing number of positive pelvic nodes is associated with paraaortic metastasis [55, 56]. Fujimoto et al. reported the therapeutic significance of complete paraaortic

lymphadenectomy in 63 patients with stage IIIC endometrial carcinoma. Despite there was no significant difference in disease-related survival, the authors found an improvement in disease-related survival in patients with two or more positive lymph nodes [57]. Mariani et al. reported the potential therapeutic role of paraaortic lymphadenectomy in node positive patient with endometrial cancer [58, 59]. The 5-year progression free and overall survival rates were significantly better in paraaortic lymphadenectomy group. From the available studies we could conclude that paraaortic lymphadenectomy might have a therapeutic role at least for high-risk patients. However, further RCT are needed to confirm this conclusion.

5.2. Cranial Limit of Paraaortic Lymphadenectomy: Where to Arrive? Moreover, the cranial extent of paraaortic lymphadenectomy has recently been a matter of debate. A prospective study by Mariani et al. evaluated patients with high-risk endometrial cancer requiring a complete lymphadenectomy. Considering patients with positive lymph nodes, 77% of them had paraaortic metastasis above the IMA. The authors emphasized the importance of systematic pelvic and paraaortic lymphadenectomy up to the renal vessels with excision of the gonadal veins [20].

5.3. Number of Removed Lymph Nodes. Another controversial issue is the number of lymph nodes that must be removed for proper surgical staging. Lutman et al. found that pelvic lymph node count ≥ 12 is an independent prognostic factor for both overall and progression-free survival in patients with FIGO stage I and II with high-risk histology [18]. Another study by Cragun et al. confirmed that patients with grade 3 endometrial cancers having more than 11 pelvic nodes removed had improved overall survival and progression-free survival compared with patients with 11 or fewer nodes removed [19]. Chan et al. have shown a correlation between the increasing number of lymph nodes removed and number of nodal metastasis. They concluded that the removal of 21 to 25 nodes was considered to significantly increase the probability of detecting at least one lymph node metastasis [60].

6. Surgical Approach for Staging of Endometrial Cancer

Surgical treatment of endometrial cancer has traditionally been through laparotomy. Nevertheless, in the last 15 years, the use of minimally invasive techniques is getting widely accepted by many authors [61–64]. The laparoscopic approach can be either laparoscopic-assisted vaginal hysterectomy (LAVH) or total laparoscopic hysterectomy (TLH). These procedures proved feasible and safe when compared with laparotomy [61–69].

The primary endpoint for trials comparing laparoscopic and laparotomic approach is to demonstrate the equivalence in terms of staging completeness and survival rates. Other endpoints are hospital stay, postoperative pain, quality of life (QOL), and health costs of the procedures. The randomized study of the Gynaecologic Oncology Group (GOG-LAP2) considered the laparoscopic and laparotomic surgery for stage I-IIa, grade 1–3 endometrial cancer. There were no significant differences in terms of staging completeness, lymph node metastasis, rate of perioperative complications, and mortality between the two procedures. This trial verified that although the laparoscopic approach has a longer operative time, it has the advantage of a shorter hospital stay [61]. The quality of life is another important index in evaluation of the therapeutic role of laparoscopy in endometrial cancer. The same study (GOG-LAP2), through examination of QOL indicators and from the results of validated questionnaire SF-36, demonstrated that laparoscopy has a significant advantage in terms of quality of life within the first 6 weeks. Data from GOG-LAP2 on rate of relapse and long-term survival are not yet available [61].

A recent meta-analysis showed that, in early stages, laparoscopic approach is equally effective as laparotomic one in terms of overall survival, disease-free, and cancer-related survival. Both techniques were proven equal in terms of intraoperative complications and number of pelvic and paraaortic node yield. Laparoscopy had additional benefits like lower blood loss and fewer postoperative complications rates; however, it had other disadvantages in terms of longer operative time and learning curve [63].

6.1. Use of Laparoscopy in Obese Patients with Endometrial Cancer. The feasibility and safety of the use of laparoscopy in obese women with endometrial cancer are other issues of concern. Obesity and comorbidity were considered, for many years, contraindications for laparoscopic approach. However, comparative studies demonstrated that patients with increased surgical risk (obese and elderly) are the ones who most benefit from the minimally invasive approach, in terms of reduction of operative morbidity (e.g., laparotomic wound infections and bowel obstruction), postoperative pain, hospital stay, and time to return to full activity [65–70].

A recent study compared the safety and efficacy of laparoscopy and laparotomy in surgical staging of early stages (FIGO I-II) in obese women. Authors found no significant differences among the two groups regarding mean operative time, with a significantly higher blood loss and hospital stay in patients treated by laparotomy [67].

Another study comparing obese and nonobese women with laparoscopically treated stage I endometrial cancer found no difference in operative time, pelvic node removed, and complications, although obese group had higher blood loss [68].

6.2. Actual Use of Laparoscopy in Endometrial Cancer Management. Despite the controversies regarding endometrial cancer staging by laparoscopy, the use of this procedure in oncological practice is increasingly rising. A recent follow-up survey among members of the Society of Gynaecological Oncology found an overall increase in the use and indications for minimally invasive surgery in gynaecological oncology. 91% of responders indicated that they perform

laparoscopy in their surgical practice. Laparoscopic hysterectomy for endometrial cancer staging was the most frequent procedure performed (43%) [71].

6.3. Robotic-Assisted Surgical Approach. Since 2005, there has been a considerable increase in the published literature describing the use of robotic-assisted surgery for endometrial cancer staging [70–84]. When compared to laparotomy, the robotic-assisted surgery had significantly longer mean operative time, but lymph node yields were comparable to the open surgery. The length of hospital stay, blood loss, and postoperative complication rates were significantly lower for robotically operated patients [79, 80].

Boggess et al. compared three surgical methods for endometrial cancer staging: laparotomy, laparoscopy, and robotic-assisted approach. Patients operated by robotic technique had shortest hospital stay, lowest estimated blood loss, and highest lymph node yield. Operative time was the longest for laparoscopy followed by robotics, with a similar laparotomic conversion rates for robotic and laparoscopic groups [81]. Robotic-assisted approach has been also proposed as a good and feasible option for comprehensive surgical staging in obese women with endometrial cancer [82]. Moreover, this technique may have particular advantages for both the obese and morbidly obese patients affected with endometrial cancer, when compared to laparoscopic approach [83, 84].

7. Conclusions

Surgical staging for endometrial cancer represents certain benefits: firstly, it is the gold standard to assess the disease extent. Secondly, it also has a prognostic role and guides for further treatment. The therapeutic value of lymphadenectomy has not been proven in prospective studies, especially in low-risk cases at preoperative staging.

There are many predictors of lymph nodes involvement useful to evaluate patient's risk categories and to guide surgical management. TVS and MRI may accurately detect the depth of myometrial invasion and cervical spread of the disease, but preoperative imaging cannot accurately assess lymph node involvement. Intraoperative assessment of node involvement and myometrial invasion does not have the sensitivity and specificity to select women who can avoid lymphadenectomy from the surgical procedure.

A great challenge in surgical management of endometrial cancer is standardisation of pelvic and paraaortic lymphadenectomy strategies, in order to avoid unnecessary procedures and to offer complete staging with high survival rates.

The morbidity of lymphadenectomy appears to be reduced with the use of laparoscopy. Numerous trials have demonstrated the safety and feasibility of laparoscopy in complete surgical staging for early stages of endometrial cancer with similar nodes yields, recurrence and survival outcomes. As expected, significant improvements in early and late postoperative complications, a shorter hospital stay, a better quality of life, and less overall treatment costs were demonstrated in many comparative studies between laparotomy and laparoscopy. Laparoscopic approach is safe and feasible also in obese and elderly woman with early stage endometrial cancer, with low rate of conversion, shorter hospital stay, and a faster return to full activity compared with laparotomy.

The role of robotics in endometrial cancer staging continues to evolve and has yet to be determined definitively. Most studies about robotic surgery show that it is a feasible and safe option, especially for obese patients.

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Clinical Study

Systemic Lymphadenectomy Cannot Be Recommended for Low-Risk Corpus Cancer

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Objective. The objective of this study is to ascertain whether omission of lymphadenectomy could be possible when uterine corpus cancer is considered low-risk based on intraoperative pathologic indicators. *Patient and Methods*. Between 1998 and 2007, a total of 83 patients with low risk corpus cancer (endometrioid type, grade 1 or 2, myometrial invasion $\leqq$50%, and no intraoperative evidence of macroscopic extrauterine spread, including pelvic and paraaortic lymph node swelling and adnexal metastasis) underwent the total abdominal hysterectomy and bilateral salpingo-oophorectomy without lymphadenectomy. A retrospective review of the medical records was performed, and the disease-free survival (DFS), overall survival (OS), peri- and postoperative morbidities and complications were evaluated. *Results*. The 5-year DFS rates and the 5-year OS rates were 97.6% and 98.8%, respectively. No patient presented postoperative leg lymphedema and deep venous thrombosis. *Conclusion*. Omission of lymphadenectomy did not worsen the DFS or OS. The present findings suggest that systemic lymphadenectomy could be omitted in low-risk endometrial carcinoma.

1. Introduction

Endometrial cancer is the most frequently occurring gynecologic malignancy. It accounts for 6% of all cancers in women, and causes approximately 42,000 deaths annually, which represents 3% of cancer deaths in women in the United States [1]. Most of the cancers are detected at an early stage by common symptom such as postmenopausal bleeding, with the tumor confined to the uterine corpus, so the prognosis is generally favorable and surgery alone may result in a cure. The five-year survival rate for stage IA or IB disease is reported to be over 90% [2, 3].

The International Federation of Gynecology and Obstetrics (FIGO) recommended in 1988 that adequate surgical staging requires a total abdominal hysterectomy, bilateral salpingo-oophorectomy (TAH-BSO) including pelvic and paraaortic lymphadenectomy [4], and according to this recommendation, some surgeons believe that lymphadenectomy should be performed in all cases to enable the accurate staging and to assess the necessity for postoperative treatment. However, there are some risks to lymphadenectomy such as postoperative deep vein thrombosis or leg lymphedema which may impair the patients' quality of life. Mariani et al. reported that low-risk corpus cancer (endometrioid type, grade 1 or 2 tumor, myometrial invasion $\leqq$50%, and no intraoperative evidence of macroscopic extrauterine spread) could be treated optimally with hysterectomy only [5]. We retrospectively reviewed the cases of low-risk corpus cancer, which were treated in our hospital, and clarified that lymphadenectomy did not provide a significant survival advantage, and increased peri- and postoperative morbidities and complications [6]. According to these results, since 1998, lymphadenectomy have been omitted in low-risk corpus cancer in our hospital. We retrospectively reviewed these cases and evaluated whether omission of lymphadenectomy for low-risk corpus cancer worsen the disease-free survival (DFS), overall survival (OS), and avoid peri- and postoperative morbidities and complications.

2. Patients and Methods

Eighty-three patients (median age: 55 years, range: 27–80 years) with endometrioid corpus cancer, grade 1 or 2 tumor, myometrial invasion $\leqq$50%, and no intraoperative evidence of macroscopic extrauterine spread, including pelvic and paraaortic lymph node swelling and adnexal

Table 1: Patients characteristics ($n = 83$).

Age (years)	
Mean ± SD	56.2 ± 12.1
Median	55
Range	27–80
WHO* performance status, no.	
0	59
1	14
>2	0
FIGO** surgical stage, no.	
Ia	32
Ib	43
Ic	3
IIIa	5
Adjuvant chemotherapy, no.	
None	74
Paclitaxel/carboplatin§	9
Follow up interval (months)	
Median (range)	72 (4–120)

WHO*: World Health Organization, FIGO**: International Federation of Gynecology and Obstetrics Paclitaxel/carboplatin §: Paclitaxel (180 mg/m^2) and carboplatin (area under the curve; AUC 5).

Table 2: Characteristics of the histopathological prognostic features ($n = 83$).

Histological grade, no.	
G1	72
G2	10
G3	1
Depth of myometrial invasion >50%, no.	
None	32
≦50%	48
>50%	3
Lymphvascular space involvement, no.	
Yes	5
No	78
Peritoneal cytology, no.	
Positive	5
Negative	78
Tumor diameter, no.	
<20 mm	44
≧20 mm	39

metastasis, were treated surgically at the Department of Obstetrics and Gynecology of University of Toyama during the period 1998 to 2007. In all these cases, we preoperatively assessed whether endometrial cancer is considered low-risk (myometrial invasion ≦50%, no lymphadenopathy and grade 1 or 2 endometrioid corpus cancer), using computed tomography, magnetic resonance imaging, glucose analog [18F]-fluoro-2-deoxy-D-glucose positron emission tomography and endometrial biopsy.

All patients routinely underwent TAH-BSO without lymphadenectomy. If the depth of myometrial invasion was determined to be >50%, or the tumor was classified grade 3 endometrioid corpus cancer based on intraoperative frozen-section analysis, we performed systemic lymphadenectomy. In cases which lymph nodes were enlarged or suspicious, we performed selective lymph node sampling. Non-endometrioid histologic types such as serous or clear cell type and grade 3 tumor were excluded from this study, since all of these patients underwent TAH-BSO with lymphadenectomy because of their poor prognosis. After operation, patients were seen every month for one year, and every 3 months thereafter for 120 months.

We performed a retrospective review of the medical records, and the disease-free survival (DFS; the interval between the date of operation and the date of recurrence of disease), overall survival (OS; the interval between the date of operation and the date of death), and peri-operative morbidities including operative time, estimated blood loss during operation, and the percentage of patients requiring transfusion were evaluated. We also estimated the incidence of postoperative complications such as leg lymphedema and deep vein thrombosis diagnosed by nuclear venography. The DFS and OS curves were estimated using the Kaplan-Meier method.

3. Results

Patients' characteristics are shown in Table 1. The median age of the patients was 55 years (range, 27–80 years). The distribution of FIGO surgical stage was Ia, 32; Ib, 43; Ic, 3, IIIa, 5; and 8 cases (9.6%) were upstaged postoperatively. Pelvic lymph node sampling was performed in 7 cases, which were diagnosed with negative nodes. Adjuvant chemotherapy consisting of intravenous paclitaxel (180 mg/m^2) and carboplatin (AUC 5) was administered to 9 upstaged, upgraded or lymphvascular space involvement-positive cases. No patients received adjuvant radiotherapy. The median followup period was 72 months (range, 4–120 months).

Characteristics of the histopathological prognostic features are shown in Table 2. The distribution of histological grade was grade 1, 72; grade 2, 10; grade 3, 1; and 1 case (1.2%) was upgraded postoperatively. Depth of myometrial invasion was >50% in 3 cases. Lymphvascular space involvement was observed in 5 cases. Positive peritoneal cytology was observed in 5 case. Thirty-nine patients had tumor diameter ≧20 mm.

The DFS curve and the OS curve are shown in Figure 1 (left; the DFS curve, right: the OS curve). The 5-year DFS rates and the 5-year OS rates were 97.6% and 98.8%, respectively.

Peri- and postoperative morbidities and complications are shown in Table 3. The mean operative time was 129 ± 28 minutes. The mean estimated blood loss during operation was 244 ± 192 mL, and the percentage of transfusion requirement was 2.4%. No patient presented with postoperative leg lymphedema or postoperative deep venous thrombosis.

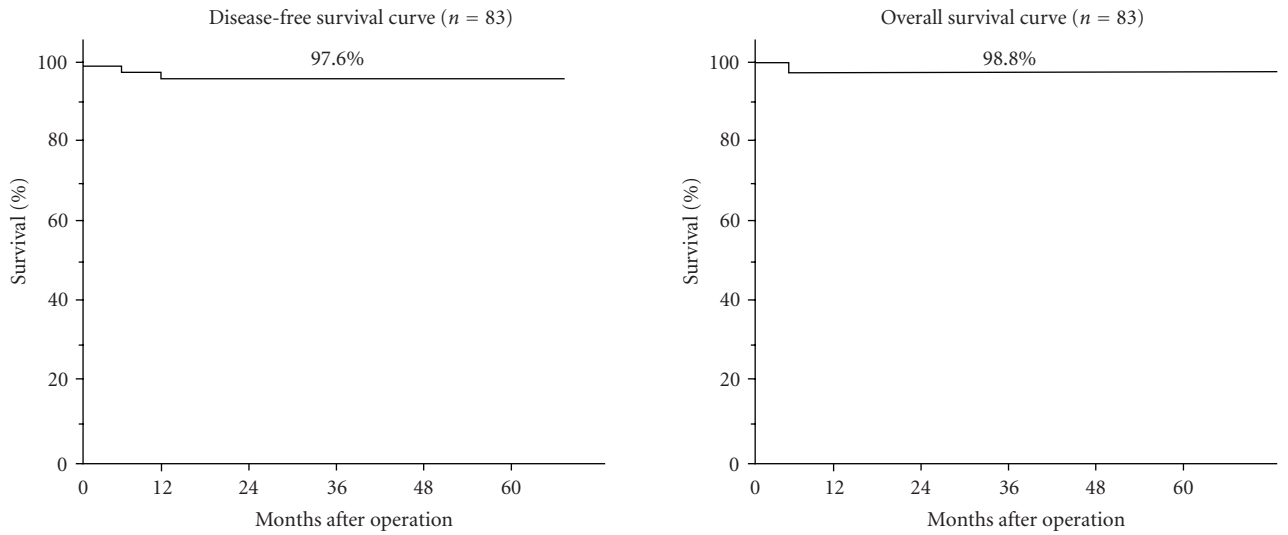

Figure 1: Survival curves.

Table 3: Peri- and postoperative morbidities and complications.

Peri- and postoperative factors	
Operative time* (min)	129 ± 28
Estimated blood loss during operation* (mL)	244 ± 192
Transfusion requirement, no.	2
Postoperative leg lymphedema (≧grade 2, NCI-CTC ver. 2.0), no.	0
Postoperative deep vein thrombosis, no.	0

* The values were expressed as the mean ± SD.

4. Discussion

In 1988, FIGO recommended a systemic surgical staging system for corpus cancer [4]. According to this recommendation, many gynecologic oncologists believe that systemic surgical staging including pelvic and paraaortic lymphadenectomy is the best surgical treatment to achieve a good prognosis for corpus cancer patients. However, controversy has persisited regarding the need for lymphadenectomy [5–9]. There is no doubt that surgical staging is more accurate than clinical staging, and there are some cases which need upstaging to higher stages after surgery [10–12]. However, Morrow et al. reported that only 18 (2%) out of 895 patients had positive pelvic lymph nodes in the abscence of operative findings by palpation [13]. Creasman et al. demonstrated by multivariate analysis that in clinical stage I patients with grade 1 or 2 and depth of invasion within the middle 1/3, the incidence of pelvic lymph node metastases was only 3.6% [7]. Chi et al. showed that the incidence of pelvic lymph node metastases in low-risk corpus cancer (grade; 1, 2, and depth of myometrial invasion; none or inner half) was 5.3% (14/162) [14]. As for grading, Ben-Shachar et al. reported that only 6 (3.3%) of 181 patients preoperatively diagnosed with grade 1 disease by biopsy were upgraded after surgical staging [15]. In this study, 8 of the 83 were upstaged or upgraded after surgical staging.

Regarding the role of lymphadenectomy on prognosis, Mariani et al. reported that patients who had grade 1 or 2 endometrioid corpus cancer with greatest surface dimension ≦2 cm, myometrial invasion ≦50%, and no intraoperative evidence of macroscopic disease could be treated optimally with hysterectomy only with favorable prognosis of up to 97% for 5-year overall cancer-related survival [5]. Furthermore, Trimble et al. demonstrated that the 5-year relative survival for 6,363 women with stage I endometrial cancer who did not undergo lymph node sampling was 98%, compared to 96% for 2,831 women who did undergo lymph node sampling at the time of hysterectomy with a no significant difference, and concluded that lymph node sampling did not appear to convey survival benefit, especially in stage I, grade 1 or 2, endometrial cancer by subgroup analysis [9] Recently, Kitchener et al. compared the standard surgery group (hysterectomy and bilateral salpingo-oophorectomy, peritoneal washings, and palpation of para-aortic nodes; $n = 704$) and the lymphadenectomy group (standard surgery plus lymphadenectomy; $n = 704$) for histolgically proven endometrial carcinoma thought preoperatively to be confined to the corpus in a randomised study and showed that the hazard ratio (HR) for overall survival was 1.04 (0.74–1.45; $P = .83$) and HR for recurrence-free survival was 1.25 (0.93–1.66; $P = .14$), both in favour of standard surgery, and concluded that there was no evidence of benefit in terms of overall or recurrence-free survival for pelvic lymphadenectomy with early endometrial cancer, and that pelvic lymphadenectomy cannot be recommended as routine procedure for therapeutic purposes outside of clinical trials [16]. Panici et al. also, compared the pelvic systematic lymphadenectomy arm ($n = 264$) and no lymphadenectomy arm ($n = 250$) for preoperative FIGO stage I endometrial carcinoma and showed that the 5-year

disease-free and overall survival rates were similar between the two arms (81.0% and 85.9% in the lymphadenectomy arm and 81.7% and 90.0% in the no-lymphadenectomy arm) [17]. In summary, omission of complete lymphadenectomy is possible in selected cases in which the risk of lymph node spread is low, in other words, low-risk cancer. The definition of low-risk in corpus cancer at the operation is controversial; however, taking many reports into consideration, we regard grade 1 or 2 endometrioid corpus cancer with myometrial invasion $\leqq$50%, and no intraoperative evidence of macroscopic disease as low-risk [5–9, 18, 19].

There were 8 upstaged patients on final pathology who were thought low-risk on pre- and intraoperative evaluation. This result means that there is some limitation about the accuracy of pre- and intraoperative evaluation of myometrial invasion and tumor grade. Montalto et al. reported that accuracy of intraoperative frozen section diagnosis for grade of differentiation and depth of myometrial invasion were 84.3% and 94.3%, respectively [20]. For those upgraded, upstaged or lymphvascular space involvement-positive cases, as well as, non-endometrioid adenocarcinoma such as uterine papillary serous carcinoma, which is clinically aggressive, adjuvant treatment should be considered. Recently, paclitaxel has been shown to be effective against advanced and recurrent endometrial carcinoma [21–25]. Therefore, we added systemic chemotherapy (a paclitaxel/carboplatin regimen) as adjuvant treatment for upgraded, upstaged or lymphvascular space involvement-positive cases.

Several investigators have reported that addition of lymphadenectomy to TAH-BSO increases the risk of complications and morbidities such as more blood transfusions, longer hospital stay, lymphedema, gastrointestinal injury, and the development of lymphocysts [26–28]. Framarino et al. reported that addition of pelvic and paraaortic lymphadenectomy to TAH-BSO significantly increased mean operative time, mean estimated blood loss, and postoperative hospital stay compared to TAH-BSO alone, without improving mortality [28]. Panici et al. showed that postoperative complications occurred statistically significantly more frequently in patients who had received pelvic systematic lymphadenectomy (81/264; 30.7% in the lymphadenectomy arm and 34/250; 13.6% in the no-lymphadenectomy arm, $P = .001$) [17]. Also in our previous study, mean operative time, mean estimated blood loss during operation, the percentage of cases requiring transfusion, and the incidence of leg lymphedema were significantly ($P < .001$) increased by addition of lymphadenectomy [6]. In any case, postoperative complications are expected from the surgical procedure itself, and addition of lymphadenctomy may increase the incidence of those complication, especially in corpus cancer patients, many of whom have morbidities such as hypertension, obesity, diabetes mellitus, and older age [29, 30].

5. Conclusion

A clinically important goal of surgical treatment including lymphadenectomy for low-risk corpus cancer patients is not only to determine the extent of disease and an accurate prognosis, but also to obtain a favorable prognosis without causing any complications. Our data demonstrate that omission of lymphadenectomy did not worsen the disease-free or overall survival, and as a result, peri- and post-operative morbidities and complications could be avoided. The present findings suggest that systemic lymphadenectomy could be omitted in low-risk endometrial carcinoma. These results should be confirmed in future prospective large-scale randomized clinical trials.

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Review Article

Controversies in the Management of Endometrial Cancer

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Endometrial cancer (EC) remains the most common malignancy of the female genital tract. The median age at diagnosis is the sixth decade, with abnormal uterine bleeding at the presentation in 90% of the patients. Surgical treatment, including complete hysterectomy, removal of remaining adnexal structures, and an appropriate surgical staging, represents the milestone of curative therapy for patients with EC. Adjuvant therapy is necessary in patients at high risk of recurrence. Conservative treatment approaches should be used in selected cases for women with a desire of fertility preservation. This review summarizes the management of EC and discusses current controversies regarding the role of lymphadenectomy and radiotherapy in patients with intermediate-risk tumors confined to the uterus.

1. Introduction

Endometrial cancer (EC) remains the most common malignancy of the female genital tract. It will develop in 2,6% of women in the United States during their lifetime [1]. The age-standardized death rate is 3.6 per 100,000 women and the median age at diagnosis is the sixth decade, although 20 to 25% of cases will be diagnosed premenopausally [2, 3] (Figure 1). It has been suggested that the overall distribution of tumour stage and survival are similar for younger and older women; however, women with stage I disease and younger than 45 years are more likely to have low-grade disease localized to the endometrium [4, 5].

2. Risk Factors

The most important risk factors for EC are postmenopausal status, excessive fat consumption, body mass index (BMI) of 25 kg/m^2 or more, nulliparity, anovulation, and unopposed exogenous estrogen use. However, only half of patients present with identifiable risk factors, while the other half appear to be at low risk [6].

In particular, obesity, recently considered the most common risk factor responsible of the development of all endometrial carcinomas, increases the risk of EC through a number of mechanisms that cause hormonal alteration and consequently endometrial cell proliferation, apoptosis inhibition, and angiogenesis promotion. In premenopausal women, obesity causes insulin resistance, ovarian androgen excess, anovulation, and chronic progesterone deficiency. On the other hand, in postmenopausal women, the conversion of androgens to estrogens is enhanced in peripheral fat stores. Pregnancy, with intense placental production of progestins and grand multiparity protect against EC, whereas nulliparity increases the risk, especially when it is associated with infertility. It is well established that oral contraceptives with the addition of progesterone to estrogen, lower the adverse effects of estrogens on the endometrium and the risk of EC [7]. Smoking appears to reduce the risk of EC through its effects on estrogen production and metabolism [8]. Instead, the use of tamoxifen in patients with breast cancer triples the risk of EC and also increases the chance of developing benign endometrial polyps, hyperplasia, and even carcinoma in some patients. However, the beneficial effects of tamoxifen on breast cancer recurrence and its association primarily with ECs of low grade and early stage support its continued use in an appropriate patient population [1].

While the incidence and mortality rates from several other cancers have plateaued or decreased in the last decade,

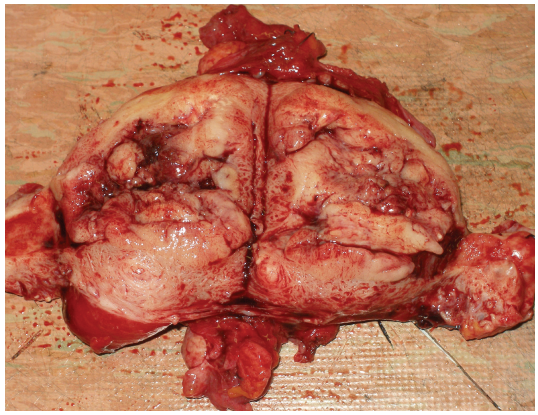

Figure 1: Adenocarcinoma of the uterine corpus.

rates for EC continue to rise [9]. This fact may be related to an increased rate of advanced-stage cancers and high-risk histologies including uterine papillary serous carcinoma (UPSC), that is histologically similar to serous epithelial ovarian carcinoma and represents approximately 10% of all endometrial cancer [10].

Bokhman [11] proposed the existence of two categories of endometrial carcinoma characterized by distinct microscopic appearance, epidemiology, and clinical behaviour. Type I carcinoma with an endometrioid histology, that typically arises in relatively younger women with obesity, hyperlipidemia, and signs of hyperestrogenism (endogenous or exogenous); and type II carcinomas that include poorly differentiated endometrioid, clear cell, and serous histologies. They often arise in thinner, older women and demonstrate no hormonal risk factors. Moreover type I endometrial carcinomas are commonly diagnosed at an early stage and have a favourable prognosis, often with surgical treatment alone; recurrences are usually local (pelvis being the most common site) and frequently curable with tumor-directed radiotherapy. Alternatively, type II endometrial carcinomas are more likely to present with metastatic disease at diagnosis and carry a poorer prognosis [12].

3. Diagnostic Approach

Abnormal uterine bleeding is present in 90% of patients with EC. Therefore, any vaginal bleeding in a postmenopausal woman warrants an initial evaluation for EC, that is found approximately in 10% of patients with postmenopausal bleeding (PMB) [1]. Because of this symptom, 75% of ECs are diagnosed at an early stage. Atypical endometrial hyperplasia (AEH) is felt to be a precursor of lesion and it may progress, over time, to EC in 5% to 25% of patients. In addition, AEH is associated with a coexisting EC in approximately 20% of patients [13, 14].

Diagnostic approaches to the assessment of abnormal uterine bleeding are divided into invasive and noninvasive methods.

3.1. Invasive Methods

3.1.1. Dilatation and Curettage (D&C). Traditionally considered the standard for investigation of abnormal uterine bleeding.

3.1.2. Endometrial Biopsy. A variety of instruments (the Pipelle, the Pipette, the Tis-U-Trap and the Z-sampler) has been developed over the last decade for using in the office as alternatives to the expense, risk, and inconvenience of fractional D&C. With the use of these devices, the sensitivity for detecting endometrial cancer ranges from 67% to 96%.

3.1.3. Hysteroscopy and Directed Biopsy. Some consider this method as the standard for the diagnosis of abnormal uterine bleeding. However, a recent study of 373 patients which retrospectively compared hysteroscopy and D&C, concluded that hysteroscopy did not improve upon the sensitivity of D&C in the detection of endometrial hyperplasia or carcinoma. On the contrary, Clark et al. found that hysteroscopy is highly accurate and useful in diagnosing, rather than excluding, endometrial cancer in women with abnormal uterine bleeding [15]. A recent study performed by Bedner and Rzepka-Gorska compared the effectiveness of D&C with hysteroscopy and guided biopsy in perimenopausal women at risk of endometrial hyperplasia or cancer. They found that hysteroscopy with directed biopsy was more sensitive than D&C for detecting all types of uterine lesions [16]. Several retrospective studies have found increased positive peritoneal cytology in women who underwent hysteroscopy, but recent studies have indicated that there is currently no evidence to suggest that diagnostic hysteroscopy increases the risk of malignant cells spreading into the peritoneal cavity, or worsens the prognosis in women with EC.

3.2. Noninvasive Methods

3.2.1. Ultrasonography. Two large studies of 930 women and of 138 women reported experiences with transvaginal ultrasound in women with postmenopausal bleeding. Both studies used a biendometrial (double layer) thickness of four millimetres as a cut-off point. The sensitivity was 96% to 98% and the specificity was 36% to 68%. The false positive rate was 44% to 56%. Thickness could not be measured in 3% to 4.7% but the reason for this was not stated. One of the studies reported two cancers in patients with a thickness less than 3.5 mm, giving a false negative rate of two per 930 (0.2%) [2].

3.2.2. Endometrial Cytology. This is not felt to be useful in diagnosis of EC, due to low accuracy and it will not be discussed further. In a prospective study conducted by Karlsson et al. [17], on 1168 women with PMB underwent to transvaginal ultrasonography followed by uterine curettage, the risk of endometrial abnormality was 6.1%, considering a threshold of 5 mm or less, with a sensitivity of 94%, a specificity of 78%, a positive predictive value (PPV) of 69%, a negative predictive value (NPV) of 96%, and a rate of

accuracy of 84%. With this threshold, it was determined a risk of endometrial abnormalities of 6,1% (upper 95% confidence level of 8.5%) and ECs were undetected. The high NPV of this test lends itself well to excluding a diagnosis of EC in patients who cannot undergo endometrial sampling. However, it should be emphasized that the aforementioned results are limited to patients with PMB. Screening for EC using transvaginal ultrasonography alone in asymptomatic postmenopausal women has a poor PPV (9%) and is not recommended, whereas the combination of transvaginal ultrasonography and endometrial biopsy has shown a sensitivity of 100% [18].

Evaluation for systemic disease is typically limited to chest radiography and laboratory evaluation performed in preparation for surgery, but magnetic resonance imaging (MRI), that is superior to computed tomography for visualizing uterus and pelvic tissues [19], is recommended as knowledge of extrauterine spread or cervix involvement by tumor. On the other hand, baseline cancer antigen levels can be useful, but they are not enough sensitive to predict the status of disease. We recently showed [20] that transvaginal sonography (TVS) when carried out by expert hands shows a comparable accuracy to MRI in depicting myometrial infiltration of endometrial carcinoma, thus we recommend a combination of both techniques for detecting an accurate myometrial invasion. In detection of subclinical nodal disease, to define extent of disease, integrated PET/CT imaging has been investigated by Montejo et al. and only modest improvement was achieved over to conventional imaging, with an overall sensitivity and specificity of 50% and 86.7%, respectively [21].

4. Treatment of Precursor Lesions

Continuous stimulation of the endometrium by either endogenous or exogenous estrogen is the most important risk factor for endometrial hyperplasia and EC consequently. The World Health Organization (WHO) classifies the endometrial hyperplasia in simple, a benign proliferation of endometrial glands involving mild or moderate glandular crowding (adenomatous hyperplasia) and complex, that is characterized by back-to-back cellular crowding and an irregular cellular outline. Both simple or complex hyperplasia could be associated with cellular atypia. It can be subdivided into mild atypia (nuclear enlargement and rounding with evenly dispersed chromatin) or moderate atypia (larger nuclear size, prominent nucleoli, and clumped chromatin). Hyperplasia without atypia, either simple or complex, has a low likelihood (1% and 3%, respectively) of progressing to carcinoma. In contrast, atypical endometrial hyperplasia is believed to be the direct precursor to endometrioid EC [11, 12].

A recent investigation by The Gynecologic Oncology Group (GOG) [22] found that from 19% to 62% of endometrial biopsy specimens interpreted as atypical endometrial hyperplasia were associated with an invasive EC at hysterectomy. For this reason, simple and complex hyperplasia can be treated with progestational therapy only, whereas hysterectomy is mandatory for all patients with atypical hyperplasia. Medroxyprogesterone acetate or megestrol acetate, the agents used in most retrospective studies to treat endometrial hyperplasia without atypia, can be administered in either a cyclic or continuous fashion.

Atypical hyperplasia regresses after treatment with progestins in 60% to 95% of patients [23]. However, because of the high rate of frankly invasive EC in patients with atypical hyperplasia [24] and the high risk of progression to EC, hysterectomy is the standard treatment, while progestins therapy should be reserved for those women who desire a fertility-preserving management. Continuous administration of local progestational agents via the levonorgestrel (LNG)-releasing intrauterine device (IUD) has been evaluated as an alternative delivery mechanism in treating endometrial hyperplasia, both with and without atypia. It has an efficacy of 100% with lasting results during a minimum of 5 years of follow-up, although only small numbers of patients were included in the studies published to date [25].

The LNG-releasing IUD has also been evaluated as an alternative to hysterectomy for women with low-grade, presumed early-stage EC who are poor operative candidates. Cure rates up to 75% have been reported [26]. The current committee opinion from the American College of Obstetrics and Gynecology acknowledges that larger studies are needed to evaluate the efficacy of noncontraceptive uses of LNG-releasing IUDs before they can be recommended as a treatment alternative for atypical endometrial hyperplasia or low-grade EC. Follow-up endometrial biopsy or curettage is performed every 3 to 6 months until regression to normal endometrium or lesion progression occurs [27]. However, well-designed randomized trials for an optimal endometrial hyperplasia management are lacking, and guidelines for follow-up are also unclear. If vaginal bleeding resumes, another endometrial biopsy should be performed [28, 29].

5. Fertility-Sparing Treatment of Endometrial Cancer

Considering that patients with stage I disease and younger than 45 years are more likely to have low-grade disease localized to the endometrium [30], a conservative management of uterine cancer has been advocated as a safe alternative for those women with desire of childbearing. Anyway, there is still no consensus about which will be the optimal procedure.

We recently proposed an innovative method [31] to preserve fertility in young women with stage IA EC, based on the hysteroscopic resection of the tumor followed by hormone therapy regimen of megestrol acetate (160 mg/day) for six months, for consolidation. This methods consists of a conservative resectoscopic treatment using a three-step technique in which each step is characterized by a pathologic analysis: (1) the removal of the tumor, (2) the removal of the endometrium adjacent to the tumor, and (3) the removal of the myometrium underlying the tumor. This technique, under a close postsurgical follow-up, might represent a novel therapeutic option. The results of transvaginal ultrasound examination and diagnostic hysteroscopy with target biopsies at 3, 6, 9, and 12 months after surgery were negative

for atypia or malignancy and four out of six patients (66%) achieved childbearing.

Moreover successful hormone therapy as an option for appropriately selected young women who desire to preserve fertility, with early-stage low-grade endometrial cancer, has been reported in small series [32, 33].

This conservative management of EC should not be considered standard of care, and the dosage and duration of treatment, selection criteria, and follow-up surveillance are not established definitely. In a 2004 meta-analysis, Ramirez et al. reviewed the literature regarding hormonal treatment of grade I EC, including 27 articles with a combined total of 81 patients. A variety of progestational agents were used, most often medroxyprogesterone acetate or megestrol acetate. It was observed an overall response rate of 77% (62/81), the median time to regression was 12 weeks and among responders the recurrence rate was 24% [34].

All recurrences occurred within 1 year of diagnosis and all patients who remained disease free (76% of the initial responders) required treatment with progesterone for only 1 month to achieve a response. Twenty patients achieved pregnancy after treatment. The 23% (19/81) of patients of the original cohort never responded to treatment, and only 68% had any documented follow-up endometrial sampling. Today there is no clear consensus on the optimal follow-up interval. However, appropriate patient selection and exclusion criteria remain undefined, so patients must be counseled that failure to identify recurrence or extension of disease during progestational treatment could lead to a delay in definitive surgery and ultimately a compromised prognosis [35].

On the other hand, progestational therapy can be used successfully to treat patients with atypical hyperplasia and well-differentiated presumed stage I EC while preserving fertility.

6. Surgical Treatment of Endometrial Cancer

Surgical treatment, including complete hysterectomy, removal of remaining adnexal structures, and appropriate surgical staging represents the milestone of curative therapy for patients with EC. Survival is heavily dependent on surgical stage, which is determined adopting the classification recently revised by the International Federation of Gynecology and Obstetrics (FIGO) in 2008 (Table 1).

Most women with endometrial cancer have disease confined to the uterus and they are usually managed with extra-fascial or simple total hysterectomy with bilateral salpingo-oophorectomy (BSO) either as a laparotomic or laparoscopic procedure. Lymph node involvement is an adverse prognostic factor; it is influenced chiefly by the depth of myometrial invasion and the tumor grade. Regarding the role of lymphadenectomy in women with disease that clinically seems to be confined to the uterus, there has been much debate. Although lymphadenectomy forms part of the International Federation of Gynecology and Obstetrics (FIGO) surgical staging system [28], evidence from a large randomized controlled trial, A Study in the Treatment of Endometrial Cancer (ASTEC), showed that this approach does not provide therapeutic benefit [29].

Table 1: Carcinoma of the corpus uteri (FIGO 2008).

Stage I*	Tumour confined to the corpus uteri.
IA*	No or less than half myometrial invasion.
IB*	More than half myometrial invasion.
Stage II*	Tumour invades cervical stroma, but does not extend beyond the uterus.**
Stage III*	Local and/or regional spread of the tumour.
IIIA*	Tumor invades the serosa of the corpus uteri and/or adnexae#.
IIIB*	Vaginal and/or parametrial involvement#.
IIIC*	Metastases to pelvic and/or para-aortic lymph nodes#.
IIIC1*	(i) Positive pelvic nodes
IIIC2*	(ii) Positive paraortic lymphnodes with or without positive pelvic lymphnodes.
Stage 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 lymph nodes.

*Either G1, G2, or G3.
**Endocervical glandular involvement only should be considered as Stage I and no more as Stage II.
#Positive cytology has to be reported separately without changing the stage.

Panici et al. conducted a randomized clinical trial to determine whether the addition of pelvic systemic lymphadenectomy to standard hysterectomy with bilateral salpingo-oophorectomy improves overall and disease-free survival. They found that significantly it improved only surgical staging and neither overall or disease-free survival [36].

A comparison of other two important studies, GOG-99 and Postoperative Radiation Therapy in EC (PORTEC), seems to suggest that lymphadenectomy does not affect disease-related and recurrence-free survival in patients with intermediate-risk tumors confined to the uterus [7, 37]. However, 60% of the patients enrolled in the PORTEC trial were actually grade 1 (thus their prognosis was even more favourable) whereas doubts have been raised concerning the adequacy of surgical staging performed in the GOG-99 trial.

When the EC presents a cervical extension (stage II FIGO), a radical hysterectomy, with an extensive dissection to expose the ureters and secure the uterine vessels at the origin rather than at their entry into the uterus, may be considered. This type of surgery allows to remove the parametrial tissue and facilitates safe dissection of the bladder away from the uterus and cervix such that a significant cuff of upper vagina can be removed [38]. Parametrial metastasis does not form part of the FIGO staging system, but their involvement is associated with a poor prognosis [28].

Mariani et al. reported the results of 34 women with surgical stage II EC treated primarily with surgery. The

disease-free survival at 5 years was 100% for women who had radical hysterectomy with histologically negative nodes versus a 5-year disease-free survival rate of 73% for women who received simple hysterectomy [39].

Boente also evaluated 202 patients with stage II disease, reporting a 5-year survival for radical hysterectomy and nodal dissection of 86% compared with 77% for simple hysterectomy [40].

However, some questions about the adequacy of lymphadenectomy, like the minimum number of nodes to remove, if the para-aortic nodes should be resected and if the hystotype of endometrial cancer should determine the extent of lymphadenectomy, remain still unclear.

A small number of women are found to have advanced endometrial cancer at presentation thus, to date there are no prospective randomized data available to aid general consensus about an appropriate management of these patients. The appropriate extent of surgery in this setting of patients and the true value of radical surgery in advanced disease are still not clear. Pliskow et al. published a retrospective study of 41 women with clinical stage III and IV endometrial cancer, and suggested that the extent of disease and tumour bulk have greater prognostic value than histological subtype, grading, or depth of myometrial invasion. Other recent studies propose that the primary cytoreductive surgery for advanced endometrial cancer offers a survival benefit as in epithelial ovarian cancer [41, 42].

7. Radiotherapy

The role of adjuvant radiotherapy in EC remains controversial. Early endometrial cancer with low-risk pathological features can be successfully treated by surgery alone. Several trials, which have mainly included women at intermediate or high risk of recurrence in stage 1, have been shown that postoperative radiotherapy is able to reduce the risk of isolated local recurrence without improving recurrence-free or overall survival. In particular the PORTEC and the GOG-99 trial randomized patients with intermediate risk stage 1 showing that external pelvic radiotherapy (EBRT) improves local control but does not substantially increase survival in patients with EC confined to the uterus, with or without surgical staging [37, 43].

The ASTEC trial, randomizing patients with IC-IIA or IA-IIAG3 or serous papillary/clear cell for lymphadenectomy, did not show a survival benefit for adjuvant radiotherapy in women with intermediate- or high-risk early stage EC. Thus, the use of postoperative radiotherapy should be limited to patients with sufficiently high-risk of local recurrence based on known risk factors such as age ≥ 60, grade 2-3, depth of myometrial invasion, and cervical and lymphovascular space involvement. The PORTEC-2 trial, which compared the efficacy of brachytherapy (BRT) versus EBRT in patients with intermediate- or high-risk early stage EC, concluded that BRT is effective as EBRT in preventive vaginal recurrences with less toxicity. Therefore BRT should be considered the standard for these patients. However, as in the original PORTEC trial, surgical staging is not required, raising questions on the generalizability of these data. In fact, if an appropriate surgical staging is not performed, the administration of pelvic RT could lead to overtreatment of those patients who have negative lymph nodes and undertreatment of those with positive pelvic lymphnodes who eventually present disease in the para-aortic area.

Patients with advanced EC (stage IIB, III FIGO) should be considered for adjuvant external beam radiotherapy that would reduce local recurrence, with or without vaginal vault brachytherapy [44].

Bruckman et al. reported a retrospective review on EC patients treated with adjuvant pelvic RT and low-dose rate vaginal brachytherapy. Patients with extrauterine disease limited to the ovary or fallopian tube had significantly improved relapse-free survival and overall survival compared with those patients with disease spread beyond the adnexa to other pelvic structures. Women with extrauterine disease limited to the adnexa experienced relapse-free survival rates of 80% and overall survival rates of 80% compared with 15% and 40%, respectively, for those patients with disease to other pelvic structures beyond the adnexa [45].

8. Chemotherapy in Postoperative Treatment of Endometrial Cancer

The use of chemotherapy for patients with locally advanced or metastatic EC is becoming nowadays more common. Platinum compounds, taxanes, and anthracyclines provide the major effective drug classes in the treatment of advanced and recurrent EC, all producing response rates of 20% to 30%. For patients able to tolerate aggressive therapy, multiagent chemotherapy produces higher response rates than single-agent therapy [46]. The most active regimen tested in randomized trials is the triplet consisting of cisplatin ($50\,mg/m^2$), doxorubicin ($45\,mg/m^2$), and paclitaxel ($160\,mg/m^2$), a myelotoxic regimen, which requires granulocyte growth factor support [47].

Carboplatin and paclitaxel are used frequently because of their ease administration and promising phase 2 results. The GOG is currently comparing cisplatin-doxorubicin-paclitaxel chemotherapy to carboplatin-paclitaxel in a large randomized trial of patients with metastatic disease (GOG-209).

In a prospective study by the GOG in patients with relapsed or metastatic EC, doxorubicin and cisplatin were chosen to compare chemotherapy to radiotherapy [48]. All women with stage III or IV disease of any histology and with less than 2 cm of residual disease after maximal surgical debulking were eligible for the trial. Patients were randomized to whole abdominal radiotherapy or 8 cycles of doxorubicin and cisplatin chemotherapy. Toxicity was higher in the chemotherapy group; only 63% of women completed all 8 cycles of chemotherapy. Patterns of failure analysis revealed that the initial site of failure was within the pelvis in 13% of patients who underwent irradiation versus 18% of those who received chemotherapy. To further improve the results of chemotherapy alone, the GOG-184 study, required all patients to receive tumor-directed

radiotherapy (pelvic irradiation with or without para-aortic irradiation, depending on lymph node involvement) followed by randomization to cisplatin and doxorubicin or cisplatin, doxorubicin, and paclitaxel. This trial has been completed and data are awaiting maturation. It is hoped that the combination of chemotherapy and targeted radiotherapy will improve on historical results.

An important trial coordinated by the European Organization for Research and Treatment of Cancer (EORTC) was recently presented in abstract form at the annual meeting of the American Society of Clinical Oncology [49]. Women with stage I to IIIA or IIIC (pelvic lymph nodes only) disease who were at high risk (>50% myometrial invasion, Grade 3 or DNA nonploidy, clear or serous histology) were randomized to external pelvic radiotherapy or combined chemoradiotherapy. During a 10-year period, 372 patients were enrolled, with a median follow-up of 3.5 years. The investigation was closed early because of slow recruitment, and multiple chemotherapeutic regimens were allowed in combination with radiotherapy. The hazard ratio for progression-free survival was 0.58 for chemoradiation (95% confidence interval [CI], 0.34–0.99; $P = .046$). This translates to an estimated absolute difference in 5-year progression-free survival of 7% (from 75% [95% CI, 67%–82%] to 82% [95% CI, 73%–88%]). The ongoing PORTEC-3 trial is also investigating whether chemoradiation is superior to radiation alone [50]. Patients are randomized to receive pelvic radiotherapy or pelvic radiotherapy with concurrent cisplatin followed by adjuvant carboplatin and paclitaxel chemotherapy. Because many patients with recurrent or stage IV EC are elderly, have received prior pelvic radiotherapy, or have limited hematologic reserve, chemotherapeutic regimens are often limited by toxicity.

The possible role of adjuvant hormonal therapy for stage I EC has also been investigated but currently the evidences are still insufficient [51] to reach any conclusion.

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Review Article

Controversies in the Management of Endometrial Carcinoma

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Endometrial carcinoma is the most common type of female genital tract malignancy. Although endometrial carcinoma is a low grade curable malignancy, the condition of the disease can range from excellent prognosis with high curability to aggressive disease with poor outcome. During the last 10 years many researches have provided some new valuable data of optimal treatments for endometrial carcinoma. Progression in diagnostic imaging, radiation delivery systems, and systemic therapies potentially can improve outcomes while minimizing morbidity. Firstly, total hysterectomy and bilateral salphingo-oophorectomy is the primary operative procedure. Pelvic lymhadenectomy is performed in most centers on therapeutic and prognostic grounds and to individualize adjuvant treatment. Women with endometrial carcinoma can be readily segregated intraoperatively into "low-risk" and "high-risk" groups to better identify those women who will most likely benefit from thorough lymphadenectomy. Secondly, adjuvant therapies have been proposed for women with endometrial carcinoma postoperatively. Postoperative irradiation is used to reduce pelvic and vaginal recurrences in high risk cases. Chemotherapy is emerging as an important treatment modality in advanced endometrial carcinoma. Meanwhile the availability of new hormonal and biological agents presents new opportunities for therapy.

1. Introduction

Endometrial carcinoma is the most common type of female genital tract malignancy. It is estimated that 42,160 cases of endometrial carcinoma were diagnosed in the United States in 2008 and 7780 women would die from the disease [1]. Since the primary symptom is abnormal uterine bleeding in postmenopausal women, most patients would have a better chance of survival if diagnosed at an early stage of the disease. However, there still remain a lot of challenges in the clinical treatment of endometrial carcinoma. At the diagnostic stage, the condition of the disease can range from excellent prognosis with high curability to aggressive disease with poor outcome. In this paper, our goals are to discuss current challenges in the management of endometrial carcinoma and to provide an overview of the new approaches that would help overcome these challenges.

2. Pathological and Biologic Type

Pathological examination is the cornerstone in diagnosing endometrial carcinoma. There are different types of endometrial carcinomas, as shown in Table 1. The endometrioid tumors are further classified according to the degree of morphological differentiation. As defined by the International Federation of Gynecology and Obstetrics (FIGO), endometrioid carcinoma of grade 1 consists of well-formed glands, with no more than 5% solid nonsquamous areas (areas of squamous differentiation are not deemed to be solid tumor growth). Carcinomas of grade 2 consist of 6–50% and grade 3 consists of more than 50% solid nonsquamous areas. The tumor is upgraded from grade 1 to 2, or from grade 2 to 3 if striking cytological atypia is found [2].

It is considered that the different molecular biology of the different histological type is probably related to different behavior and prognosis. With more understanding about biologic behavior of endometrial carcinoma, we know that histological grading is far from enough to evaluate degrees of malignancy of endometrial carcinomas. Although about 80% of all endometrial carcinomas are of the endometrioid type, several subtypes or variants of endometrioid carcinoma provide more valuable information for guiding therapy. Most of all, special subtypes may be associated with higher

Table 1: WHO histological classification of endometrial carcinoma.

Endometrioid adenocarcinoma
Variants: with squamous differentiation
Villoglandular
Secretory
with ciliated cells
Other adenocarcinomas
Mucinous carcinoma
Serous carcinoma
Clear-cell carcinoma
Mixed carcinoma
Squamous-cell carcinoma
Transitional-cell carcinoma
Small-cell carcinoma
Undifferentiated carcinoma

death rate, for example, uterine papillary serous tumors and clear cell carcinoma. On the basis of their Pathological and biologic features, endometrial carcinomas are classified into 2 subtypes [2].

About 80% of all endometrial carcinomas are type I carcinoma (endometrioid type), arise from atypical complex hyperplasia, which seems to affect mainly pre- and perimenopausal women and presents with less myometrial invasion, lower grade disease. The type I tends to arise in the setting of prior estrogen stimulation because it is usually estrogen receptor positive and associated with hyperestrogenism [3, 4]. Other associated findings include late onset of menopause, nulliparity, diabetes mellitus, and hypertension. The patients with Type I endometrial carcinoma have a better prognosis since the lesion is limited to the uterus in 70% of the cases; the 5-year survival rate of these patients is more than 85%.

In contrast, type II tends to occur in elderly postmenopausal women with high risk of relapse and metastatic disease, often with aggressive histologies such as serous or clear cell [3, 4]. Type II endometrial carcinomas appear to be unrelated to high estrogen levels. These tumors are not oestrogen driven and often develop in nonobese women. Type II endometrial carcinomas appear to be associated with endometrial atrophy; the histological type is either poorly differentiated endometrioid or nonendometrioid. A high proportion of tumors, even those with little or no myometrial invasion, have extensive extrauterine spread with complete surgical staging. More than 60% of patients with type II endometrial carcinoma present with advanced disease; 5-year survival is 43% for patients with stage III disease and 3% for patients with stage IV disease. Without adjuvant chemotherapy or vaginal brachytherapy, the recurrence rate is 23% in patients with stage I disease [4].

The molecular basis for different progression of these two subtypes is still unknown. However, a lot of clinical observations exhibited that gene alterations are specific for carcinomas of types I and II, which supports a dualistic model of endometrial carcinogenesis [5–10]. Type I endometrial carcinomas display a high incidence of alterations in KRAS oncogene, PTEN tumor suppressor gene [5, 6, 11–13], the β-catenin gene [14, 15], as well as defects in mismatch repair that results in microsatellite instability [10, 16]. In contrast, type II endometrial carcinomas are more likely to be characterized by p53 mutation and ERBB-2 (HER-2/neu) expression, and less commonly associated with E-cadherin and widespread aneuploidy [17–21]. However, there is some discrepancy in gene alterations report between two types of endometrial carcinomas (i.e., BUB1, CCNB2, MYC, STK15, etc.) [22]. Wong et al. performed an integrated, genome-wide analysis of gene expression in endometrioid adenocarcinomas and compared with normal endometrium controls. Supervised analysis identified 15 genes significantly upregulated and 132 genes downregulated in endometrial carcinoma, as compared with normal control. The gene expression profiles in endometrial carcinoma were classified in mutually dependent 6 function sets, resulting in 10 biological processes according to gene ontology. The gene ontology analysis showed that endometrial carcinogenesis underwent complete down-regulation of integrin binding and cell adhesion activity. Gene pathway analysis revealed the interaction among the genes of interest and its role in the endometrial carcinogenesis. The results from this preliminary study highlight novel molecular features of endometrioid endometrial carcinoma [23].

These data indicated that distinct patterns of gene expression characterize various histological types of endometrial carcinoma. An understanding of the molecular heterogeneity could potentially lead to better individualization of treatment in the future. Although some inconsistencies between single-gene and the whole-genomic approach have been observed, gene-array studies should be useful to disentangle molecular pathways and to identify potential targets for molecular-based treatments.

3. Diagnostic Approach

Endometrial carcinoma presents with abnormal uterine bleeding in 90% of patients. But other diseases could also cause abnormal uterine bleeding such as endometrial hyperplasia, and endometrial polyps. Proper treatment requires adequate preoperative work-up consisting of histopathology confirmation and imaging. The clinical approach to postmenopausal bleeding requires prompt and efficient evaluation to exclude or diagnose carcinoma.

One of the most convenient methods of achieving this is transvaginal ultrasound. Transvaginal ultrasonography can be useful in the triage of patients in whom endometrial sampling was performed but tissue was insufficient for diagnosis. Endometrial thickness is the most valuable parameter to prognosticate both endometrial carcinoma and any endometrial pathology (sensitivities of 90% and 89%, and specificities of 79% and 94% with optimal cutoffs of 9.6 and 7.7 mm, resp.) [24]. The majority of these studies reported that a thin (4-5 mm) endometrial measurement on transvaginal sonography can exclude malignancy in the majority of postmenopausal women with vaginal bleeding. This has a negative predictive value of 96% when

the endometrial echo is $\leqslant 4$ mm thick, whereas an echo >4 mm indicates the need for a biopsy [25].

When scanning demonstrates the possibility of pathology, outpatient hysteroscopy and biopsy are the gold standard for investigating the endometrial cavity [26]. Hysteroscopy, a significantly more accurate diagnostic method for the detection of endometrial pathology than transvaginal ultrasonography (TVS), has better specificity and should be considered for all patients with abnormal uterine bleeding with an endometrial thickness of more than 4 mm. For women showing abnormal or suspicious lesions, it is necessary to perform hysteroscopy with eye-directed biopsy because some cases of endometrial carcinoma are unlikely recognized by ultrasonography with an endometrial thickness less than 4 mm, the possibility of missing is 0.8% [27, 28]. It can be stated that there is a high level of concordance between findings of hysteroscopic studies and the directed endometrial biopsy [29]. But it is a pity that hysteroscopy is not warranted as a first line investigation for postmenopausal bleeding [30].

When the diagnosis is confirmed histopathologically, imaging is recommended to identify stages of the disease radiologically prior to surgery. The accuracy/sensitivity/specificity of TVS, CT, and MRI in detecting deep myometrial invasion were 89%/90%/88%, respectively. The sensitivity and accuracy of MRI in detecting deep myometrial invasion were significantly higher than those of TVS and CT [25]. For diagnosis of deep myometrial infiltration, cervical invasion, or both, MRI sensitivity and specificity were 56% and 85%; 47% and 83%; and 67% and 77%, respectively. However MRI has limited value in identifying patients with endometrial carcinoma who are at risk of lymph node metastasis [31].

Positron emission tomography (PET) is a new imaging technology in detection of subclinical nodal disease. Several investigators have demonstrated the value of PET in screening endometrial carcinomas [32, 33]. Recently, Signorelli et al. reported that patient-based sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of 18F-FDG PET/CT for detection of nodal disease were 77.8%, 100.0%, 100.0%, 93.1%, and 94.4%, respectively. Nodal lesion site-based sensitivity, specificity, positive predictive value, negative predictive value and accuracy of 18F-FDG PET/CT were 66.7%, 99.4%, 90.9%, 97.2%, and 96.8%, respectively. It seems that 18F-FDG PET/CT is an accurate method for the presurgical evaluation of pelvic nodes metastases. High negative predictive value may be useful in selecting patients who only may benefit from lymphadenectomy in order to minimize operative and surgical complications [34]. Kitajima and his colleagues compared the accuracy of integrated 18F-FDG PET/CT with intravenous contrast medium in detecting pelvic and paraaortic lymph node metastasis in patients of uterine carcinoma with surgical and histopathological findings used as the reference standard. They found that FDG-PET is only moderately sensitive in predicting lymph node metastasis preoperatively in patients with endometrial carcinoma [35]. Horowitz has similar conclusion about the sensitivity and specificity of FDG-PET for detecting pelvic and paraaortic lymph node metastasis in patients with uterine corpus carcinoma before surgical staging. The sensitivity and specificity of FDG-PET were 60% and 98%, respectively. A notable question is this imaging modality should not replace lymphadenectomy, but may be helpful for patients on whom lymphadenectomy cannot be, or was not, performed [36].

4. Treatment Overview

The cornerstone of curative for patients with endometrial carcinoma is surgical treatment, including complete hysterectomy, removal of remaining adnexal structures, and appropriate surgical staging in patients considered at risk for extrauterine disease. During the last 10 years interest in endometrial carcinoma has increased considerably and investigations into the following areas have increased our understanding of how we could reduce the risk of acquiring the disease and how we could best use the surgical and nonsurgical treatments available to us:

optimal use of adjuvant radiotherapy;

effect of hormonotherapy;

role of chemotherapy;

effectiveness of lymphadenectomy;

genetic predisposition to the disease; and

influence of less common histotypes.

5. Surgical Therapy

Treatment has remained relatively unchanged over the last 40 years relying principally on surgery to achieve cure. Survival is heavily dependent on surgical stage, which is determined by the classification system adopted by the FIGO in 1988. The foundation of primary treatment is hysterectomy, during which nodal assessment and surgical staging offer the opportunity for the most accurate assessment/detection of occult extrauterine malignancy in all women whose disease appears clinically confined to the uterus. Although these tenets are universally acceptable, the integration and implementation of these concepts when performing the "proper or appropriate" surgical procedure remain contested.

6. Surgical Staging

Surgical staging of endometrial carcinoma was first recommended 20 years ago by the FIGO. The development of surgical staging in the management of endometrial carcinoma has arisen over the last several decades with anticipated benefits including prognostic information, tailoring of adjuvant treatment, and a possible therapeutic effect. Twenty years later, the FIGO Committee introduced changes in the staging criteria [37]. Firstly, The FIGO Committee recognized the favorable prognosis for both the former Stage IA and IB patients and elected to merge these substages. Furthermore, the ambiguity of defining cervical invasion, based on the involvement of the cervical mucosa only, was recognized and the Committee merged the former

Stage IIA with Stage I disease. Secondly, the Committee eliminated the isolated positive peritoneal cytology criterion from the new staging system presumably based on the uncertain prognostic importance of isolated positive peritoneal cytology. Thirdly, the Committee incorporated some tumor characteristics (such as positive peritoneal cytology, invasion of the adnexa or vagina, or uterine serosa) by subdividing Stage IIIC patients into 2 different risk categories based on the presence (IIIC2) or absence (IIIC1) of metastatic disease in the paraaortic area.

Recently, Mariani et al. focused on the examination of paraaortic metastases relative to the inferior mesenteric artery (IMA), and found that 77% of patients with paraaortic node involvement had metastases above the IMA, whereas nodes in the ipsilateral paraaortic area below the IMA and ipsilateral common iliac basin were declared negative in 60% and 71%, respectively. In 25 patients with paraaortic node metastases which gonadal veins were excised, 28% patients had documented metastatic involvement of gonadal veins or surrounding soft tissue. These data indicates the need for systematic pelvic and paraaortic lymphadenectomy up to the renal vessels including consideration of excision of the gonadal veins [38].

7. Lymphadenectomy

As will be referred to shortly, there has been a vigorous debate about the benefits of pelvic (plus or minus paraaortic) lymphadenectomy. Although the assessment of the pelvic and paraaortic lymph nodes has been recommended since 1988, FIGO failed to define either the anatomical extent of the lymphadenectomy or the number of lymph nodes harvested to be considered adequate for the assessment of pelvic and paraaortic node basins. This question is further complicated when people try to assess the adequacy of lymphadenectomy that was performed.

There is also lack of consensus on the extent of surgical staging in endometrial carcinoma. Some authors suggest performing complete pelvic and paraaortic lymphadenectomy on all endometrial carcinoma patients because positive lymph nodes (including isolated paraaortic lymph nodes) are common in all grades [39]. It is reported that the carcinoma related survival and the recurrence free survival were better with standard surgery plus lymphadenectomy than with with adjuvant radiotherapy in treating the endometrioid adenocarcinoma type at high risk [40]. Other studies have assessed readily discernible parameters intraoperatively to identify patients having an extremely low probability of lymphatic spread in order to minimize under- and over-treatment [38, 41]. A recent report by Mariani et al. showed that sixty-three (22%) of 281 patients undergoing lymphadenectomy had lymph node metastases: both pelvic and paraaortic in 51%, only pelvic in 33%, and isolated to the paraaortic area in 16%. Furthermore, 77% of patients with paraaortic node involvement had metastases above the inferior mesenteric artery. Conversely, lymphadenectomy does not benefit patients with grade 1 and 2 endometrioid lesions with myometrial invasion $\leqslant$50% and primary tumor diameter $\leqslant$2 cm [38]. In the most recently published prospective randomized trials that aimed to test the therapeutic benefit of lymphadenectomy, Benedetti Panici reported that both early and late postoperative complications occurred more frequently in patients who had received pelvic systematic lymphadenectomy. Although systematic pelvic lymphadenectomy statistically significantly improved surgical staging, it did not increase disease-free or overall survival rate [42].

Researchers are concerned about the results of ASTEC surgical trial that showed no evidence of benefit in terms of overall or recurrence-free survival for pelvic lymphadenectomy in women of early endometrial carcinoma [43]. However, Amant et al. argued that there are several reasons why the ASTEC trial did not show improved overall survival with routine lymphadenectomy [44]. First, the number of lymph nodes resected was insufficient in many patients. Second, the high rate of inclusion of low-risk patients and the low number of lymph nodes removed are the reasons for the low rate of involved lymph nodes seen in the lymphadenectomy group. Third, the study group did not assess the paraaortic nodes. Fourth, the ASTEC trial was too small to detect an overall survival difference because the expected proportion of isolated pelvic lymph-node recurrences is as low as 2-3% in early endometrial carcinoma.

Without clear standard recommendations, surgical staging will continue to be a confusing topic, with no appropriate quality control. There are still many unanswered questions. Are there a critical minimum number of nodes that should be resected? Do the paraaortic nodes always need to be resected? Should the histologic type of uterine carcinoma determine the extent of lymphadenectomy? Do the modern robotic-assisted or laparoscopic approaches provide surgeons adequate exposure to perform sufficient lymphadenectomy? The ideal surgical staging for endometrial carcinoma remains a subject of active debate. We are hoping that more prospective randomized trials will solve them.

8. Laparoscopy

The standard surgical surgery of endometrial carcinomas includes total hysterectomy, bilateral salpingo-oophorectomy, and lymphoidectomy. However, the application of laparoscopy in the management of gynecologic malignancy has received much attention and given rise to considerable debate. During the past few years, several investigators have demonstrated that total or vaginally-assisted laparoscopic hysterectomy, associated with laparoscopic pelvic lymphadenectomy, represents a valid alternative to open surgery [45–48]. The potential health gain of performing a laparoscopic hysterectomy instead of an abdominal hysterectomy in patients with early stage endometrial carcinoma is expected in lower rate of intraoperative complications, less blood loss; lower transfusion rate and haemoglobin decrease, shorter hospital stay, as well as a faster return of bowel activity and quicker return to activities in daily life. Nevertheless, laparoscopic hysterectomy does not seem to modify the disease-free survival and the overall survival, laparoscopic approach is an effective procedure for treating early stage endometrial carcinoma [49–51]. Randomized

trials and long-term follow-up at various medical centers are necessary to evaluate the overall oncologic outcomes of this procedure.

9. Radiotherapy

Due to the difficulty in detecting cervical involvement preoperatively, treatment paradigms for stage II endometrial carcinoma often call for adjuvant radiotherapy postoperatively [52]. The debate regarding whether postoperative radiotherapy could improve survival has been fueled by multiple retrospective studies which have presented conflicting conclusions.

Several studies suggested that survival rate increases if a surgery is performed in conjunction with adjuvant pelvic radiotherapy, external beam radiotherapy (EBRT) or brachytherapy (BT). For high-risk disease, the standard care has always been pelvic radiotherapy. Clearly, there are advantages as shown in meta-analyses and by the Cochrane group [53, 54]. In the Gynecologic Oncology Group's prospective evaluation of adjuvant radiation, which included patients with occult stage II tumors, radiation decreased the risk of pelvic recurrence [55]. In a report of 162 stage II endometrial carcinoma patients, Cohn et al. noted that the 5-year disease-free survival was improved (94% versus 76%) in patients who underwent radical hysterectomy [52]. Likewise, the studies by Rossi teams came to similar conclusions. They found that women with Stage IIIC endometrial carcinoma receiving adjuvant EBRT and EBRT/BT had improved overall survival compared with patients receiving no additional radiotherapy. When direct extension of the primary tumor was present, the addition of BT to EBRT was even more beneficial [56]. Up to date, Wright and his colleagues examined 1577 women with stage II endometrial adenocarcinoma and analyzed the role of radical hysterectomy and radiation in management of endometrial adenocarcinoma. They found that women who did not receive radiation were 48% more likely to die from their tumors. The benefit of adjuvant radiation is most pronounced in women with high-risk pathologic features who underwent radical hysterectomy [57].

In contrast, other investigators have been unable to show a survival benefit based on the type of surgical procedure performed. In the paper by Kong, there is undoubtedly a benefit in local control when adjuvant pelvic radiotherapy is given but again no survival advantage. This is further supported by a presentation at ECCO 2007 from Cornes and Johnson in which they showed that there is up to a 10% survival advantage for patients with IC G3 tumors treated with pelvic radiotherapy [58]. They have also shown that for low-risk patients adjuvant EBRT is probably detrimental whilst for intermediate-risk patients although there may be a small benefit for some patients, this is offset by additional morbidity leading to an overall neutral effect. There are also two papers looking at data from the Survival, Epidemiology, and End Results (SEER) database [59, 60]. Both Lee et al. and Chan et al. analyzed the SEER data and showed that patients with high-grade IC G3 tumors appeared to benefit but failed to show any benefit to other patients. The data from a prospective, multicenter randomized trial of 645 evaluable low-risk endometrial carcinoma patients was showed that the impact of postoperative brachytherapy on even the locoregional recurrence rate seems to be limited in patients with low-risk endometrial carcinoma. The overall recurrence rate and survival were similar in postoperative vaginal irradiation and surgery alone groups [61].

The fresh data of ASTEC/EN.5 randomized trials was published recently. There was no evidence that overall survival with external beam radiotherapy was better than observation. Combined data from ASTEC and EN.5 in a meta-analysis of trials confirmed that there was no benefit in terms of overall survival (hazard ratio 1.04; 95% CI 0.84–1.29) and can reliably exclude an absolute benefit of external beam radiotherapy at 5 years of more than 3%. Interpretation adjuvant external beam radiotherapy cannot be recommended as part of routine treatment for women with intermediate-risk or high-risk early-stage endometrial carcinoma with the aim of improving survival [62]. Meanwhile, we should notice that adjuvant external beam radiotherapy did result in a small reduction in isolated local recurrence, but this analysis only included women who had local recurrence alone, ignoring 65% of women who had local and distant recurrence at the same time, or distant recurrence alone. The small reduction in isolated local recurrence does not translate into an effect on overall or recurrence-free survival.

Up to this point, it was emerging that patients with low-risk disease do not need any adjuvant treatment and can be treated by surgery and careful follow up. Patients with intermediate-risk disease are more problematic and may still be treated with external beam radiotherapy. Although the majority of retrospective data has not demonstrated a benefit for radiation, it has been suggested that women who undergo simple hysterectomy and are found with cervical disease may benefit from radiotherapy [63]. Feltmate et al. reported excellent outcomes in a series of 65 patients with stage II endometrial carcinoma, the majority of whom were treated surgically and followed by adjuvant radiation. In their cohort, 5-year disease-specific survival was 93% with recurrences in 15% [64]. Among 203 subjects with endometrial carcinoma, Sartori et al. noted a statistically significant improvement in 5-year survival from 74% with simple hysterectomy to 94% with a radical procedure [65].

Some clinical trials investigated the optimal of radiotherapy mode. It is considered that brachytherapy is a more convenient treatment than external beam radiotherapy and might be associated with less toxicity. In the PORTEC1-trial, the 5-year risk of vaginal and pelvic recurrence for high- intermediate risk patients was 19% without further treatment, compared to 5% after EBRT. Since most recurrences were located in the upper vagina, Phase II trials suggested vaginal brachytherapy (VBT) to be as effective as EBRT. PORTEC-2 is the first randomized trial comparing the efficacy of VBT and EBRT to determine which treatment provides optimal local control with best quality of life. The data suggested that vaginal brachytherapy is effective in preventing vaginal recurrence. Despite the slightly but significantly increased pelvic failure rate in the VBT arm,

rates of distant metastases, OS, and RFS were similar. As indicated by the patient survey on quality of life after treatment, VBT was shown to be better than EBRT, VBT should be the treatment of choice for patients with high-intermediate risk endometrial carcinoma [66]. First results of the randomized PORTEC-2 trial are evaluation about quality-of-life (QOL) after pelvic radiotherapy or vaginal brachytherapy for endometrial carcinoma. Patients in the VBT group reported better social functioning ($P < .002$) and lower symptom scores for diarrhea, fecal leakage, the need to stay close to the toilet, and limitation in daily activities because of bowel symptoms ($P < .001$). Vaginal brachytherapy provides a better quality of life than external-beam radiotherapy for Endometrial Carcinoma, and should be the preferred treatment from a quality of life perspective [67].

Nevertheless, the data is important and add to our understanding of the optimal management of endometrial carcinoma. Data from these data banks and the Cochrane reviews may help to address the question of which is the optimal treatment for this group. A further approach is to withhold radiation in the intermediate-risk group and offer careful surveillance and use salvage radiotherapy for relapses confined to vagina or vault. In the meantime we should consider that either immediate external beam radiotherapy or a watch and see policy with salvage radiation should be the standard approach.

10. Chemotherapy

Chemotherapy is emerging as an important treatment modality in advanced endometrial carcinoma. The use of neoadjuvant chemotherapy resulted in a high rate (80%) of optimal interval debulking surgery for the treatment of endometrial carcinoma with transperitoneal spread [68]. GOG 122 was the first randomized study to demonstrate a survival advantage with chemotherapy in advanced stage endometrial carcinoma [69]. At 60 months, 50% of patients received doxorubicin and cisplatin chemotherapy were predicted to be alive and disease-free when adjusting for stage compared with 38% of patients who had whole-abdominal irradiation. The data from GOG 122 showed that combination chemotherapy had a survival advantage over whole abdominal radiotherapy in Stage III and IV endometrial carcinoma.

There are several studies focused on the toxicity, tolerability, and feasibility of delivering combination chemotherapy with subsequent radiation therapy to women with advanced endometrial carcinoma, and evaluate the long-term bowel toxicity. It is notable that GOG 122 study had an extremely high toxicity rate from chemotherapy (68% Grade 4 hematologic toxicity), including 8 treatment-related deaths. It is apparent that cisplatin and/or doxorubicin-based regimens are associated with unfavorable rates of toxicity [69]. A Phase I GOG study by Soper et al. indicates that treatments comprised of whole abdomenopelvic radiation with concomitant weekly cisplatin, followed by doxorubicin and cisplatin chemotherapy, had prohibitive toxicity and did not undergo further evaluation [70]. Bruzzone et al. reported a series of 45 women who received cisplatin and cyclophosphamide followed by radiotherapy, in which 10 women (22%) completed 3 cycles or less [71]. Duska et al. reported a pilot study for advanced stage disease, which included 3 cycles of paclitaxel, doxorubicin, and carboplatin, followed by radiotherapy [72]. All patients required G-CSF support, but 50% still experienced Grade 3 or 4 acute toxicity. In RTOG 9708, in which 4 cycles of cisplatin and paclitaxel were administered after completion of radiotherapy, acute Grade 3/4 toxicity was greater than 80% [73]. In comparison, Lupe et al. used the combined modality protocol comprised of carboplatin and paclitaxel with involved field radiotherapy had a much lower acute toxicity rate, and the compliance rate was very high [74].

Meanwhile, the use of chemotherapy alone has been associated with high rates of pelvic relapse, ranging from 18% to 47% [69, 75]. Recently, Takeshima et al. reported with postoperative adjuvant chemotherapy, recurrences occurred predominantly at distant sites in the absence of pelvic radiation in surgically staged grade 3 endometrial carcinoma. Estimated 5-year disease-free survival rates were 89.8% for patients with surgical stage I-II disease, 78.6% for those with surgical stage III disease, and 87.3% overall [76]. There is an emerging consensus that chemotherapy may be insufficient for reducing the risk of pelvic relapse although it appears to be an important component of treatment. Sovak et al. reported a pelvic relapse rate of 44% in patients with Stage III and IV disease who received 6 cycles of adjuvant carboplatin and paclitaxel, of whom only 5 (10%) also received adjuvant pelvic radiotherapy [77]. In RTOG 9708, the pelvic relapse rate was only 2%. It suggested that the addition of radiation to chemotherapy does appear to be associated with a lower rate of pelvic relapse [73]. However, in that study, 23% had Stage I and 16% had Stage II disease. The low rate of pelvic relapse may be partly attributed to the more favorable stage distribution. Alvarez Secord et al. published a large retrospective study of 356 Stage III and IV patients treated with radiation alone (48%), chemotherapy alone (29%), and combined modality therapy (23%) [78]. After adjusting for stage, age, grade, and debulking status, the hazard ratios (HR) for overall survival were 1.6 (95% CI 0.88–2.89) and 2.0 (95% CI 1.17–3.48) for chemotherapy and radiation alone, respectively, compared to combined modality therapy. Matsuura et al. reported most recently that combined treatment with radiotherapy/chemotherapy was associated with a better survival rate than chemotherapy alone (78% versus 62%, resp.). In Stage IIIc endometrial carcinoma, the combined use of radiotherapy and chemotherapy could reduce pelvic recurrence (33.3% and 7.1%, resp.) and was associated with a better survival rate than chemotherapy alone (78% versus 62%, resp.) [79]. Based on this concurrent carboplatin/paclitaxel and intravaginal radiation in surgical stage I-II serous endometrial carcinoma study, surgical staging followed by involved-field radiotherapy and carboplatin/paclitaxel is well tolerated and effective in stage I-II serous endometrial carcinoma [80]. Confirmation of these results on a larger number of patients with longer follow-up is still needed.

What is the optimized chemotherapy regimen is still a subject of debate. Historically, the treatments used have been a combination of a platinum and anthracycline, usually cisplatin and doxorubicin (AP), but this can be quite a toxic regime and is often poorly tolerated, therefore it is not ideal for combining with radiation therapy. Adding paclitaxel (TAP) usually needs growth factors to support the administration. Hellenic Co-operative Oncology Group (HeCOG) studied the drug regimen comprised paclitaxel, topotecan, and carboplatin in metastatic endometrial carcinoma. With G-CSF support, the drug regimen appears active with acceptable toxicity in patients with metastatic or recurrent carcinoma of the endometrium [81]. In relapsed disease, the GOG are currently evaluating TAP versus TC [82]. In addition, the optimal regimen remains to be defined as all of them (doxorubicin/cisplatin-AP, cyclophosphamide/doxorubicin/cisplatin-CAP, paclitaxel/carboplatin-TC, and paclitaxel/doxorubicin/ cisplatin-TAP) cause significant toxicity. Although randomized evidence is limited, the combination of carboplatin and paclitaxel has been commonly used in advanced endometrial carcinoma because of its manageable toxicity and excellent response rates (64–78%) [77, 83–88]. McMeekin et al. studied the maximum tolerated dose and feasibility of weekly cisplatin and paclitaxel chemotherapy administered concurrently with whole abdominal radiation therapy in women with high-risk endometrial carcinoma. A regimen of cisplatin 25 mg/m^2 and paclitaxel 20 mg/m^2 weekly with whole abdominal radiation therapy was determined to be feasible, but is associated with moderate acute and chronic gastrointestinal toxicity [89].

Further investigations are required to define the subgroup of patients who benefit from postoperative adjuvant chemotherapy. Two randomized clinical trials are in progress in order to obtain available evidence which can help clinicians make wise decisions on treatment options, such as adjuvant chemotherapy of patients with high-risk stage I and II, as well as stage IIIA endometrial carcinoma. GOG 209 is an ongoing study randomizing women with Stage III or IV endometrial carcinoma to either doxorubicin, cisplatin, paclitaxelwith G-CSF, or carboplatin and paclitaxel. Additionally, PORTEC 3 is an ongoing randomized Phase III trial comparing concurrent chemoradiation and adjuvant chemotherapy (4 cycles of carboplatin and paclitaxel) versus pelvic radiation alone in high risk and advanced stage disease. This study is timely and necessary to determine whether radiotherapy or chemotherapy improves overall survival and failure-free survival, compare the rates of severe (grades 3 and 4) treatment-related toxicity, pelvic and distant recurrence, and evaluate quality of life of patients with high-risk and advanced stage endometrial carcinoma.

11. Functional Preservation

Although the median age of patients with endometrial carcinoma is in the early 60s, approximately 5% of patients are younger than age 40 when diagnosed. In the presence of early staged endometrial carcinoma, most have favorable outcomes, thus their quality of life after treatment is as important a consideration as a cure of carcinoma. This issue is especially imperative when endometrial carcinoma is encountered in younger or reproductive ages when the afflicted woman has not achieved her fertility function. Despite being a critical issue, there are only a few studies with definite treatment guidelines or any evidence-based recommendations concerning conservative treatment for endometrial carcinoma.

Since early 1980s, there have been several reports on conservative treatment with progestins for early-stage endometrial carcinoma in young women. Most of them were small series and retrospective studies from single institutions. Response rates and recurrence rates varied (i.e., the response rate for endometrial carcinoma and atypical endometrial hyperplasia ranged from 57% to 76% and from 83% to 92%, respectively, and the recurrence rate ranged from 11% to 50%) [90–96]. Such variations were probably due to the differences in drugs used, dosage, and duration of treatment. Daily doses of megestrol acetate ranged between 10 and 400 mg, and that of medroxyprogesterone acetate (MPA) ranged between 200 mg and 800 mg. Nevertheless, there have been no prospective trials to investigate the optimal dosage, duration of treatment, curative rate of MPA treatment, or pregnancy rate after this therapy in young women with endometrial carcinoma and atypical endometrial hyperplasia. Therefore, Ushijima et al. conducted a multicenter, prospective phase II study on MPA treatment. Their prospective study conducted to clarify the accurate complete response (CR) rate of treatment with MPA at a fixed dose of 600 mg/d for 26 weeks, has demonstrated that the CR rate for endometrial carcinoma and atypical endometrial hyperplasia was 55% and 82%, respectively, and the recurrence rate was 57% and 38%, respectively [97]. In another prospective multicentric prospective study, Ushijima et al. evaluated the efficacy of fertility-sparing treatment by MPA for endometrial carcinoma and atypical endometrial hyperplasia. Complete response was found in 44% in endometrial carcinoma and 82% in atypical endometrial hyperplasia. 9 pregnancies and 4 normal deliveries have been recorded after MPA therapy. Twelve recurrences were found in 30 complete response patients (40%) between 7 to 22 months. Data showed that even in the complete response patients, close follow-up is required because of their high recurrence rate [98]. Recently, Signorelli et al. conducted a prospective study of conservative treatment in 21 young nulliparous women with grade G1 endometrial carcinoma stage IA or atypical complex hyperplasia. All were treated with a low-dose cyclic natural progestin therapy (200 mg/day from day 14–25) and encouraged to attempt pregnancy immediately. Overall response rate to progestin therapy was 57%. Nine women conceived spontaneously (43%) and 8 women with persistent disease or partial response to hormonal treatment. Three additional complete responses were observed after delivery [99].

A largely unanswered question is the safety of ovarian preservation in young women with endometrial carcinoma. First, estrogen production from the ovaries may stimulate microscopic foci of residual endometrial carcinoma. Although vitro data [100] has suggested that estrogen stimulates the growth of endometrial carcinoma cells and

upregulates the expression of estrogen receptors, this concern has not been observed clinically so far. Several reports examined the use of estrogen replacement therapy in postmenopausal women with endometrial carcinoma. Yet, these studies have not demonstrated any increase in the risk of recurrence or death in women receiving estrogen replacement [101–103]. The new data published by Korean Gynecologic Oncology Group (KGOG) in 2009 suggest that ovarian preservation does not adversely impact the recurrence of early stage endometrial carcinoma [103]. The most influential report was a prospective trial of estrogen replacement therapy in more than 1,200 women with endometrial carcinoma conducted by the Gynecologic Oncology Group. Although the prospective trial was closed early, the absolute recurrence rate was only 2.1% (HR 1.27; 95% CI, and 0.92 to 1.77) [101]. The findings from these studies, as well as the data from Wright group, suggest that the risk of estrogenic stimulation of residual endometrial carcinoma is quite low, particularly in women with early-stage, low-risk lesions. The second potential risk of ovarian conservation is the presence of a coexisting synchronous primary tumor within the ovaries. Synchronous primary tumors of the endometrium and ovary are reported in approximately 5% of women with endometrial carcinoma [104]. However, among young women with endometrial carcinoma, the incidence of coexisting ovarian tumors is increased and has been reported with a range from 5% to 29% [104–107].

Although many studies have examined the risk of ovarian metastases in young women with endometrial carcinoma, there are no data to describe the safety of ovarian conservation. In 2009, Wright firstly reported that ovarian preservation is safe in young women with early-stage, low-grade endometrial carcinoma [108]. Their findings are notable in that ovarian preservation in premenopausal women with early-stage, low-grade endometrial carcinoma may be safe and not associated with an increased risk of carcinoma related mortality. Although the survival estimates suggest that ovarian conservation does not negatively impact outcome, it should be recognized that ovarian preservation may be associated with a two-fold or greater increase in mortality. Given the potential consequences of surgical menopause, further research to examine the safety of ovarian conservation for young women with early-stage endometrial carcinoma is clearly warranted. At present, the long-term risks and benefits of ovarian preservation should be carefully discussed with young women with endometrial carcinoma before hysterectomy.

12. Fertility Sparing

Although there is no known fertility-sparing surgical option for women with endometrial carcinoma, selected young patients of childbearing age with apparent early endometrial carcinoma who wish to preserve fertility may consider treatment with progestin therapy rather than surgery. If such treatment is contemplated, it is recommended that a thorough hysteroscopy and curettage be performed to rule out a worse lesion prior to initiation. A review of the literature indicates 101 patients with a median age of 29 years who were treated with progestin therapy rather than definitive surgery subsequently had 56 children [91]. Additionally, Gershenson et al. provided indirect evidence to support the recent concept of using the fertility-sparing or conservative surgery or therapy for malignancies in women that the use of conservative modalities can be applied in the management of endometrial carcinomas because there are many reports showing that endometrial carcinomas can be treated with a simple diagnostic dilatation and curettage followed by some potent hormone therapy, including a progestin agent, in highly selected young women who would like to preserve their fertility potential [109].

Recently, there have been a number of reports of women with uterine endometrial carcinoma who became pregnant and gave birth after the administration of medroxyprogesterone acetate (MPA) [93, 110–114]. Meanwhile subsequently assisted reproductive techniques such as transfer of embryos with intracytoplasmic sperm injection (ICSI) and preimplantation genetic diagnosis (PGD) may be valuable to achieve immediate pregnancy [115–117].

Gadducci et al. reviewed the related literature and confirmed that approximately three fourths of the women achieve a histologically documented complete response, with a mean response time of 12 weeks, but about one third of these subsequently developed a recurrence after a mean time of 20 months. Following high dose progestin therapy and confirmation of the regression of carcinoma, the patient might attempt to conceive spontaneously. However, assisted reproduction techniques might increase the likelihood of pregnancy and decrease the time interval to conception. Several successful pregnancies have occurred after a fertility-sparing treatment of endometrial atypical hyperplasia or endometrial carcinoma, more frequently with assisted reproductive technologies. The implementation of in vitro fertilisation techniques not only increases the chance of conception, but it may also decrease the interval to conception [118]. However, despite the achievements of these studies on fertility-sparing treatments, there are no definite treatment guidelines or any evidence-based recommendations and many questions still remain unanswered regarding the selection of patients. Nevertheless, the optimal dose or duration and curative rate of MPA therapy in endometrial carcinoma and atypical endometrial hyperplasia in young women are still uncertain.

It is vital to choose appropriate patients with endometrial carcinoma to adopt ovarian preservation and fertility-sparing treatment. The best candidates for progestin therapy are women who have a relative hyperestrogenic state, which is thought to cause the malignancy. Indeed, some patients would not chose fertility-sparing treatment given the lack of data on oncologic safety. Fertility-sparing treatments are successfully used; however, these treatments can be offered only to a limited number of patients which meet the pathologic criteria for a conservative approach [119]. The indications for conservative treatment include the patient's desire to preserve fertility, no medical history of thrombosis, and no abnormal levels of hemostasis, a histologic diagnosis of grade 1 endometrioid adenocarcinoma by total endometrial

curettage, no myometrial invasion or extrauterine spread of the disease observed by MRI, and hysteroscopy and total endometrial curettage must be repeated after 4–6 weeks of additional MPA therapy. Additionally, the expression of receptor for progesterone receptor (PR), PTEN gene, DNA mismatch repair gene MLH1 and phospho-AKT on tissue specimens may be useful for selecting patients fit for a conservative management [118, 120].

The opportunity of a demolitive surgery after delivery or after childbearing being no longer required is still a debated issue. Large multicenter trials are strongly warranted to better define the selection criteria for a conservative treatment, endocrine regimen of choice, the optimal dosing, the duration of treatment and follow-up protocols. Until now, the long-term outcome of children in utero exposed to oncological treatment modalities is poorly documented. Delivery should be postponed preferably until after a gestational age of 35 weeks. Further research including international registries for gynecologic carcinoma in pregnancy is urgently needed. The gathering of both available literature and personal experience suggested models for treatment of gynecologic carcinoma in pregnancy [121]. In any case, the patient should be accurately informed about the relatively high recurrence rates after complete response to hormone treatment and expectations for pregnancy.

13. Biomarker and Targeted Therapy

As previously stated, distinct molecular changes are associated with two subtypes, and these distinct molecular alterations also underscore prognostic differences. Therefore, active researches are enthusiastic about novel screening approaches that emerged from epigenetics, proteomics, and genomics in endometrial carcinoma. It is hopeful that the use of targeted therapies will improve the outcome for endometrial carcinoma.

Nowadays, several novel tumor markers with increased sensitivity and specificity for endometrial carcinoma have been identified and are considered to help monitor response to therapy and to detect recurrent disease. These potential molecular biomarkers include HE4, CA125, Cyr61, p21, p53, Cathepsin-B, MMR, and ERR[alpha] progesterone receptor (PR)-A, which are estimated to contain potential value as prognostic factors for patients with endometrioid carcinoma [122–128]. Additionally, Bidus et al. reported two cell cycle checkpoint genes, CDC2, MAD2L1, and The ZIC2 zinc finger gene were associated with lymph node metastasis in endometrial carcinomas [129]. Currently, these tumor makers are utilized in this role with limited value. Further investigation in the role of biomarker for early detection of recurrent endometrial carcinoma and monitoring response to therapy is warranted. Gene expression profiling of the primary tumors in patients with endometrioid endometrial carcinomas seems promising for identifying genes associated with lymph node metastasis. Future studies should address whether the status of nodal metastasis can be determined from the expression profiles of preoperative tissue specimens.

With the progress of advanced gene techniques, it has become possible to identify potential molecular markers of endometrial carcinoma for its diagnosis, prognosis and therapy by global gene expression profiling. It may provide a foundation for the development of new diagnostic and prognostic markers and type-specific therapies against this common female genital malignant disease. Such procedure allowed us to give shape to preliminary gene expression profile typical for neoplastic tissue and to estimate protein expression of the most significant predictors of neoplastic transformation. Comparison of obtained data with tumor grade can reveal new markers of endometrial carcinoma useful in routine diagnostic procedures [23, 130].

Genes related to the endometrial carcinoma progression and metastasis can be identified by differential gene expression profile with cDNA microarray and high-risk endometrial carcinoma may be distinguished before surgery by hierarchical cluster analysis [131]. Similarly, the dysregulation of these miRNAs appeared to be involved in the progression of endometrial carcinoma [132]. Therefore, some researchers suggested that the cDNA and miRNAs microarray techniques may be feasible to generate gene expression profiles of endometrial carcinoma. Classification based on gene expression patterns may be more accurate than histological grade and FIGO stage classification in predicting the prognosis of tumors [133]. Further extended and functional studies of these new approaches are required to confirm the potential use of them in the endometrial carcinomas.

With the applications of the target gene therapy, some valuable research had carried in advanced endometrial carcinoma. Since the year 2000, in advanced endometrial carcinoma, the GOG has conducted phase II trials with several molecular targeting agents including imatinib (Gleevec), trastuzumab (Herceptin), and gefitinib (Iressa) as single agents with negligible evidence of activity. The GOG does have active trials of chemotherapy with a molecular targeting agent such as bevacizumab (Avastin) in GOG 218, but there are no randomized molecular targeting agent trials in advanced endometrial carcinoma [134]. Some genes related with endometrial carcinoma prognosis have become a hopeful target for therapies in endometrial carcinoma, these targeting genes include mTOR inhibitors, EGFR tyrosine kinase inhibitors (erlotinib), and monoclonal antibodies to Her-2/neu (trastuzumab) [135–138]. However, acceptance of genetic consultation and testing is surprisingly low and deserves further investigation. For example, it is hypothesized that the HER-2/neu receptor could be used for targeted therapy in recurrent endometrial carcinoma. In a clinical trial, trastuzumab was of little clinical value in two cases of recurrent type II endometrial carcinoma based on the lack of response and changes in tumor biology [139]. In another trial, a multinomial design two-stage phase II study was performed to evaluate single-agent activity of erlotinib, an orally active, selective inhibitor of EGFR tyrosine kinase activity, in women who had advanced endometrial carcinoma with recurrent or metastatic disease, and were chemotherapy naive and received up to one line of prior hormonal therapy. The data showed that erlotinib is well tolerated with an overall objective response rate of 12.5% [136]. These reports underscore the importance of reassessment of targeted

treatment in endometrial carcinoma. Yet, researchers still have a long way to go in order to reach the goal of applying the targeting gene therapy in clinical practice.

14. Prevention and Surveillance

In the follow-up of endometrial carcinoma patients, pain was the most common complaint in patients with recurrent disease, followed by vaginal bleeding, general malaise, loss of weight and intestinal complaints. With the evidence from randomized clinical trials we can conclude that a follow-up program in the first three years after primary treatment of endometrial carcinoma is helpful in detecting recurrent disease.

In 2007, van Wijk et al., evaluated their clinical data of patients with recurrent endometrial carcinoma treated in the Erasmus Medical Centre in Rotterdam over a 20-year period [140]. He reported that patients with screen-detected recurrences had a 5-year survival rate of 62%. Patients with interval screening recurrences or recurrences detected by chance had a 5-year survival rate of 47%. Evaluating the patients with an endometrioid type of tumor separately, the 5-year survival rate for patients screen-detected recurrences is 68% and for patients with interval screening recurrences is 51% [140]. The reported median intervals to local and distant recurrent disease are consistent with those reported in the literatures [141, 142].

Tjalma et al. published an overview of 11 retrospective studies (evaluating 2866 patients) on routine follow-up of endometrial carcinoma. In these studies symptomatic recurrences ranged between 41% and 81% (mean 65%) of all recurrences [143]. Retrospective data from both Agboola group and Tjalma group suggest that there is no difference in survival between symptomatic and asymptomatic recurrences, or between women with recurrences detected during routine follow up visits and those with recurrences detected during the interval between routine visits [143, 144]. Furthermore, there is no economic or clinical justification for the routine use of the Pap smear and systematic radiography in the follow-up of patients with endometrial carcinoma [144, 145]. Centers advocating surveillance should focus on the detection of potentially curable vaginal recurrences, since isolated vaginal-vault recurrence of endometrial carcinoma is curable in up to 87% of cases, in patients previously not exposed to radiation [146].

Tjalma et al. pointed out that because of a difference in survival between isolated vaginal recurrence and nonvaginal recurrences, 5-year survival, respectively 50% and 6%, it is important to identify isolated vaginal recurrences early. As the sensitivity of routine follow-up schemes appears very low, tailored follow-up protocols based on high risk and low risk for recurrence are suggested [143]. Low risk patients are generally defined as patients with adenocarcinoma IA grade 1 or 2 or IB grade 1, with a recurrence rate of just under 4%, whereas high risk patients have a recurrence rate of around 23% [147]. Salvesen et al. found a low risk group, with FIGO Stage IA/IB or patient age below 60 years at primary operation was identified in multivariate recurrence-free survival analysis. No asymptomatic recurrences were found in this group. Therefore, they concluded that low risk patients should be considered for less frequent follow-up [141]. However, van Wijk et al. reported of five low risk patients with recurrent disease, only one patient, suffering from distant recurrent disease, was symptomatic. Without a follow-up program for patients with low-risk endometrial carcinoma, recurrent disease would only have been detected after symptoms had developed in four of these five patients. It was discussed that there is no reason to use different follow-up scheme for these patients, despite our low number of patients with low risk disease. Improving patient education so that early symptoms of recurrence are reported appears eminently sensible, but may serve also to heighten anxiety amongst the majority who will never develop recurrent disease [142]. For patients who have evidence of metastatic disease at time of surgery, it is nowadays generally accepted that there is a survival benefit to be gained if all gross evidence of disease can be resected or at least debulked to leave small-volume residual disease [148].

Most endometrial carcinomas are sporadic, but approximately 10% of cases have a hereditary basis [149–153]. Two genetic models have been suggested in the development of endometrial carcinoma: hereditary nonpolyposis colorectal carcinoma (HNPCC) syndrome, also known as Lynch II syndrome, and a predisposition for endometrial carcinoma alone. Both are autosomal dominant inherited carcinoma susceptibility syndrome caused by a germline mutation in one of the deoxyribonucleic acid (DNA) mismatch repair genes [153]. It is associated with early onset of carcinoma (age younger than 50 years) and the development of multiple carcinoma types, particularly colon and endometrial carcinoma. Women with Lynch syndrome have a 40-60% risk of endometrial carcinoma, which equals or exceeds their risk of colorectal carcinoma. In addition, they have a 12% risk of ovarian carcinoma. Despite limited information on the efficacy of surveillance in reducing endometrial and ovarian carcinoma risk in women with Lynch syndrome, the current gynecologic carcinoma screening guidelines include annual endometrial sampling and transvaginal ultrasonography beginning at age 30–35 years [154]. But the cost effectiveness of this screening has not been proven either. An alternative approach is primary prevention by using a progestogen device in utero, such as the Mirena IUCD. This merits full evaluation [155].

In addition, risk-reducing surgery consisting of prophylactic hysterectomy and bilateral salpingooophorectomy should be offered to women aged 35 years or older who do not wish to preserve their fertility [154]. Schmeler et al. reported a retrospective analysis of women with known germline mutations associated with Lynch syndrome. Sixty-one participants underwent prophylactic hysterectomy and were compared to over 200 matched controls with similar mutations that did not have preventive surgery. Endometrial carcinoma was eventually diagnosed in 33% of the controls with no cases in the prophylactic surgery group [156]. Pistorius et al. report detected asymptomatic muscle invasive endometrial carcinoma in two of four women who underwent prophylactic hysterectomy after requiring surgery for Lynch syndrome related colorectal carcinoma [157].

In 2006 a multiinstitutional, matched case-control study found that prophylactic hysterectomy with bilateral salpingo-oophorectomy is an effective primary preventive strategy in women with HNPCC syndrome [156]. Based on these observations, surgery as primary prevention for women at high risk due to known germline lesions or history of Lynch syndrome related malignancies may yield a meaningful reduction in progression to endometrial carcinoma.

15. Summary

Endometrial carcinoma is a low-grade curable malignancy and most patients who present with early disease have excellent survival rate. Endometrial carcinoma remains a management challenge, presenting with a full spectrum of disease ranging from that with excellent prognosis and high curability to aggressive disease with poor outcome. There are many debates and controversies about optimal treatment for women with different staging endometrial carcinoma. How do we summarize the current recommendations and how do we proceed? Clinicians must balance delivering adequate therapy while attempting to minimize treatment morbidity and must always be weighed carefully.

Improved understanding of the mechanisms of carcinogenesis may help identify molecular signatures that could predict biologic behavior of individual disease presentations and discover potential molecular candidates for targeted therapies. Total hysterectomy and bilateral salphingo-oophorectomy is the primary operative procedure. Pelvic lymhadenectomy is performed in most centers on therapeutic and prognostic grounds and to individualize adjuvant treatment. Women with endometrial carcinoma can be readily segregated intraoperatively into "low-risk" and "high-risk" groups to better identify those women who will most likely benefit from thorough lymphadenectomy. Postoperative irradiation is used to reduce pelvic and vaginal recurrences in high risk cases. Treatment planning should be conservative in order to reduce patients' morbidity and overtreatment while maintaining acceptable recurrence and survival rates. Progression in diagnostic imaging, radiation delivery systems, and systemic therapies potentially can improve outcomes while minimizing morbidity. The availability of new hormonal and biological agents presents new opportunities for therapy. Novel strategies for screening and prevention also hold promise for reducing incidence and mortality of this disease. The current evidence suggests that there remain avenues to improve management and we need to continue rigorous investigation to identify and implement the best available practice. Research in the next ten years should provide valuable new strategies not only for treatment but also for prevention.

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Review Article

Molecular Profiling of Endometrial Malignancies

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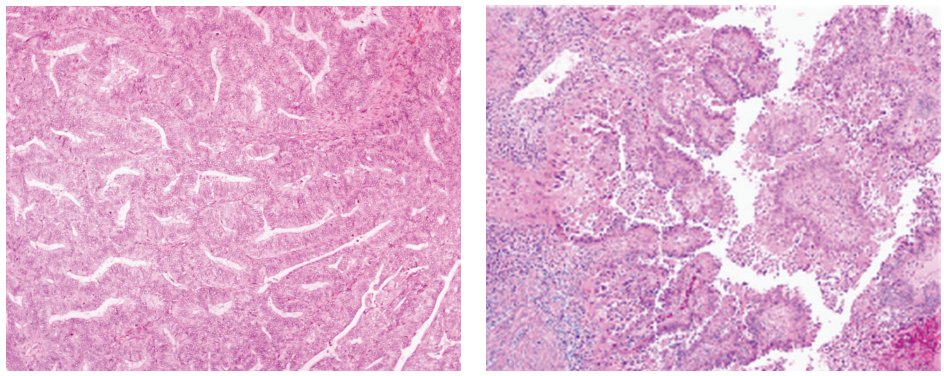
Molecular profiling of endometrial neoplasms reveals genetic changes in endometrial carcinomas that support the dualistic model, in which type I carcinomas are estrogen-dependent, low grade lesions and type II carcinomas are nonestrogen dependent and high grade. The molecular changes in type I endometrial carcinomas include mutations in *PTEN, PIK3CA, KRAS,* and β-catenin, along with microsatellite instability, whereas type II endometrial carcinomas are characterized by genetic alterations in *p53, HER2/neu, p16,* and E-cadherin. For endometrial neoplasms with a malignant mesenchymal component, *C-MYC* mutations and loss of heterozygosity are frequently seen in carcinosarcomas, and a fusion gene, *JAZF1/JJAZ1*, is distinctive for endometrial stromal sarcoma. In addition, *p53* mutations may play an important role in tumorigenesis of undifferentiated endometrial sarcoma. These molecular changes can help in the diagnosis of endometrial neoplasms, as well as form the basis of molecular targeted therapy.

1. Introduction

Endometrial malignancies can be categorized into two main groups based on the cell of origin: (i) endometrial carcinoma including carcinosarcoma and (ii) endometrial stromal sarcoma. Endometrial carcinomas show a broad spectrum of phenotypes which show various histologic appearances for example, endometrioid, serous, mucinous, squamous, urothelial, or clear cell, reflecting the differentiation potential of the müllerian epithelium and the difference in the tumorigenetic pathways of each tumor type. Women with an inherited predisposition for endometrial neoplasm have been reported, associated with autosomal dominant disorders such as hereditary nonpolyposis colorectal carcinoma (HNPCC) and Cowden syndrome. Some endometrial carcinomas undergo mesenchymal differentiation and are termed carcinosarcomas (formerly termed malignant mixed müllerian tumors). Pathogenetically and clinically, two distinct forms of endometrial adenocarcinoma, type I and type II, have been described. The molecular alterations driving endometrial carcinogenesis may follow a sequence similar to Vogelstein's model for the progression of colorectal adenoma to carcinoma. This process is accompanied by stepwise genetic changes of oncogenes and tumor suppressor genes. Endometrial stroma may give rise to neoplasms that resemble normal endometrial stromal cells. The spectrum of endometrial stromal tumors ranges from the benign stromal nodule to the malignant endometrial stromal sarcoma. An oncogenic fusion gene, *JAZF*1/*JJAZ*1 plays a significant role in tumor development of endometrial stromal sarcomas [1].

2. Molecular Profiling of Endometrial Carcinoma

2.1. Dualistic Model of Endometrial Tumorigenesis. Endometrial carcinoma is the most common malignant neoplasm of female genital tract in developed countries [2] with an estimated 42,160 new cases diagnosed in the United States for 2009 [3]. Approximately 90% of cases of endometrial carcinoma are sporadic, whereas the remaining 10% of cases are hereditary [4]. Clinically, the patients with endometrial carcinomas most often present with abnormal uterine bleeding. In advanced stages, patients may complain of pelvic pain, reflecting spread of the carcinoma. Bokhman [5] first described the pathogenetic classification of 2 different types of endometrial carcinoma, designated as type I and type II carcinomas, according to the determination of biological properties of the tumor, its clinical course, and the prognosis of the disease.



(a) (b)

Figure 1: The prototypes for the dualistic model of endometrial carcinoma. Type I endometrioid endometrial carcinoma shows glands lined by stratified neoplastic columnar cells (a), ×100; and type II serous carcinoma showing papillary structures and high nuclear grade (b), ×100.

2.1.1. Type I (Endometrioid Endometrial Carcinoma) [1, 2, 4–13]. Type I carcinomas represent the majority of sporadic cases of endometrial carcinoma, accounting for 70–80% of new cases [4, 9–12] which occur predominantly in pre- and perimenopausal women. These cancers are typically of endometrioid type (Figure 1(a)). Risk factors include obesity, hyperlipidemia, and hyperestrogenism for example, anovulation, nulliparity/infertility, late onset of menopause, and endometrial hyperplasia. The tumors in this category are generally low-grade, low-stage, and indolent. They commonly express estrogen and progesterone receptors [2, 4–11]. The rare mucinous carcinomas are also considered type I carcinomas because they usually express estrogen and/or progesterone receptors and are of low histologic grade [10, 11].

2.1.2. Type II (Nonendometrioid Endometrial Carcinoma) [1, 2, 4–13]. Type II carcinomas are less common, accounting for 10–20% of endometrial carcinoma [4, 6]. They are nonendometrioid in differentiation, most frequently papillary serous (Figure 1(b)) and less frequently clear cell, have high-grade histology, typically arise in an atrophic endometrial background, and often have deep myometrial penetration. They usually occur at an older age, approximately 5–10 years later than type I tumors. There is no relationship to estrogen stimulation. Clinically, type II cancers have an aggressive behavior, with a high frequency of distant spread to pelvic lymph nodes. Small cell, undifferentiated and squamous cell carcinomas may also be encountered among type II carcinomas, but little is known about their tumorigenesis [11]. The clinical and pathological features of the two types of endometrial carcinomas are summarized in Table 1.

2.2. Common Molecular Genetic Alterations in Dualistic Model. Evidence for divergent molecular alterations supporting the dualistic model of endometrial tumorigenesis became available approximately 10 years after Bokhman's description of the clinical and pathologic features. The two distinct histological types of carcinomas are associated with genetic alterations of independent sets of genes. These genetic changes may occur singly or in various combinations which differ between individual cases [9].

Westin and colleague [14] described that expression of estrogen-induced genes, *RALDH2, EIG121, SFRP1, SFRP4, IGF-1*, and *IGF-IR*, tend to be highest in the well-to-moderately differentiated endometrioid carcinoma. This finding supports the partitioning of endometrial carcinoma into two distinct groups by traditional estrogen-related classification. According to this model, normal endometrial cells would transform into endometrioid endometrial carcinoma through 5 different molecular changes, including, mutations of *PTEN, PIK3CA, KRAS*, and *CTNNB1* (β-catenin) genes and microsatellite instability (MSI) while non-endometrioid endometrial carcinoma is frequently related to alterations of *p*53 and chromosomal instability [7, 8, 15, 16]. Non-endometrioid endometrial carcinoma frequently demonstrates high-ordered aneuploidy and has an intact mismatch repair (MMR) mechanism [12]. Furthermore, none of the five main alterations of endometrioid endometrial carcinoma (mutations of *PTEN, PIK3CA, KRAS*, and *CTNNB1* genes and MSI) plays a major role in non-endometrioid endometrial carcinoma. However, in many endometrial carcinomas exhibit overlapping clinical, morphologic, immunohistochemical, and molecular features of the both types of carcinoma for example, a subset of endometrioid endometrial carcinoma is found with a background of atrophic endometrium or papillary serous carcinoma may occasionally develop from a pre-existing endometrioid endometrial carcinoma and may share histological and genetic features [8–10]. Matias-guiu et al. [8] described the development of non-endometrioid endometrial carcinoma through these possible pathways: (i) *de novo*, through *p*53 mutations, loss of heterozygosity (LOH) at several loci, and some other still unknown gene alterations; or (ii) through dedifferentiation of a pre-existing endometrioid carcinoma. These dedifferentiated non-endometrioid endometrial carcinomas exhibit overlapping features with type I endometrioid endometrial carcinoma [8].

Table 1: Clinical and pathological characteristics of type I and type II endometrial carcinoma [1, 2, 4–13].

	Type I	Type II
Proportion of endometrial carcinomas	4/5	1/5
Menstrual status	Pre- and perimenopausal	Postmenopausal
Endocrine-metabolic disturbance	Present	Absent
Estrogen-associated	Yes	No
Background endometrium	Hyperplasia	Atrophy
Histological type	Endometrioid	Serous, clear cell
Tumor grade	Low	High
Depth of myometrial invasion	Superficial	Deep
Behavior	Stable/indolent	Progressive/aggressive

Comparison of the major genetic alterations between type I and type II endometrial carcinomas is shown in Table 2.

Molecular genetic alterations have been extensively investigated in endometrioid and papillary serous adenocarcinomas of the endometrium. These two tumor types are characterized by distinctive molecular alterations, and their tumorigenesis follow separate pathways.

2.3. Molecular Pathology of Endometrioid Carcinomas

2.3.1. PTEN. The most frequently altered gene in endometrioid endometrial carcinoma is *PTEN* (phosphatase and tensin homologue deleted from chromosome 10), also called *MMAC1* (mutated in multiple advanced cancers 1). *PTEN* behaves as a tumor suppressor gene, is located on chromosome 10q23.3 and encodes a lipid phosphatase that antagonizes the PI3K/AKT pathway by dephosphorylating PIP3, the product of PI3K. This lipid molecule is an important second messenger that regulates the phosphorylation of a protein termed AKT, also known as protein kinase B. Decreased *PTEN* activity causes increased cell proliferation and survival through modulation of signal transduction pathways.

PTEN may be inactivated by several mechanisms such as mutation, LOH, and promoter hypermethylation. Somatic *PTEN* mutations are common in endometrial carcinoma, and they are almost exclusively restricted to endometrioid endometrial carcinomas, occurring up to 83% of them [1, 4, 11, 12]. Germline mutations of *PTEN* are responsible for Cowden syndrome [9, 12]. *PTEN* may be also inactivated by deletion, as shown by LOH in 40% of endometrial carcinomas [7–9, 17]. Promoter hypermethylation leading to *PTEN* inactivation, is found in about 20% of tumors, most of which are high-stage [10].

PTEN mutations have been detected in 15–55% of endometrial hyperplasias with and without atypia [9, 13]. Interestingly, concordance between MSI status and *PTEN* mutations has been found; the mutations occur in 60–86% of MSI-positive endometrioid endometrial carcinoma but in only 24–35% of the MSI-negative cases [7–9, 13, 17]. This suggests that *PTEN* could be a target for mutations in the context of DNA repair deficiency [13]. In addition, identical *PTEN* mutations have been also identified in hyperplasias coexisting with MSI-positive endometrioid endometrial carcinoma, which suggests that *PTEN* mutations are early events in their development [8]. On the other hand, identical *PTEN* mutations have been detected in MSI-negative endometrial hyperplasia with coexisting MSI-positive endometrioid endometrial carcinomas. Thus, some *PTEN* mutations may precede MSI, and coexistence of both alterations does not necessarily mean a cause-effect relationship [9]. Evaluation of *PTEN* inactivation in endometrial carcinoma precursor lesions by *PTEN* immunostaining has been proposed. However, commercially available antibodies (e.g., clone 10P03, 28H6, polyclonal, 6H2.1) do not have statistically significant associations with the molecular genetic alterations [7, 9, 19]. Some data suggest that *PTEN* is associated with younger age, low stage, endometrioid histology, low histologic grade, and favorable prognosis (78% 5-year survival for patients without mutations, compared with 95% and 93% for patients with one or more mutations, resp.) [7, 9]. In addition, recent data suggest that only *PTEN* mutations outside exons 5–7 may predict favorable survival, independent of the clinical and pathological features of the tumors [9].

2.3.2. PIK3CA. The *PIK3CA* (p110α catalytic subunit of PI3K) gene locates on chromosome 3q26.32. Phosphatidylinositol-3-kinase (PI3K) is heterodimeric lipid kinase consisting of a catalytic subunit (p110) and a regulatory subunit (p85) in PI3K/AKT signaling pathway. This pathway is frequently activated in endometrial carcinoma through various genetic alterations and their combinations. Activation of PI3K produces the second messenger PIP3 which subsequently activates various down-stream pathways such as AKT. This regulation involves suppression of apoptosis and enhancement of cell proliferation [9]. *PIK3CA* activation is reported in 26–36% of endometrial carcinoma and may coexist with *PTEN* (15–27%) [7, 9, 12, 15, 20] and *KRAS* mutations [9, 15, 20] suggesting that the *PIK3CA* mutations cooperate with these alterations in malignant transformation [16]. Mutations in *AKT* family members and their correlation with other gene alterations are found in endometrial carcinoma,

Table 2: Genetic alterations of type I and type II endometrial carcinomas, reported in percentages (references).

	Type I	Type II
PTEN inactivation	Up to 83% [1, 4, 11, 12]	11% [1, 2, 12]
PIK3CA mutation	26–36% [7, 9]	5% [7]
KRAS mutation	10–30% [1, 2, 4, 7–12, 17]	0–10% [2, 12]
β-catenin /*CTNNB1* mutation	14–44% [7, 8]	0–5% [1, 7, 10, 11]
Microsatellite instability	20–45% [1, 7–10]	0–11% [8, 9]
p53 mutation	10–20% [1, 4, 6, 7, 10, 11, 13, 17, 18]	90% [1, 2, 4, 6, 7, 10–13, 17]
HER2/*neu* amplification	10–30% [1, 4, 10, 17]	18–80% [13]
p16 inactivation	10% [1, 4, 7, 10, 11]	40–45% [4, 7, 10]
E-cadherin loss	10–20% [1, 4, 7, 10, 11]	60–90% [4]

including *AKT2* (D399N), *AKT2* (D32H) and *AKT3* (E438D) mutations. Mutations of *AKT3* (E438D) also have amplification of and a mutation in *PIK3CA* [21]. *AKT1 E17K* mutation is not associated with either *PTEN* or *PIK3CA* genomic alteration [21]. In vitro studies showed that activating mutations of *PIK3CA* in combination with *PTEN* mutations led to an additional increase in phosphorylated *AKT* when compared with cells with only inactivated *PTEN* [6]. Some investigators have claimed that *PIK3CA* mutations are mutually exclusive of *PTEN* mutations, suggesting that tumorigenic signaling through this pathway can occur either through activation of *PIK3CA* or inactivation of *PTEN* [9]. Recently, interactions between the *PI3K/AKT* and *p53* signaling pathways have been described in which activation of the *PI3K/AKT* pathway through *PTEN* or *PIK3CA* mutations, together with *p53* inactivation, results in malignant transformation [15]. Moreover, patients with dysregulation of PI3K/AKT signaling pathway and *p53* alterations had shorter survival than patients with only *p53* alterations [15]. Mutations were more common in mixed endometrioid-nonendometrioid adenocarcinomas (44%) than in pure endometrioid adenocarcinomas (28%) or pure nonendometrioid adenocarcinomas (21%) [15]. In fact, *PIK3CA* mutations are usually missense and cluster in exons 9 (helical domain) and 20 (kinase domain). The tumors carrying exon 9 *PIK3CA* mutations are more likely to be low-grade carcinomas; in contrast, carcinomas with exon 20 mutations or *PIK3CA* mRNA overexpression are often high-grade carcinomas associated with myometrial invasion and tended to have lymphovascular invasion [15]. Furthermore, in high-grade endometrioid adenocarcinomas and mixed carcinomas, *PIK3CA* mutations in exon 20 coexist with *p53* alterations more frequently than in nonendometrioid adenocarcinomas. However, *PIK3CA* mRNA overexpression occurs in concert with *p53* alterations only in nonendometrioid endometrial carcinomas [15]. *PIK3CA* mutations did not correlate with MSI or β-catenin/*CTNNB1* mutations [9, 18]. *PIK3CA* mutations, particularly exon 20 mutations or *PIK3CA* mRNA overexpression, are frequent in endometrioid endometrial carcinoma in association with invasion and adverse prognostic factors such as blood vessel invasion [7, 15].

2.3.3. KRAS. *KRAS* encodes a member protein of the small GTPase superfamily and is involved in signal transduction pathways between cell surface receptors and the nucleus. *KRAS* mutations have been identified in 10–30% of endometrioid endometrial carcinomas [1, 2, 4, 7–12, 17] while some investigators have reported an almost complete absence of *KRAS* mutations in serous and clear cell carcinomas of endometrium [8]. Some studies found a higher frequency of *KRAS* mutations in MSI-positive carcinomas than in MSI-negative tumors [8–10, 16] suggesting that both events may occur simultaneously before clonal expansion [10, 13]. *KRAS* mutations were detected in endometrial hyperplasias at a similar rate to that observed in endometrioid endometrial carcinomas, suggesting that *KRAS* mutations are early events in endometrial carcinogensis [9, 13]. No relationship has been found between *KRAS* mutations and tumor stage, histologic grade, depth of myometrial invasion, age, or clinical outcome in endometrioid endometrial carcinomas [9].

2.3.4. β-Catenin (CTNNB1). The β-catenin gene (*CTNNB1*) maps to 3p21. It appears to be important in the functional activities of both APC (adenomatous polyposis coli) and E-cadherin. It is a component of the E-cadherin-catenin unit, essential for cell differentiation and maintenance of normal tissue architecture and also plays an important role in Wnt signal transduction pathway. Mutations in exon 3 of *CTNNB1* result in stabilization of a protein that resists degradation, leading to nuclear accumulation of β-catenin, have been described in endometrioid endometrial carcinoma. The accumulation of β-catenin can be demonstrated by immunostaining. Several studies have analyzed endometrial carcinomas showing that nuclear accumulation of β-catenin is significantly more common in endometrioid lesions (31–47%) compared with nonendometrioid histology (0–3%) [4]. By comparison in colonic adenocarcinomas, elevated β-catenin levels caused by mutations in *CTNNB1* or APC result in activation of the Wnt/β-catenin/LEF1 pathway through a LEF1 binding site in the *cyclin D1* promotor, triggering *cyclin D1* gene expression, and subsequently, uncontrolled progression of tumor cells into the cell cycle [8, 12]. Furthermore, β-catenin might regulate the expression of

the matrix metalloproteinase-7 that would have a role in the establishment of the microenvironment necessary for the initiation and maintenance of growth of the primary tumor and metastasis [8, 12]. The reported frequency of *CTNNB1* mutations in endometrioid endometrial carcinoma ranges from 14–44% [7, 8]. They seem to be independent from the presence of MSI and the mutations of *PTEN* and *KRAS*, suggesting that the Wnt pathway may play an independent role in endometrial cancer [10, 13]. In all cases, the mutations were homogeneously distributed in different areas of the tumors suggesting that they play a role in early steps of endometrial tumorigenesis. Alterations in β-catenin have been reported in endometrial hyperplasias with squamous metaplasia [7, 9]. Although there was a good correlation between *CTNNB1* mutations and β-catenin nuclear immunostaining, the presence of cytoplasmic and nuclear β-catenin immunoreactivity in some endometrial carcinomas without *CTNNB* mutation suggests that the changes of other genes in the Wnt/β-catenin/LEF-1 pathway may be responsible for the stabilization and putative transcription activator role of β-catenin [7, 8]. Endometrioid endometrial carcinomas with *CTNNB1* mutations are characteristically early stage tumors associated with favorable prognosis [7, 9]. Two members of the secreted frizzled-related protein (SFRP) family, SFRP1 and SFRP4, were more frequently down-regulated in MSI-positive carcinomas compared with MSI-negative carcinomas. This down-regulation was associated with frequent promoter methylation of SFRP1 and led to an activation of the β-catenin pathway. In addition, the Wnt-target fibroblast growth factor 18 was up-regulated in endometrioid carcinomas with MSI compared with normal endometrium [1].

2.3.5. Microsatellite Instability. Microsatellite DNA sequences are polymorphic, short-tandem repeats distributed throughout the genome. The most common microsatellite in human is a dinucleotide repeat of CA, (CA)n, and there are 50,000 to 100,000 (CA)n repeats scattered in the human genome [8, 9]. Microsatellite instability (MSI) is a condition manifested by damaged DNA because of defects in normal DNA repair process. Mammalian mismatch repair (MMR) genes encode for nine proteins (MLH1, MLH3, PMS1, PMS2, MSH2, MSH3, MSH4, MSH5, and MSH6) that interact with each other to form complexes and heterodimers that mediate distinct functions in MMR-related system. This repair process plays a central role in promoting genetic stability by repairing DNA replication errors, inhibiting recombination between non-identical DNA sequences and participating in responses to DNA damage. MSI is a common genetic abnormality that has been detected in 20–45% of sporadic endometrioid endometrial carcinoma [7–10]. In addition, MSI in nonendometrioid endometrial carcinomas has been reported (0–11%) [8, 9], particularly in mixed endometrioid and serous carcinomas, but not in pure serous carcinomas [10]. In sporadic endometrial carcinoma, epigenetic cause of MSI is more common involving MLH1 promotor hypermethylation which is the main cause of MMR deficiency [7–9, 13, 15]. This epigenetic inactivation usually occurs in atypical hyperplasia, most of which coexists with carcinomas. Thus, MLH1 hypermethylation is an early event in the pathogenesis of endometrioid endometrial carcinoma, which precedes the development of MSI [7–9, 15]. The remaining unmethylated MLH1 cases reveal MSH2 mutations (15%) and MSH6 mutations (60%), of which almost half are germline mutations. Thus, MSH6 mutations seem to be a frequent cause of MSI [11, 12]. Tumors with MSI of CpG island methylation in the promoter region have been identified in some other genes, for example, *p16*, *PTEN*, and E-cadherin (*CDH1*), suggesting altered methylation may be a coexisting independent early change [9]. The presentation of some small short-tandem repeats such as mononucleotide repeats located within the coding sequence of important genes for example, transforming growth factor β receptor type II (*TGF-βRII*), *BAX*, insulin-like growth factor II receptor (*IGFIIR*), *MSH3, MSH6, caspase-5*, and *PTEN* may promote MSI-positive endometrial carcinoma [8, 9]. Secondary mutations at one or more mononucleotide tracts found in 72.7% of tumors with MSI, are responsible for tumor progression [7–9]. International Federation of Gynecology and Obstetrics (FIGO) grade has been found to be higher in endometrioid endometrial carcinomas with MSI in some, but not all studies, similar to the well-established association between MSI and high-grade colorectal carcinomas [16]. By multivariate analysis, a significant correlation between MSI-positive tumors and tumor-infiltrating lymphocytes in endometrioid endometrial carcinoma was found: 40 tumor-infiltrating lymphocytes/10 high power fields has a sensitivity of 85% and a specificity of 46% in predicting MSI [16].

2.4. Molecular Pathology of Nonendometrioid Carcinomas

2.4.1. p53. The *p53* tumor suppressor gene locates to chromosome 17p13.1. While *p53* mutations occur in 90% of non-endometrioid endometrial carcinoma, they are only present in 10–20% of endometrioid endometrial carcinoma, which are mostly high-grade [7, 18]. The abnormal p53 expression has been found in 11% of grade 1 endometrioid endometrial carcinoma [18]. This finding supports that *p53* mutations may influence progression of endometrioid endometrial carcinomas to non-endometrioid endometrial carcinomas [9]. In fact, *p53* mutation is the most characteristic genetic alteration of non-endometrioid endometrial carcinomas [9, 10] and may be useful in their distinction from endometrioid endometrial carcinomas [22]. In *p53* positive endometrioid endometrial carcinoma, p53 protein accumulation may be secondary to changes in its upstream regulatory proteins rather than the *p53* gene itself. Several genes, including *MDM2* and *p14 AR*, that regulate *p53* levels have been shown to cause detectable levels of *p53* in the absence of *p53* mutation. Alternatively, nonspecific DNA damage such as that induced by irradiation is also known to induce accumulation of wild-type *p53* [12]. In normal cells, *p53* is rapidly degraded and thus cannot be detected by immunostaining. *p53* mutations produce a non-functional protein that resists degradation and can be visualized by

immunostaining [11, 18]. However, loss of function of *p53* resulting from LOH may not correlate with protein overexpression. In addition, frameshift mutations and stop codons lead to a truncated protein, which is not detected by antibodies and leads to negative immunohistochemistry [11, 18] After DNA damage, nuclear *p53* accumulates and causes cell cycle arrest by inhibiting *cyclin D1* phosphorylation of the *Rb* gene and thereby promoting apoptosis [9, 13]. Overexpression of *p53* is associated with high histological grade and advanced stage as well as unfavorable prognosis [9, 18]. Endometrial intraepithelial carcinoma (EIC), the putative precursor lesion to serous carcinomas [4, 13, 18, 22, 23], characterized by replacement of the surface epithelium by malignant cells exhibiting cytological features similar to those of serous carcinoma [9, 23]. EIC has been reported in nearly 90% of uteri containing serous carcinoma that is often extensive and multifocal [23]. Mutations of *p53* are also found in 75–80% of EIC. It is postulated that mutation in one allele occurs early during the development of serous carcinoma, and loss of the second normal allele occurs late in the progression to carcinoma [4]. *p53* mutations are almost always associated with aneuploidy and do not seem to occur with *PTEN* mutations in the same tumor [10, 11].

2.4.2. HER2/neu. Epidermal growth factor receptor II or *HER2/neu* is an oncogene that codes for a transmembrane receptor tyrosine kinase involved in cell signaling and located at the long arm of human chromosome 17q12. *HER2/neu* overexpression or amplification is more frequently found in non-endometrioid endometrial carcinoma (18–80%) [13] than in grade 2 and 3 endometrioid carcinoma (10–30%) [7, 9, 10] and has been associated with adverse prognostic parameters including advanced stage, high histologic grade, and low overall survival [9, 13].

2.4.3. p16. *p16* plays an important role in regulating the cell cycle. It is a tumor suppressor gene located on chromosome 9p21 [10]. *p16* inactivation can lead to uncontrolled cell growth. Inactivation of *p16* is more frequent in non-endometrioid endometrial carcinoma (40–45%) than in endometrioid endometrial carcinoma (10%) [4, 7, 10]. The underlying mechanism is unclear [7, 11], because neither promoter hypermethylation nor deletion or mutation is frequently found [11]. Loss of *p16* expression is correlated with *KRAS* and *p53* mutations and is associated with high stage, high grade, and poor survival [10].

2.4.4. E-Cadherin. Cadherins are a family of adhesion molecules essential for tight connection between cells. E-cadherin is encoded by *CDH1* gene and locates on chromosome 16q22.1. It is thought to be a tumor suppressor gene, the loss of which has been demonstrated to promote tumor invasion and metastasis. Decreased expression of E-cadherin is frequent in endometrial carcinoma and may be caused by LOH or promotor hypermethylation. LOH at 16q22.1 is seen in almost 60% of non-endometrioid endometrial carcinoma, but in only 22% of endometrioid endometrial carcinoma [7]. In endometrial carcinoma, partial or complete loss of E-cadherin expression correlates with aggressive behavior [9].

Among type II carcinomas, clear cell carcinomas seem to follow a separate pathway that shows some overlap with serous and endometrioid carcinomas. *p53* mutations are only present in about 30–40% of clear cell carcinomas compared to 90% of serous carcinomas. However, the frequency of MSI and *PTEN* alterations in clear cell carcinoma is higher than in serous carcinoma (15% versus <5 for MSI and 30% versus 10% for *PTEN*) but lower compared with endometrioid carcinoma (20–40% and 35–50%, resp.) [24]. A recent molecular study demonstrated that the majority of pure clear cell carcinomas do not show mutations in either *PTEN* or *p53*, the most commonly altered genes in type I and type II tumors, respectively. These findings suggest that clear cell carcinoma may arise through a distinct pathologic pathway [6].

2.4.5. Apoptosis Resistance in Endometrial Carcinoma. Several of the molecular abnormalities that have been detected in EC may be associated with apoptosis deregulation. Apoptosis can be initiated by two main mechanisms: (i) the "intrinsic pathway" activated by released mitochondrial proteins, such as cytochrome-c; and (ii) the "extrinsic pathway" activated by ligand-bound death receptors such as tumor necrosis factor (TNF), Fas or TNF-related apoptosis including ligand (TRAIL) receptors. Some studies have shown that cellular apoptosis susceptibility (*CAS*) gene, *BCL2, BAX*, and caspase-3 are apparently involved in the progressive deregulation of proliferation and apoptosis, leading from simple and complex endometrial hyperplasia to adenocarcinoma. As described above, *PTEN* antagonizes the PI3K/AKT pathway by dephosphorylating PIP3, resulting in decreased translocation of AKT activation. Thus, loss of *PTEN* function leads to increased levels of phospho-AKT, activation of anti-apoptotic protein, and cell cycle progression [9]. NF-κB, frequently activated in endometrioid endometrial carcinomas, may inhibit apoptosis by activation of target genes such as *FLIP* and *Bcl-XL*. Furthermore, there are reports that apoptosis-related protein survivin is frequently overexpressed in endometrial carcinomas [7, 9] and correlates inversely with *PTEN* expression [9]. Where widespread genetic abnormalities exist that cannot be corrected, MMR proteins initiate apoptosis as a more energy efficient option of universal genomic preservation [16]. MMR deficiency lowers the apoptotic rate, leading a survival advantage to the mutated cells [16].

2.4.6. cDNA Array Studies. cDNA analyses have demonstrated that the expression profiling of endometrioid endometrial carcinoma is different from that of non-endometrioid endometrial carcinoma. These studies have identified gene signatures specific for non-endometrioid endometrial carcinomas as well as genes specifically up- or down-regulated in endometrioid endometrial carcinomas when compared with normal endometrium. Intestinal trefoil protein, *TFF3, AGR2* developmental gene, estrogen-regulated genes (*MGB2, LTF, END1, MMP11*), *FOXA2*,

and *MSX2* were significantly up-regulated in endometrioid endometrial carcinomas, while increased expression of *FOLR*, genes involved in the regulation of mitotic spindle checkpoint (*STK15, BUB1, CCNB2*), *IGF2, PTGS1* and *p16* were seen in non-endometrioid endometrial carcinomas. *STK-15* also known as *BTAK,* Aurora-A, is a serine/threonine kinase which is essential for chromosome segregation and centrosome functions [7, 9]. Overexpression of *STK15* induces increased numbers of centrosomes, aneuploidy, and malignant transformation. One study found *STK15* amplification in 9 of 15 (60%) non-endometrioid endometrial carcinomas but in none of endometrioid endometrial carcinomas [9]. Furthermore, a different expression profile was also found between endometrial carcinoma associated with MSI and stable endometrial carcinoma. *SFRP1* and *SFRP4* were more frequently down-regulated in endometrial carcinoma with MSI. One study compared the expression profiles of similar histological subtypes of ovarian and endometrial carcinomas, and showed that clear cell carcinomas had a very similar profile, regardless of the organ of origin. In contrast, differences were seen when comparing endometrioid and serous carcinomas of ovarian and endometrial origin [7].

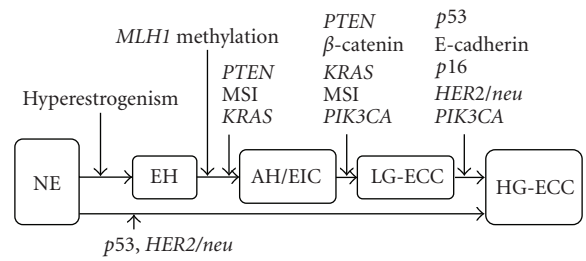


Figure 2: A progression model for endometrioid carcinoma. Tumor initiation and progression are characterized by acquisition of various molecular alterations. *PTEN* alterations appear central to the initiation of proliferative lesions that then acquire mutations in other cancer-causing genes (e.g., DNA mismatch repair genes, *KRAS*, *β*-catenin) in the carcinogensis. An alternative pathway bypasses atypical hyperplasia and low-grade carcinoma to high-grade carcinoma by *p53* mutation and *HER2/neu* amplification. NE, normal endometrium; EH, endometrial hyperplasia without hyperplasia, AH, atypical endometrial hyperplasia; EIC, endometrial intraepithelial carcinoma; LG-ECC, low grade endometrioid endometrial carcinoma; HG-ECC, high grade endometrioid endometrial carcinoma.

3. Genetic Changes in Endometrial Carcinogenesis (Progression Models) of Endometrioid and Serous Carcinomas, Including Molecular Changes of Premalignant Disease (Hyperplasia/EIC)

By epidemiological and molecular evidence, endometrial hyperplasia represents a true precursor lesion for endometrioid endometrial carcinomas, whereas non-endometrioid endometrial carcinomas are frequently associated with endometrial intraepithelial carcinoma (EIC) [13].

3.1. Progression Model for Endometrioid (Type I) Carcinomas. A progression model of endometrioid carcinoma resembling the Vogelstein progression model for colorectal carcinoma has been proposed. This hypothesis is supported by the evidence that (i) some of the genetic alterations found in endometrioid endometrial carcinomas are already present in atypical hyperplasia, (ii) increased genetic alterations are found in well-differentiated endometrioid carcinoma compared with atypical hyperplasia, (iii) the number of genetic alterations increase according to higher histologic grade, and (iv) more chromosomal imbalances are identified in endometrial carcinoma compared with atypical hyperplasia, using comparative genomic hybridization (CGH) [11].

Most simple hyperplasias and a subset of complex hyperplasias are polyclonal and considered reactive processes due to hyperestrogenism, which may regress through progesterone therapy [11, 23]. In contrast, most atypical hyperplasias are monoclonal. A subset of complex hyperplasia without atypia has been reported to be monoclonal. In addition, the number of chromosomal aberrations in complex hyperplasia is significantly higher than simple hyperplasia and close to the number found in atypical hyperplasia. Most of the genetic alterations identified in endometrioid endometrial carcinoma seem to occur very early in the development of endometrioid carcinoma, although it is not clear which alterations are associated with the earliest changes of malignant transformation and progression to neoplasia [10, 11]. In atypical hyperplasia, alterations of *PTEN*, *β*-catenin, *KRAS*, and MSI are present, with *PTEN* inactivation occuring in about 50% of the cases. However, *PTEN* and *KRAS* mutations seem to occur earlier, since they were found in simple hyperplasia, partially associated with monoclonality. *PTEN* inactivation has been reported in normal endometrial glands but its significance is yet unknown [11]. The inactivation of E-cadherin gene by methylation seems to play a role during progression of endometrioid carcinoma, since it is most frequently found in grade 3 and least frequently in grade 1 tumors [10]. Furthermore, *p53* mutations, *HER2/neu* overexpression or amplification, and *p16* inactivation are considered in late events during carcinogenesis of endometrioid carcinoma, since they are predominantly identified in grade 3 tumors, but rarely in grade 1 tumors, and are absent in atypical hyperplastic lesions. Hypothetically, *p53* mutations and *HER2/neu* amplification might also be early events in *de novo* poorly differentiated endometrioid carcinomas [10, 11] (Figure 2). Endometrial pre-cancers (e.g., EIC) have been postulated to share common genetic alterations with endometrioid endometrial carcinoma, including *PTEN* mutations and MSI [13].

3.2. Progression Model for Nonendometrioid (Type II) Carcinomas. Mutations of *p53* were found in approximately 80% of EIC, but in contrast to most serous carcinomas, there is no LOH at the locus TP53. Thus, it is hypothesized that *p53* mutation of one allele occurs early, whereas loss of the normal second allele accompanies progression into serous carcinoma [10, 11]. The alterations of E-cadherin,

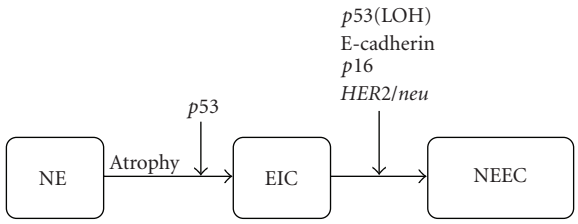


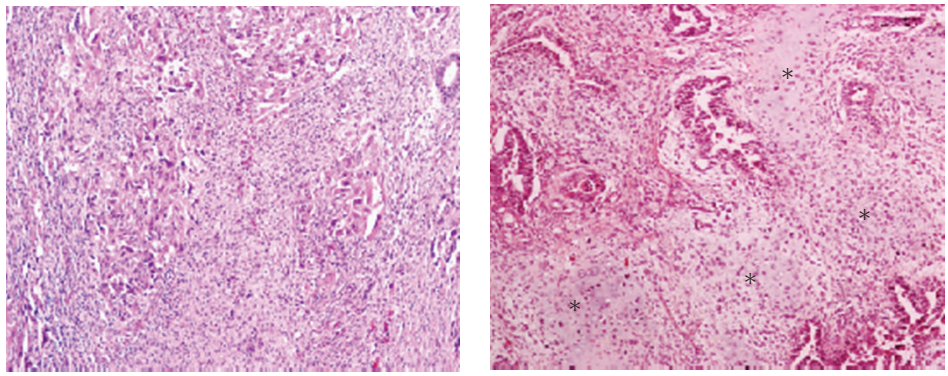
Figure 3: A progression model for nonendometrioid (type II) carcinomas. *p53* mutations play a critical role in the conversion of atrophic endometrium to an intraepithelial form of serous carcinoma. NE, normal endometrium; EIC, endometrial intraepithelial carcinoma; NEEC, non-endometrioid endometrial carcinoma.

p16, and *HER2/neu* seem to affect the progression from EIC to serous carcinoma [10]. Another group hypothesized that serous carcinoma may develop from endometrioid carcinoma through *p53* mutation based on findings in mixed endometrioid and serous carcinomas. Early genetic alterations during carcinogenesis are not clear, as these authors presented no data for EIC [10, 11] (Figure 3).

4. Hereditary Endometrial Carcinoma

Hereditary endometrial carcinoma has been found in 2–5% of endometrial cancer [24]. Hereditary nonpolyposis colon cancer (HNPCC), also known as Lynch syndrome or cancer family syndrome, accounts for the majority of inherited cases [24]. It is an autosomal dominant syndrome that predisposes its carriers to multiple malignancies particularly colorectal, and endometrial carcinomas [25], caused by a germline mutation in one of the DNA MMR genes occurring in 30–60% of cases [8, 9]. Endometrial carcinoma is the most common extracolonic malignancy in patients with HNPCC. In women with HNPCC, the incidence of endometrial carcinoma equals or exceeds that of colorectal carcinoma, compared with 1% in the general population [26], and in more than 50% of HNPCC cases, these women present with a gynecological cancer as their first or "sentinel" malignancy [25]. The frequency of germline DNA MMR gene mutations among unselected patients with endometrial carcinoma has been found to be 1.8–2.1%, which is similar to the frequency of HNPCC in colorectal carcinoma [25]. Patients with endometrial carcinoma in the HNPCC population have an inherited germline mutation in *MLH1, MSH2, MSH6*, or *PMS2* (first hit) but endometrial carcinoma develops only after the initiation of a deletion or mutation in the contralateral *MLH1, MSH2, MSH6*, or *PMS2* allele (second hit) in endometrial cells [7, 8]. Once the 2 hits have occurred, the deficient MMR function of *MLH1, MSH2, MSH6*, or *PMS2* causes the acquisition of MSI and subsequent tumor development [7–9]. Unlike HNPCC associated colorectal carcinoma, which appears to frequently have *MLH1* and *MSH2* mutations, endometrial carcinomas have a higher probability of *MSH2* and *MSH6* mutations [13, 25]. Women with HNPCC who carry *MSH2* and *MSH6* mutations have a higher chance to present initially with endometrial rather than colorectal cancer [16]. MSI has been detected in 75% of endometrial carcinoma associated with HNPCC [8, 9]. Many studies have shown that MSI is associated with endometrioid histologic type. However, 14–21% of HNPCC-associated endometrial carcinomas are non-endometrioid, but only 3.3–4.5% of sporadic MSI tumor [16]. Women with an inherited predisposition for endometrial neoplasia tend to develop the disease 10 years earlier than the general population [9]. There is 18–23% incidence of HNPCC syndrome in endometrial carcinoma patients younger than 50 years old [16]. In addition to endometrial carcinoma arising from HNPCC, occasional families show clustering of endometrial cancer alone, without colon or other cancers. This group was termed as "familial site-specific endometrial cancer" [10]. Loss of protein expression seems to occur frequently for both *MLH1* and *MSH2* in endometrial hyperplasia and is considered an early event during tumor development [11]. *PTEN* inactivation by mutation seems to also be involved in tumorigenesis, since it occurs in about 90% of type I carcinomas [11]. Currently, there are no data to suggest that the prognosis for women with HNPCC-associated endometrial cancers is either better or worse than for women with sporadic cancers [16, 24]. In one study, endometrial carcinoma in HNPCC kindreds was a cause of death in 12% of cases; in 61% of cases these patients had a second primary malignancy; and 15% of cases had more than 2 additional primary cancers. Nieminen et al. [26] studied serial endometrial biopsy samples taken during a 10-year followup of HPNCC mutation carriers and found abnormal MMR protein expression, MSI, or tumor suppressor promotor hypermethylation in various endometrial histologies, including normal and hyperplastic endometria. The most frequently methylated genes were *CDH13, RASSF1A*, and *GSTP1*. These defects in MMR and methylation appeared up to 12 years before endometrial carcinoma [26].

PTEN hamartoma tumor syndrome, caused by a germline mutation in *PTEN* gene on chromosome 10q, comprises a group of disorders including Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome, Proteus syndrome, Proteus-like syndrome, and autism spectrum disorder with macrocephaly [27, 28]. Cowden syndrome, also known as multiple hamartoma syndrome, is an autosomal dominant disorder with high risk of breast, thyroid, and endometrium cancer. The incidence of Cowden syndrome remains unclear due to underdiagnosis from variable penetration and subtle clinical findings [29]. Cowden syndrome is characterized by the development of intestinal hamartomas, facial trichilemmomas and mucocutaneous papillomatosis [29, 30], and is rarely identified before adulthood [28]. *PTEN* mutations in exon 5, coding for the active site and flanking amino acids, is a common site for mutations in patients with Cowden syndrome, and missense mutations are only found in this active area [30]. However, germline *PTEN* mutation has been detected in approximately 80% of Cowden syndrome patients [27]. The lifetime risk for endometrial carcinoma in Cowden syndrome is approximately 5–10%, compared with a 2.5% lifetime risk of women in the general population [27, 28]. Cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome have overlapping phenotypic features.



(a) (b)

Figure 4: Carcinosarcoma is composed of two malignant components, carcinomatous and sarcomatous. The epithelial component is usually high grade carcinoma for example, serous/clear cell type. The mesenchymal part comprises either homologous (a), ×100 or heterologous element for example, cartilage or bone. Chondrosarcomatous element (∗) is present in (b), ×100.

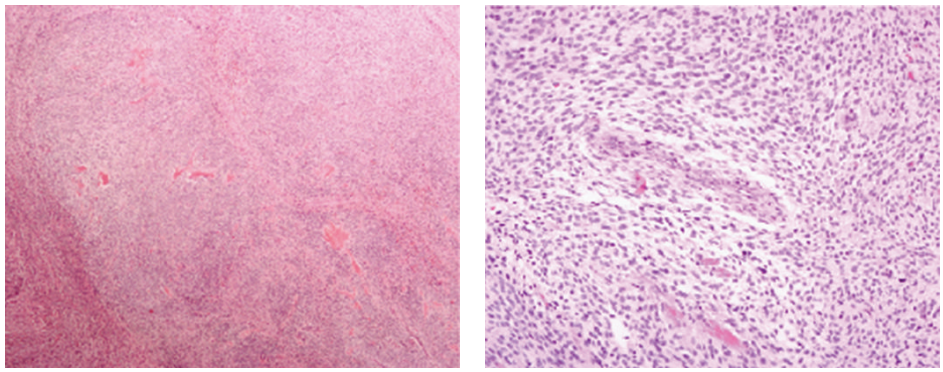
Bannayan-Riley-Ruvalcaba syndrome is a congenital, autosomal dominant condition manifested by macrocephaly, hamartomatous intestinal polyposis, lipomas, developmental delay or autism or both, and pigmented penile macules [29, 31]. Unlike Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome tends to be diagnosed at early life [28]. Approximately 60% of Bannayan-Riley-Ruvalcaba syndrome patients have an identifiable germline mutation in *PTEN* gene [27]. This syndrome also has the same increased risk of cancer as Cowden syndrome [29].

5. Carcinosarcoma

Carcinosarcomas (formerly known as malignant mixed mesodermal or mullerian tumors) are highly aggressive, biphasic neoplasms composed of carcinomatous and sarcomatous components (Figure 4). Carcinosarcomas account for 1-2% of all malignancies of uterine corpus [1] and usually present in postmenopausal women. Uterine bleeding is the most frequent presenting symptom. These tumors have traditionally been regarded as a subtype of uterine sarcomas or as a mixture of true carcinoma and sarcoma, but they are now regarded as metaplastic carcinomas or carcinomas with sarcomatous metaplasia [1, 18, 32–34]. Carcinosarcomas can be classified as type II endometrial carcinomas and their epithelial component can resemble high grade endometrioid, serous or clear cell carcinoma [35]. Etiologically, a few cases may be secondary to prior pelvic irradiation. In addition, an association between long term tamoxifen therapy and development of uterine carcinosarcoma has been suggested [32].

Schipf et al. [36] analyzed a series of 30 paraffin-embedded carcinosarcomas, including 24 ovarian and 6 uterine, using fluorescence in situ hybridization (FISH) and CGH. Many carcinosarcomas contained aberrations on chromosome 8 and 20 detected by FISH. FISH showed *C-MYC* (8q24.12) and *ZNF217* (20q13.2) amplification in 78% and 87%, respectively. The results demonstrate a uniform pattern of chromosomal gains and losses in CGH analysis. Gains or amplifications of 8q are the most common genetic aberration in carcinosarcomas [35]. One of the genes located within 8q is *C-MYC* (8q24) found to be amplified in 18 of 23 uterine and ovarian carcinosarcomas through FISH and overexpression in 9 of 9 uterine carcinosarcomas through immunostaining. *C-MYC* amplification is often present in carcinomas but was also present in 6 of 12 uterine leiomyomas and 11 of 23 uterine leiomyosarcomas [35].

LOH was seen in 5 of 6 uterine carcinosarcomas, and identical alleles were lost in the epithelial and mesenchymal components. *p53* mutations and LOH for TP53 occur frequently in both carcinosarcoma components which are associated with frequent protein overexpression. Sherman et al. [18] reported immunoreactivity of p53 in 7 (70%) of 10 carcinosarcomas and noted that the similar staining pattern presented in both carinomatous and sarcomatous areas. In about 20% of carcinosarcomas, MSI-high was described with an 83% concordance between the carcinomatous and sarcomatous components [1]. One study found identical mutations of *p53* and *KRAS* in the two components [33]. Fujii et al. [37] analyzed allelic status with polymorphous microsatellite markers on 172 carcinomatous/sarcomatous foci after microdissection of 17 carcinosarcomas. A close relationship between the carcinomatous and the sarcomatous component was found. No difference was seen in CGH patterns of carcinosarcomas [36]. Moreover, there is evidence that in most carcinosarcomas, the carcinomatous and the sarcomatous components are genetically the same, as shown for 21 of 25 carcinosarcomas (84%) using the human androgen receptor (HUMARA) for detection of X-chromosome inactivation. These results support a monoclonal origin of uterine carcinosarcomas and one can hypothesize that either the sarcomatous component develops from the carcinomatous component (conversion theory) or both are derived from a stem cell that undergoes divergent differentiation (combination theory) [33]. In the process of epithelial-mesenchymal transition, cells of epithelial origin lose epithelial characteristics and polarity acquiring a mesenchymal phenotype with increased migratory behavior.



(a) (b)

Figure 5: Endometrial stromal sarcoma, low grade is circumscribed from the surrounding myometrium (a), ×40; and higher magnification of endometrial stromal sarcoma shows round uniform tumor cells resembling the stroma of proliferative endometrium with low mitotic rate (b), ×200.

By molecular mechanisms, down-regulation of epithelial markers and up-regulation of mesenchymal markers result in acquisition of a fibroblast-like morphology with cytoskeleton reorganization and increase in motility, invasiveness, and metastatic capacity. A hallmark of epithelial-mesenchymal transition is loss of E-cadherin expression. A number of specific transcription factors, including Snail, Slug, SIP-1, and Twist, contribute to induction of epithelial mesenchymal transition, acting as transcriptional repressors of the E-cadherin gene. The oncogenic serine/threonine kinase AKT also promotes the process, modulating several signaling and transcriptional networks linking Wnt/β-catenin, NF-κB/p65, and Rb [38]. However, some investigators also found that a subset of carcinosarcoma was biclonal tumor, consisting of independent unrelated carcinomas and sarcomas, according to X chromosome inactivation and clinicopathological criteria [35]. In two collision reported tumors, the carcinomatous and sarcomatous components were histologically separate, with no intermingling, and there was a nodal metastasis that consisted purely of the sarcomatous element from one of these tumors [33]. One study examined 26 carcinosarcomas and found adenosarcoma-like components in 4 cases, suggesting that many of the true collision lesions may arise from malignant transformation of either benign epithelium within an adenosarcoma or adjacent benign endometrium [35]. The prognosis of the collision tumor depends on the most aggressive component, and may be better than for a carcinosarcoma of similar stage [33]. Overall, the carcinomatous component has been shown to have a more aggressive behavior and be a better predictor of clinical outcome in carcinosarcomas [35].

6. Endometrial Stromal Sarcoma and Undifferentiated Endometrial Sarcoma

Endometrial stromal sarcoma and undifferentiated endometrial sarcoma are in the same neoplastic spectrum. Diagnosis of endometrial stromal tumors has been based on histologic criteria. Low grade endometrial stromal sarcoma is composed of uniform, oval to spindle-shape cells of endometrial stromal-type with numerous small arterioles that resemble the spiral arterioles of late secretory endometrium. Mitotic rate is not a consideration in the distinction between low and high grade stromal sarcoma. In addition, characteristic tongue-like growth of the stromal cells into the myometrium and/or myometrial vasculature is noted [39, 40] (Figure 5). Endometrial stromal sarcoma usually occurs in middle aged women [41], and most present with uterine bleeding. Undifferentiated endometrial sarcoma, on the other hand, is defined as a high-grade neoplasm that lacks specific differentiation and bears no histological resemblance to endometrial stroma. Also, undifferentiated endometrial sarcomas have marked nuclear pleomorphism with high mitotic rate and display destructive myometrial invasion [40, 42]. Undifferentiated endometrial sarcomas should be diagnosed only after extensive sampling to exclude smooth or skeletal muscle differentiation, to exclude high grade leiomyosarcoma or rhabdomyosarcoma. Carcinosarcoma or adenosarcoma with sarcomatous overgrowth should also be excluded before making the diagnosis of undifferentiated endometrial sarcomas [39, 40].

In endometrial stromal sarcomas, the tumor cells are typically immunoreactive for estrogen and progesterone receptors, CD10, vimentin, and sometimes focally with actin, while they are generally negative for desmin, and h-caldesmon. Expression of androgen receptor is observed in 41% of examined sarcoma cases [41]. Approximately 70% of low grade endometrial stromal sarcomas also expresses epidermal growth factor receptor (EGFR; HER1). Undifferentiated endometrial sarcomas are estrogen and progesterone receptor negative, but a high proportion is EGFR positive. Endometrial stromal sarocmas are typically diploid with a low S-phase fraction whereas S-phase fraction exceeds 10% in undifferentiated endometrial sarcomas [41]. No c-kit (CD117) expression has been demonstrated in endometrial stromal sarcomas [43]. Liegl et al. [43] found 22 of 37 endometrial stromal sarcomas showed platelet-derive growth factor (PDGF)-α (CD140α) and 8 of 37 endometrial stromal sarcomas showed PDGF-β expression.

In contrast to epithelial endometrial carcinoma, endometrial stromal tumors are characterized by distinct cytogenetic abnormalities, particularly translocations leading to gene fusion. Cytogenetic studies reported to-date are primarily for low grade endometrial stromal sarcomas, mostly showing rearrangement of chromosomes 6, 7, and 17 [44, 45]. Loss of chromosome arm 7p (55.6% of the cases) is the most frequent aberration and may play a role in tumor development and progression [41]. Reverse transcription polymerase chain reaction (RT-PCR) and FISH studies on large series showed the presence of t(7;17)(p15;q21), leading to the fusion of two zinc finger genes, *JAZF1* (juxtaposed with another zinc finger gene 1) and *JJAZ1* (joined to *JAZF1*; also named *SUZ12*, suppressor of zeste-12 protein). *JAZF1* is expressed in normal endometrial stroma, but the specific functions of the *JAZF1* and the *JJAZ1* genes as well as the *JAZF1/JJAZ1* fusion gene are still unknown [1, 42]. Based on the evidence of loss of expression for normal versions of *JAZF1* in multiple tumors suggests a possible role of this gene as a tumor suppressor [42]. This gene fusion is a distinctive molecular genetic alteration for endometrial stromal sarcoma and benign endometrial stromal nodules [1, 41]. The *JAZF1/JJAZ1* fusion gene is frequently present in classical endometrial stromal sarcomas and less often in cases with variant histology [46]. However, of seven high-grade endometrial stromal sarcomas/undifferentiated endometrial sarcomas studied, only three cases showed evidence of the fusion [42]. In contrast, many studies reported the fusion gene to be absent in undifferentiated endometrial sarcomas [41]. The fusion gene is not present in normal endometrial stroma [41]. The presence of the *JAZF1/JJAZ1* fusion gene within the spectrum of endometrial stromal tumors from benign to malignant raises possibility that the endometrial stromal nodule may transform into malignant endometrial stromal sarcoma [41, 47]. The frequencies of this gene fusion in low grade endometrial stromal sarcoma have been reported in many studies showing a wide range of positivity, 23–80% [44, 46, 48, 49]. The studies with RT-PCR only can give false-positive results due to PCR contamination. FISH may be useful as a complementary technique to exclude the possibility of false positive contamination of cases by RT-PCR [44]. Although the *JAZF1/JJAZ1* fusion gene seems to be the major molecular alterations in endometrial stromal sarcomas, there is some evidence for alternative pathways in the development of endometrial stromal sarcomas. A major subgroup of endometrial stromal sarcomas has been found to have translocations involving short arm of chromosome 6, particularly band 6p21 [41, 44, 45]. Micci et al. [50] showed that the *PHF1* (PHD finger protein 1) gene in 6p21 was recombined with two different partners, (i) with *JAZF1* gene showing a 6p;7p rearrangement, which results in the formation of a *JAZF1/PHF1* fusion gene and (ii) with *EPC1* (enhancer of polycomb) gene in 10p11 that had a 6;10;10 translocation. Panagopoulos et al. [45] introduced that a low-grade endometrial stromal sarcoma cell line carrying a der(7)t(6;7)(p21;p22) also harbors a *JAZF1/PHF1* fusion. Both t(7;17) and t(6;7) comprise 62% of the reported endometrial stromal sarcomas [44]. Additionally, few endometrial stromal sarcoma cases were reported with a t(X;17)(p11.2;q23) and a t(10;17)(q22;p13) [51–53]. Although *JAZF1/JJAZ1* fusion may not be universally present in all low grade endometrial stromal sarcoma, this aberration may still be diagnostically useful [44]. The *JAZF1/JJAZ1* fusion has been identified in areas of smooth muscle differentiation in endometrial stromal neoplasms (50% of the cases). This finding supports that the endometrial stromal and smooth muscle components of these tumors have the same origin, either from a common precursor cell with pluripotential differentiation or from endometrial stromal cells that have undergone smooth muscle metaplasia [44, 54]. Halbwedl et al. [55] described 9 cases of low grade endometrial stromal sarcoma and 3 cases of undifferentiated endometrial sarcoma in aCGH study revealing a variety of gains and losses that apparently did not correlate with morphology. There is no accumulation of aberrations in undifferentiated endometrial sarcoma compared to endometrial stromal sarcoma, indicating these two types of uterine sarcomas are probably not related to each other.

LOH and MSI have been evaluated in both low grade endometrial stromal sarcomas (20 cases) and undifferentiated endometrial sarcomas (3 cases). LOH with at least one polymorphic DNA marker was identified in all 3 cases (100%) of undifferentiated endometrial sarcomas, 10 (50%) low-grade endometrial stromal sarcomas and 2 (50%) benign endometrial stromal nodules. Moreover, concurrent and independent LOH were noted in adjacent normal appearing myometrium or endometrium, either close to or at a distance from the tumors [41]. LOH was mostly identified at *PTEN*, a tumor suppressor gene located on chromosome 10q [56]. No tumor was associated with MSI [41, 55]. Loss of functions of certain tumor suppressor genes such as *PTEN* in surrounding nontumor uterine tissues could influence and facilitate tumor proliferation, cellular spread, and invasion by malignant endometrial stromal cells [41]. However, one should keep in mind the false positive scoring of LOH in normal tissues may occur both from the imperfect methodology and from contamination by tumor samples/cells. The use of repeated experiments and several polymorphic markers has been advised to overcome these methodology problems [56]. Other frequently altered loci by LOH were at 14q32 (D14S267) and 3p (D3S1300). The former locus is frequently altered in uterine leiomyosarcoma but, in addition, in a variety of epithelial neoplasms such as ovarian, colorectal and esophageal carcinoma. Locus D3S1300 harbors the *FHIT* gene which is frequently mutated in cervical carcinoma of the uterus. LOH for TP53 and p53 overexpression are rarely present in endometrial stromal sarcomas (5% and 15%, resp.). The importance of *p53* mutations for the development of undifferentiated endometrial sarcomas is not evident, but p53 overexpression was detected in three of four high-grade stromal sarcomas [1]. Furthermore, Kurihara et al. [49] have recently found frequent nuclear accumulation of p53 and *TP53* gene missense mutations in undifferentiated endometrial sarcoma with nuclear pleomorphism, 3 (50%) of 6 cases. There is no evidence of *p53* aberration in 18 low grade endometrial stromal sarcomas and 7 cases undifferentiated endometrial sarcoma with nuclear uniformity. *p53* alteration may be

Table 3: Typical immunoprofile of type I endometrioid carcinoma and type II serous carcinoma.

	Endometrioid carcinoma	Serous carcinoma
Estrogen and progesterone receptors	+	−
PTEN	−	+
β-catenin	+	−
p53	−	+
HER2/neu	−	+

+: positive result, −: negative result

one different pathway that contributes the tumorigenesis of undifferentiated endometrial sarcoma. Expression of *SFRP4* and β-catenin is also detected. *SFRP4* acts in Wnt-signaling pathway, which is a complex cascade of heterogeneous molecules playing an important role in organ development, via β-catenin. *SFRP4* is expressed in normal endometrial stromal cells but not in glandular epithelium. Compared with normal endometrium, the expression of *SFRP4* was decreased in both low grade endometrial stromal sarcomas and undifferentiated endometrial sarcomas. Through its involvement in the Wnt signaling pathway, *SFRP4* may act as a tumor suppressor by regulating the cytosolic β-catenin pool in the cell. Beta-catenin regulates in the opposite manner to *SFRP4*, being particularly increased in undifferentiated sarcoma [57]. Dysregulation of these pathways allows β-catenin to accumulate and translocate to the nucleus, where it forms complexes with T-cell factor/lymphoid enhancing factor (TCF/LEF) leading to uncontrolled cell growth and carcinogenesis [57]. High level nuclear staining for β-catenin was seen in 40% of endometrial stromal sarcomas and may be used as a diagnostic tool [42].

7. Diagnostic Utility Based on the Molecular Knowledge

7.1. Endometrioid Carcinoma versus Serous/Clear Cell Carcinoma. At times, the histological type of endometrial carcinoma is not clearly defined, especially in poorly differentiated tumors, and knowledge of the dualistic model, with the common molecular changes in each type, can help clarify the diagnosis. If there is non-carcinomatous endometrium present, the presence of hyperplasia is supportive evidence of an endometrioid carcinoma, whereas atrophic endometrium is supportive of non-endometrioid carcinoma.

Molecular studies on endometrium are not often performed in most hospital surgical pathology laboratories today; however, immunohistochemical studies can detect the abnormal protein products of the gene mutations. Therefore, we can exploit our knowledge of the dualistic model and their typical gene mutations and use the immunoprofile as a diagnostic tool, in concert with the histomorphologic features to specify the tumor type, particularly in difficult cases such as in the differentiation between high-grade endometrioid carcinoma and serous carcinoma (Table 3).

7.2. Endometrial Stromal Sarcoma versus Undifferentiated Sarcoma. The distinct molecular alteration described in the majority of endometrial stromal sarcomas is the t(7;17)(p15;q21) leading to the formation of fusion gene *JAZF1/JJAZ1*, which can be detected by RT-PCR or FISH assays. Thus, in the problematic cases in which the differentiatial diagnosis is between endometrial stromal sarcoma and undifferentiated sarcoma, we look for the fusion gene to make this distinction.

7.3. Uterine Smooth Muscle Neoplasm versus Endometrial Stromal Tumors. Uterine smooth muscle neoplasm is defined as a mesenchymal tumor composed of cells with smooth muscle differentiation, particularly highly cellular leiomyomas may have morphologically overlapped features of endometrial stromal tumors. According to histologic criteria for differential, immunostainings may help to correct the final diagnosis, particularly in difficult cases. Neoplastic endometrial stromal cells typically express vimentin, muscle-specific and smooth muscle actin and may be positive for desmin. In addition, CD10, initially thought to be a specific marker for endometrial stromal tumors, can be demonstrated in uterine smooth muscle tumors, commonly in highly cellular leiomyomas and leiomyosarcomas. Other antibodies that give positive staining in smooth muscle tumors useful in this differential diagnosis includes h-caldesmon, histone deacetylase 8 (HDAC8), smooth muscle myosin and oxytocin receptor [39]. However, none of these markers can completely specify the smooth muscle/endometrial stroma lineage of the tumor, a panel of the antibodies should be used [39].

The molecular alterations in smooth muscle tumor are complex, especially in leiomyosarcomas. The translocation t(12;14)(q15;q23-24) has been noted in a high proportion of leiomyomas [41, 58]. By CGH, leiomyosarcomas have the most frequent losses including 10q, 11q, 13q, and 2p while the most common gains are Xp, 1q, 5p, 8q, 12q, 17p and 19p [41, 59, 60]. There are a variety of genetic changes and mutations inclusive of *TP53* and *MDM2* expression associated with progression of leiomyosarcomas [41]. LOH of 10q is found in more than half of leiomyosarcomas [41]. Leiomyosarcomas exhibit a significantly higher frequency of allelic loss (52%) compared with benign leiomyomas (18%) and smooth muscle tumors of uncertain malignant potential (21%) [41].

8. Therapeutic Considerations: Molecular Targeted Therapy

Development of targeted anticancer drugs is the direct result of knowledge of the molecular profile of endometrial neoplasms. Drug targets may focus on genes that affect apoptosis, signal transduction, epigenetic modification, drug resistance, protein folding and degradation, cell cycle progression, hormone receptor activity, and angiogenesis [4]. The drugs that comprise targeted therapy include small molecular weight inhibitors, monoclonal antibodies, antisense and gene therapy [61]. At this time, essentially only

endometrial carcinomas have been tested with targeted therapy. Carcinosarcomas and endometrial stromal sarcomas are relatively uncommon neoplasms, and there has little experience with specific therapies for these tumors, though there is definitely future potential.

8.1. mTOR Inhibitors. The phosphatidylinositol-3-kinase (PI3K)-serine/threonine kinase (AKT)-mammalian target of the rapamycin (mTOR) signaling pathway plays a central role in the regulation of cell growth, proliferation, and apoptosis. In in vitro studies, cells with *PTEN* inactivation in endometrioid carcinoma are sensitive to mTOR inhibitors, since the loss of *PTEN* leads to constitutive activation of downstream components, which in turn up-regulates mTOR activity [62]. Potential therapies targeting the mTOR pathway include the mTOR inhibitors temsirolimus (CCI-779), everolimus (RAD001), and deforolimus (AP23573) [4]. In a phase II study of temsirolimus activity in patients with advanced or recurrent endometrial cancer, 5 of 19 (26%) evaluable patients had a partial response and 12 (63%) had stable disease [62, 63]. In addition to mTOR inhibitors, other agents targeting components of the mTOR-AKT-PI3K-PTEN pathway have also been developed, including enzastaurin (a PI3K inhibitor) and triciribine (an AKT inhibitor) [4].

8.2. EGFR Inhibitors/Anti-HER2/neu. Epidermal growth factor receptor (EGFR) family members (ERBB1 (EGFR or HER1), ERBB2 (HER2/neu), ERBB3 (HER3), ERBB4 (HER4)) are tyrosine kinase receptors that are activated by binding to epidermal growth factor (EGF)-like growth factor, leading to downstream phosphorylation or dephosphorylation of signaling molecules that involved in cell cycle and apoptosis [63]. Sixty to 80% of endometrial carcinomas overexpress EGFR [4]. In addition, EGFR expression has been described in approximately 70% of endometrial stromal sarcomas [41]. EGFR overexpression has been reported in high grade carcinomas with deep myometrial invasion, positive peritoneal washings and poor survival [61, 63]. The anti-EGFR agents result in down regulation of the MAPK and PI3K/AKT signaling pathways. However, the anti-tumor activity has been described in a minority of the patients treated. Antagonists to EGFR include small molecule tyrosine kinase inhibitors (gefitinib, erlotinib, and lapatinib) and the anti-EGFR monoclonal antibody cetuximab [62]. Experimental observation data have been shown that EGFR inhibitors could be more effective in endometrioid endometrial carcinoma than in uterine papillary serous carcinoma [63]

As described above, *HER2/neu* gene overexpression and amplification have been found in up to 80% of nonendometrioid endometrial carcinoma, and in 10–30% of endometrioid endometrial carcinoma. The usage of trastuzumab, a monoclonal antibody directed against HER2/neu, has been tested in endometrial carcinomas. Villella's group found 5 out of 19 (26%) patients with papillary serous carcinoma showed HER2/neu overexpression. One of 5 positive HER2/neu patients with advanced disease treated with trastuzumab achieved a complete response and a second patient's disease stabilized [63]. However in another study, Gynecologic Oncology Group (GOG)-0181-B, investigated trastuzumab in advanced, recurrent, or persistent endometrial cancer, and its preliminary results showed minimal activity, even in cancers with high overexpression of HER2/neu [4]. Several other monoclonal antibodies targeting members of the ERBB/HER family, including pertuzumab, cetuximab, and panitumumab, are currently being investigated [4].

8.3. Antiangiogenics. Vascular endothelial growth factors (VEGF) expression has been found in 56–100% of endometrial carcinomas [63] and has been correlated with high histologic grade, deep myometrial invasion, angiolymphatic invasion, nodal metastasis, and short disease-free survival [63, 64]. VEGF, particularly VEGF-A, plays a key role in angiogenesis and increased permeability of tumor-associated blood vessels. Monoclonal antibodies targeting VEGF, bevacizumab and sorafenib, have been developed. Kamat and coworkers [64] injected Ishikawa cell line into uterine horn of nude mice in one group and Hec-1A cell lines in the other group and treated the mice with docetaxel and/or bevacizumab. The combination of both agents had a greater efficacy in tumor growth inhibition than a single agent. Currently, GOG-229-E is being studied in a phase II trial of single agent bevacizumab in patients with recurrent endometrial carcinoma [64].

9. Conclusion

Knowledge of the molecular profiles of endometrial neoplasms assists in the diagnosis, prognosis, and treatment of endometrial neoplasms. Endometrial carcinoma can be broadly divided into two categories based on clinical behavior and morphologic phenotype, with good correlation to the molecular findings. Type I endometrial carcinoma represents an estrogen-related tumor, which usually arises in the setting of endometrial hyperplasia and have good prognosis. They are associated with a number of well-described genetic alterations including mutations of *PTEN*, *KRAS*, β-catenin, *PIK3CA*, and inactivation of DNA mismatch repair. Targets for molecular therapy in endometrial carcinoma include agents that inhibit components of the AKT-PI3K-PTEN pathway. Type II endometrial cancers are not estrogen-related and have poor prognosis. Mutations of *p53* are present in approximately 90% of this tumor type. Carcinosarcoma is considered to be a high-grade carcinoma with sarcomatous differentiation and a high frequency of *C-MYC* mutations and LOH of *p53*. The majority of endometrial stromal nodules and stromal sarcomas seem to originate from the abnormal *JAZF1/JJAZ1* gene fusion. The molecular biology of undifferentiated endometrial sarcomas is still not clearly delineated. In the near future; additional molecular studies should further elucidate the unclear pathogenesis and provide new targets for diagnosis and treatment.

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Review Article

Preclinical Studies of Chemotherapy Using Histone Deacetylase Inhibitors in Endometrial Cancer

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Because epigenetic alterations are believed to be involved in the repression of tumor suppressor genes and promotion of tumorigenesis in endometrial cancers, novel compounds endowed with a histone deacetylase (HDAC) inhibitory activity are an attractive therapeutic approach. In this review, we discuss the biologic and therapeutic effects of HDAC inhibitors (HDACIs) in treating endometrial cancer. HDACIs were able to mediate inhibition of cell growth, cell cycle arrest, apoptosis, and the expression of genes related to the malignant phenotype in a variety of endometrial cancer cell lines. Furthermore, HDACIs were able to induce the accumulation of acetylated histones in the chromatin of the $p21^{WAF1}$ gene in human endometrial carcinoma cells. In xenograft models, some HDACIs have demonstrated antitumor activity with only few side effects. In this review, we discuss the biologic and therapeutic effects of HDACIs in treating endometrial cancer, with a special focus on preclinical studies.

1. Introduction

Endometrial cancer is the seventh most common malignancy among women worldwide. Despite the fact that most cases are diagnosed at an early stage, the death rate has increased steadily over the past 20 years. The lack of an effective, standardized adjuvant treatment for women at a high risk of recurrence has contributed to these disappointing results (reviewed in [1]). The most frequent genetic alteration in type I endometrioid carcinoma is PTEN inactivation by mutation, followed by microsatellite instability and mutations of K-ras and β-catenin. In type II cancers, p53 mutation is the most frequent genetic alteration, followed by inactivation of p16 and e-cadherin and amplification of Her2/neu (reviewed in [1]).

One of the most important mechanisms in chromatin remodeling is the post-translational modification of the N-terminal tails of histones by acetylation, which contributes to a "histone code" determining the activity of target genes [2]. Transcriptionally silent chromatin is composed of nucleosomes in which the histones have low levels of acetylation on the lysine residues of their amino-terminal tails. Acetylation of histone proteins neutralizes the positive charge on lysine residues and disrupts the nucleosome structure, allowing unfolding of the associated DNA with subsequent access by transcription factors, resulting in changes in gene expression. Acetylation of core nucleosomal histones is regulated by the opposing activities of histone acetyltransferases (HATs) and histone deacetylases (HDACs). HDACs catalyze the removal of acetyl groups on the amino-terminal lysine residues of core nucleosomal histones, and this activity is generally associated with transcriptional repression. HDACs remove the acetyl groups which then induce a positive charge on the histones, and this suppresses gene transcription, including tumor suppressor genes silenced in cancer. Moreover, acetylation of histones facilitates destabilization of DNA-nucleosome interaction and renders DNA more accessible to transcription factors [3]. Aberrant recruitment of HDAC activity has been associated with the development of certain human cancers [4]. HDAC inhibitors (HDACIs) can inhibit cancer cell growth in vitro and in vivo, revert oncogene-transformed cell morphology, induce apoptosis, and enhance cell differentiation.

The classes of HDACIs that have been identified are: (a) organic hydroxamic acids (e.g., Trichostatin A (TSA) and suberoylanilide bishydroxamine (SAHA)) (b) short-chain

Table 1: Overview of frequently used histone deacetylase inhibitors that are available for clinical and research purposes.

Substance groups	Derivatives	Isotype
Hydroxamates	Trichostatin A (TSA)	I, II
	Suberoylanilide hydroxamic acid (SAHA, vorinostat)	I, II, IV
	LBH589 (panobinostat)	I, II, IV
	PCI24781 (CRA-024781)	I, IIb
	LAQ824	I, II
	PXD101 (belinostat)	I, II, IV
	ITF2357	I, II
	SB939	Unknown
	JNJ-16241199 (R306465)	I
	m-carboxycinnamic acid bishydroxamide (CBHA)	
	Scriptaid	
	Oxamflatin	
	Pyroxamide	
	Cyclic hydroxamic acid containing peptides (CHAPs)	
Short chain fatty acids	Butyrate	I, IIa
	Valproate	I, IIa
	AN-9	
	OSU-HDAC42	
Benzamides	MS-275 (entinostat)	1, 2, 3, 9
	MGCD0103	1, 2, 3, 11
	Pimelic diphenylamide	1, 2, 3
	M344	
	N-acetyldinaline (CI-994)	
Cyclic tetrapeptides	Apicidine	I, II
	Trapoxins	
	HC-toxin	
	Chlamydocin	
	Depsipeptide (FR901228 or FK228) (romidepsin)	1, 2, 4, 6
Sulfonamide anilides	N-2-aminophenyl-3-[4-(4-methylbenzenesulfonylamino)-phenyl]-2-propenamide	
Others	Depudecin	
	NDH-51	
	KD5150	Pan-HDACI

Class I: HDAC1, -2, -3 and -8; class IIa: HDAC4, -5, -7, and -9; class IIb: HDAC 6, and -10; class III: SIRT1-7; class IV: HDAC11.

fatty acids (e.g., butyrates and valproic acid (VPA)), (c) benzamides (e.g., MS-275), (d) cyclic tetrapeptides (e.g., trapoxin), and (e) sulfonamide anilides [5] (see Table 1).

In this review, we discuss the biologic and therapeutic effects of HDACIs in treating endometrial cancer, with a special focus on preclinical studies.

2. Mechanism of Action

Histone deacetylases (HDACs) comprise a family of 18 genes that are subdivided into four classes [6]. Classes I, II, and IV are referred to as "classical" HDACs and are generally simultaneously targeted by most HDACIs (Table 1). HDACIs were initially discovered on the basis of their ability to reverse the malignant phenotype of transformed cells in culture. It has been shown that HDACIs carry the potential to activate differentiation programs on one hand, while on the other hand they were also shown to inhibit cell proliferation by cell cycle arrest in the G1 and/or G2 phases of the cell cycle and to induce apoptosis in cultured transformed cells. $p21^{WAF1}$ and $p27^{KIP1}$ are cyclin-dependent kinase inhibitors (CDKIs) that bind to cyclin-dependent kinase complexes and decrease kinase activity, and may act as key regulators of the G0/G1 accumulation (reviewed in [7]). The $p21^{WAF1}$ expression in particular is induced by HDACIs in various cell lines. Additionally, this event is associated with both an increase in histone acetylation in the promoter region of the $p21^{WAF1}$ gene and a selective loss of a specific HDAC enzyme, HDAC1, in the same region [8]. Therefore, the upregulation of $p21^{WAF1}$ is a direct consequence of HDACIs on $p21^{WAF1}$ transcription. In the future, testing should be conducted using $p21^{WAF1}$-negative cell lines to see if $p21^{WAF1}$ is absolutely required for HDACI-induced growth arrest.

Takai et al. examined the effect of HDACIs on the expression of $p21^{WAF1}$ and $p27^{KIP1}$ in endometrial cancer cells by Western blot analysis. HDACIs markedly upregulated the level of $p21^{WAF1}$ and $p27^{KIP1}$ proteins, which were expressed at negligible levels in the untreated cell lines. Conversely, HDACIs decreased the levels of cyclin D1 and cyclin D2. HDACIs decreased the bcl-2 levels. E-cadherin binds to β-catenin and can act as a tumor suppressor gene; its promoter has CpG islands which are frequently methylated in selected cancers. HDACIs markedly increased the expression level of E-cadherin in endometrial cancer cells and exhibited antiproliferative activity in these cells [9–14]. HDACIs have also been shown to generate reactive oxygen species (ROS) in solid tumor and leukemia cells [15–17], which may contribute to the mechanism. HDACIs have been shown to inhibit angiogenesis. HDACIs repress the expression of proangiogenic factors such as HIF1α, VEGF, VEGF receptor, endothelial nitric oxide synthase, IL-2 and IL-8 and the induction of antiangiogenic factors, such as p53 and von Hippel-Lindau (reviewed in [18]). HDACIs should not be considered to act solely as enzyme inhibitors of HDACs. A large variety of nonhistone transcription factors and transcriptional co-regulators are known to be modified by acetylation. HDACIs can alter the degree of acetylation nonhistone effector molecules and thereby increase or repress the transcription of genes by this mechanism. Examples include: ACTR, cMyb, E2F1, EKLF, FEN 1, GATA, HNF-4, HSP90, Ku70, NFκB, PCNA, p53, RB, Runx, SF1 Sp3, STAT, TFIIE, TCF, YY1, and so forth, (reviewed in [18]).

3. Overview and Preclinical Studies of HDACIs

A variety of structurally distinct classes of compounds that inhibit deacetylation of both histone and non-histone proteins have gradually been identified (Table 1). Despite the shared capacity of each class of HDACIs to promote histone acetylation, individual HDACIs exert different actions on signal transduction and the induction of differentiation and/or apoptosis. Table 2 shows data from different reports investigating endometrial cancer cell lines treated with different classes of HDACIs. Many of the in vitro studies use the Ishikawa cell line. Nishida. succeeded in establishing of a well-differentiated endometrial adenocarcinoma cell line, Ishikawa cells, from a 39-year old Japanese patient more than 20 years ago [19]. Because this cell line bears estrogen and progesterone receptors, the cells have been used in numerous basic research areas such as reproductive biology and molecular science.

Table 2: Data investigating endometrial cancer cell lines treated with different classes of HDACIs.

HDACI	Cell line	ED50 (M)
TSA	Ishikawa	5.2×10^{-8}
	HEC-1B	5.1×10^{-8}
	HEC59	7.0×10^{-8}
	RL95-2	9.8×10^{-8}
	KLE	7.2×10^{-8}
	AN3CA	1.9×10^{-8}
	Ark2	2.5×10^{-8}
SAHA	Ishikawa	7.8×10^{-7}
	HEC-1B	7.8×10^{-7}
	HEC59	1.2×10^{-6}
	RL95-2	2.4×10^{-6}
	KLE	2.5×10^{-6}
	AN3CA	3.1×10^{-6}
CBHA	Ishikawa	1.8×10^{-6}
	HHUA	2.5×10^{-6}
	HEC-1B	2.2×10^{-6}
Scriptaid	Ishikawa	9.0×10^{-6}
NaB	Ishikawa	8.3×10^{-4}
	HEC-1B	8.4×10^{-4}
	HEC59	1.8×10^{-3}
	RL95-2	3.0×10^{-3}
	KLE	3.9×10^{-3}
	AN3CA	4.1×10^{-3}
VPA	Ishikawa	7.0×10^{-4}
	HEC-1B	7.5×10^{-4}
	HEC59	8.2×10^{-4}
	RL95-2	2.5×10^{-3}
	KLE	2.3×10^{-3}
	AN3CA	3.8×10^{-3}
MS-275	Ishikawa	9.7×10^{-7}
	HEC-1B	2.2×10^{-6}
	RL95-2	1.0×10^{-6}
	HHUA	7.8×10^{-7}
	AN3CA	5.0×10^{-7}
	Ark2	5.0×10^{-7}
M344	Ishikawa	2.3×10^{-6}
Apicidine	Ishikawa	1.0×10^{-6}
PsA	Ishikawa	7.5×10^{-6}
Oxamflatin	Ishikawa	2.5×10^{-7}
	AN3CA	2.5×10^{-7}
	Ark2	2.5×10^{-7}

3.1. Trichostatin A (TSA). The trichostatins were initially isolated from Streptomyces hygroscopicus as antifungal antibiotics in 1976 [20, 21]. About 10 years later, TSA and its analogues were discovered to induce cell differentiation of murine erythroleukemia cells and to induce hyperacetylation of histone proteins at nanomolar concentrations. TSA has been extensively studied; it has antitumor activity and can induce differentiation of some cancer cell lines, but its clinical utility has been restricted because of toxic side-effects in vivo [22]. TSA causes mitotic arrest through the formation of aberrant mitotic spindles, probably by interfering with chromosome attachment, but does not affect mitotic microtubules [22]. This effect may account for the higher cytotoxicity of TSA in comparison to other HDACIs

(i.e., suberoylanilide bishydroxamine). HDAC inhibition is not believed to have a generalized effect on the genome, but only on the transcription of a small subset of the genome. Differential display analysis of transformed lymphoid cell lines revealed that the expression of only 2%–5% of transcribed genes is changed significantly after treatment with TSA [23]. The effective dose of TSA that inhibited 50% clonal growth (ED50) of the endometrial cancer cell lines (Ishikawa, HEC-1B, HEC59, RL95-2, KLE, and AN3CA) was calculated, and ranged between 5.1×10^{-8} M and 1.9×10^{-7} M [9] (Table 2). Dowdy et al. demonstrated that combined treatment with TSA and paclitaxel caused synergistic inhibition of cell growth of Ark2 and KLE endometrial cancer cells [24]. These effects were confirmed in a mouse xenograft model. Treatment with TSA and paclitaxel led to a significant increase in acetylated tubulin and microtubule stabilization. This study provides the evidence of nonhistone protein acetylation as one possible mechanism by which HDACIs reduce cancer growth.

3.2. Suberoylanilide Bishydroxamine (SAHA, Vorinostat). Hydroxamic acid type inhibitors make up the largest and broadest group of HDACIs described to date. The inhibition of HDACs by SAHA occurs through a direct interaction with the catalytic site of the enzyme, as shown by X-ray crystallography studies [25]. Among the synthetic HDACIs, SAHA is the most advanced candidate as a cancer therapeutic drug, and is under phase I and II clinical trials [26, 27]. SAHA has significant antitumor activity against many tumor types at dosages that can be tolerated by patients when administered intravenally and orally [28]. Some HDACIs (e.g., TSA and trapoxin) are of limited therapeutic use due to poor bioavailability in vivo and have toxic side effects at high doses. SAHA, however, is relatively safe and non-toxic in vivo. The effective dose of SAHA that inhibited 50% clonal growth (ED50) of the endometrial cancer cell lines (Ishikawa, HEC-1B, HEC59, RL95-2, KLE, and AN3CA) was calculated and ranged between 7.8×10^{-7} M and 3.1×10^{-6} M [9] (Table 2).

3.3. m-carboxycinnamic Acid Bishydroxamide (CBHA). CBHA is a member of a recently synthesized family of hybrid polar compounds that have been shown to be inhibitors of HDAC [29] and potent inducers of transformed cell growth arrest and terminal differentiation at micromolar (LD50 range, 1–4 μM) concentrations [30]. The effective dose of CBHA that inhibited 50% clonal growth (ED50) of the endometrial cancer cell lines (Ishikawa, HEC-1B, HHUA) was calculated and ranged between 1.8×10^{-6} M and 2.5×10^{-6} M for CBHA [10] (Table 2). On the other hand, normal endometrial epithelial cells were viable after treatment with the same doses of CBHA that induced growth inhibition of endometrial cancer cells [10].

3.4. Scriptaid. Using a high-throughput system based on a stably integrated transcriptional reporter to screen a library of 16,320 compounds (DIVERset, Chembridge, San Diego, CA), Su et al. identified a novel HDACI, termed Scriptaid [31]. Nullscript, which possesses a shorter side-chain (3C) than Scriptaid (5C) between the tricyclic core and the carbonyl group, was inactive in transcriptional facilitation. This confirms that the linker chain has to be a certain length for HDAC inhibition to occur. Scriptaid has a common structure with TSA and SAHA, that is, a hydroxamic acid zinc-binding group linked via a spacer (5 or 6 CH2) to a hydrophobic group [31]. Using an immunoblotting assay of histone deacetylation, Su et al. demonstrated that Scriptaid is a potent HDACI with a >100-fold increase in histone acetylation, with relatively low toxicity [31]. Scriptaid conferred the greatest effect on augmentation of the signal transduction TGFβ pathway, including a number of human suppressor genes such as SMAD4 [31]. The effect of Scriptaid in human cancers, however, has not been fully examined. A recent study by Keen et al. indicated that Scriptaid had a significant growth-suppressing effect on ER-negative human breast cancer cells [32]. The effective dose of Scriptaid that inhibited 50% clonal growth (ED50) of the Ishikawa endometrial cancer cell line was calculated at 9.0×10^{-6} M [11] (Table 2). On the other hand, normal endometrial epithelial cells were viable after treatment with the same doses of Scriptaid that induced growth inhibition of endometrial cancer cells [11].

3.5. Sodium Butyrate (NaB). It was first reported in 1978 that millimolar concentrations of sodium butyrate (NaB) inhibited HDACs in vitro [33]. NaB is normally present in the human colon as a product of the metabolic degradation of complex carbohydrates by colonic bacteria and regulates the physiological differentiation of colonocytes, suggesting its possible use in the prevention of colorectal cancer and the treatment of premalignant and neoplastic lesions. Butyrate and its derivatives have a long history of safe clinical use in the treatment of inherited and acquired metabolic disorders. Some studies suggest that many of the cellular activities of phenylbutyrate are more dependent on its butyric acid component than its phenyl group. A recent study by Terao et al. indicated that NaB had a significant growth-suppressing effect on human endometrial and ovarian cancer cells irrespective of their p53 gene status [34]. NaB, a low-potency HDACI, has been extensively studied; it has antitumor activity and can induce differentiation of some cancer cell lines, but its clinical utility has been restricted by its short half-life (5 minutes), limiting the ability to achieve a therapeutic plasma level. NaB and phenylbutyrate are degraded rapidly after i.v. administration and therefore require high doses exceeding 400 mg/kg/day [35]. Furthermore, these compounds are not specific for HDACs as they also inhibit phosphorylation and methylation of proteins as well as DNA methylation [35]. The effective dose of NaB that inhibited 50% clonal growth (ED50) of the endometrial cancer cell lines (Ishikawa, HEC-1B, HEC59, RL95-2, KLE, and AN3CA) has been calculated and ranged between 8.3×10^{-4} M and 4.1×10^{-3} M for NaB [9] (Table 2).

3.6. Valproic Acid (VPA). Valproic acid, a shortchain fatty acid, has been approved for clinical use in the treatment of epilepsy and is frequently used in clinical trials and for in

vitro research based on its HDAC inhibitory effect at comparatively high (millimolar) concentrations [36]. Valproic acid has also been identified as an antiproliferative agent and HDACI [37]. Some HDACIs (e.g., TSA and trapoxin) are of limited therapeutic use due to poor bioavailability in vivo as well as toxic side effects at high doses, but VPA is relatively safe and non-toxic in vivo. The effective dose of VPA that inhibited 50% clonal growth (ED50) of the endometrial cancer cell lines (Ishikawa, HEC-1B, HEC59, RL95-2, KLE, and AN3CA) has been calculated and ranged between 7.0×10^{-4} M and 3.8×10^{-3} M [9] (Table 2).

A previous study tested the ability of VPA to inhibit the growth of human HEC-1B endometrial cancer tumors growing in immunodeficient mice [9]. Administration of VPA remarkably suppressed the growth of the tumors ($P < .01$). No significant differences in either the mean weights, histology of the internal organs, and mean blood chemistries, including liver parameters and hematopoietic values, were found between diluent-treated mice and those that received 5 weeks of therapy. These tumors were sampled for the expression of $p21^{WAF1}$ using immunohistochemistry on formalin-fixed paraffin-embedded sections. HEC-1B endometrial cancer cells treated with VPA showed strong nuclear staining. Control cancer cells from untreated mice had negative or focal weak staining for $p21^{WAF1}$. This in vivo study shows that VPA at 0.3–1.5 mM inhibited cell proliferation, induced cell cycle arrest and stimulated apoptosis in endometrial cancer cells. This range of concentrations of VPA can be achieved in a patient's serum when that patient is receiving a daily dose of 20–30 mg/kg for epilepsy. These data are also consistent with the in vitro data. This anticancer activity occurred without any major side-effects, raising hopes that VPA may become a useful therapy for endometrial cancers. Furthermore, VPA has convenient pharmacokinetic properties with a significantly longer biological half-life than the other HDACIs [38].

3.7. MS-275 (Entinostat). MS-275 (MS-27-275) is a synthetic novel benzamide which exerts HDAC inhibitory activity and also induces the expression of the cyclin-dependent kinase inhibitor $p21^{WAF1}$ and gelsolin, and changes the cell cycle distribution [38, 39]. MS-275 has shown antiproliferative activity in various in vitro and in vivo human tumor models [40, 41], and is currently being tested in clinical trials involving patients with solid tumors or hematological malignancies [42]. The effective dose of MS-275 that inhibited 50% clonal growth (ED50) of the endometrial cancer cell lines (Ishikawa, HHUA, HEC-1B and RL95-2) was calculated and ranged between 7.8×10^{-7} M and 2.2×10^{-6} M [12] (Table 2). On the other hand, normal endometrial epithelial cells were viable after the treatment with the same doses of MS-275 that induced growth inhibition of endometrial cancer cells [12]. Jiang et al. reported that over the course of 4 days, there was a 60% reduction in the serous endometrial cancer cell line Ark2 cell counts by MS-275 (which they called HDAC-I1) (0.5 μM) treatments, as compared to controls treated with DMSO solvent (Table 2). They reported growth inhibition of both endometrioid (Ishikawa and AN3) and serous (Ark2) endometrial carcinomas [43].

3.8. M344. Synthetic amide analogs were discovered to have a common structure with TSA [44]. Using an in vitro enzyme inhibition assay of histone deacetylation, Jung et al. demonstrated that M344 is a potent HDACI and an inducer of terminal cell differentiation [44]. The effective dose of M344 that inhibited 50% clonal growth (ED50) of the Ishikawa endometrial cancer cell line was calculated at 2.3×10^{-6} M [13] (Table 2). On the other hand, normal endometrial epithelial cells were viable after the treatment with the same doses of M344 that induced growth inhibition of endometrial cancer cells [13].

3.9. Apicidin. Cyclic peptide HDACIs can be further divided into two classes: those with an epoxyketone group such as HC-toxin and trapoxin, and those without such a group (apicidin, depsipeptide or FK228). Apicidin is a novel cyclic tetrapeptide with a potent broad spectrum of antiprotozoal activity against Apicomplexan parasites [45]. Its structure is related to trapoxin, a potent HDACI, and some biological activity, including antiproliferative and toxic effects, have been shown in some cancer cell lines [46]. The effective dose of apicidin that inhibited 50% clonal growth (ED50) of the Ishikawa endometrial cancer cell lines was calculated at 1.0×10^{-6} M [14] (Table 2). On the other hand, normal endometrial epithelial cells were viable after the treatment with the same doses of HDACIs that induced growth inhibition of endometrial cancer cells [14]. Ueda et al. [14] and Ahn et al. [47] independently demonstrated that apicidin has antitumor properties on Ishikawa endometrial cancer cells by selectively inducing the genes related to cell cycle arrest and apoptosis.

3.10. Psammaplin A. Psammaplin A (PsA) is a natural bromotyrosine derivative from a two-sponge association, *Poecillastra sp*. and *Jaspis sp.*, which was first isolated from the *Psammaplysilla* sponge [45]. It was reported that PsA has antibacterial and antitumor properties, and also inhibits various enzymes including topoisomerase II, farnesyl protein transferase, leucine amino peptidase, and chitinase (reviewed in [48]). Recently, it was reported that PsA inhibits both HDAC and DNA methyltransferase (DNMT) as epigenetic modifiers of the tumor suppressor gene [49]. PsA caused antiproliferative activity and induced cell cycle arrest or apoptosis in Ishikawa human endometrial cancer cells. PsA inhibited the proliferation of Ishikawa cells in a dose-dependent manner. The 50% inhibitory concentration (IC50) of PsA was found to be 5 μg/mL (7.5×10^{-6} M) after 48 h treatment (Table 2). PsA increased the proportion in the G1 phase and G2/M phases of the cell cycle [48].

3.11. Oxamflatin. Oxamflatin is an aromatic sulfonamide derivative with a hydroxamic acid group that was identified as a compound inducing the morphological reversion of v-K-*ras*-transformed NIH3T3 cells from a chemical library [50]. In addition, the morphology of NIH3T3 cells transformed by various other oncogenes such as v-*sis*, v-*src*, MEK^{EE} or v-*fos* was also reverted by oxamflatin. Kim et al. analysed the effect of oxamflatin on the proliferation of eight mouse and

human tumor cell lines. The 50% inhibitory concentrations of oxamflatin for all the cell lines except CCD-19Lu, a normal human lung cell line, were below 0.72 μg/mL, while that for CCD-19Lu was 1.4 μg/mL [51]. Over the course of 4 days, there was a 78% reduction in the serous endometrial cancer cell line Ark2 cell counts by oxamflatin (0.25 μM) treatments, as compared to controls treated with DMSO solvent. The most striking observation is the 95% reduction in cell counts following the administration of 0.75 μM oxamflatin to Ark2 cells [43]. This report resulted in growth inhibition of both endometrioid (Ishikawa and AN3) and serous (Ark2) endometrial carcinomas.

4. Conclusions

In this review, we summarize recent preclinical studies on the use of HDACIs, especially in human endometrial cancer cells. Many questions are currently still unanswered with respect to HDACI specificities for definite tumor subtypes and the molecular mechanisms underlying HDACI-induced differentiation, cell cycle arrest and apoptosis. In addition, the regulation mechanisms of the specific gene expression and recruitment of HDAC complex to the specific promoter sites remain still to be determined. Also, it is still unclear to what extent different HDACs exhibit different and potentially overlapping functions, and it is important to distinguish the HDAC specificity of HDACIs for the development of selective therapy on the molecular level. Further work is needed to improve our understanding of why transformed cells are more susceptible to the effect of HDACIs than normal cells. Also, combinations of HDACIs with differentiation-inducing agents, with cytotoxic agents, and even with gene therapy may represent novel therapeutic strategies and new hope for the treatment of endometrial cancer.

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Review Article

Hypoxia-Inducible Factor-1 as a Therapeutic Target in Endometrial Cancer Management

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In the Western world, endometrial cancer (EC) is the most common malignant tumor of the female genital tract. Solid tumors like EC outgrow their vasculature resulting in hypoxia. Tumor hypoxia is important because it renders an aggressive phenotype and leads to radio- and chemo-therapy resistance. Hypoxia-inducible factor-1α (HIF-1α) plays an essential role in the adaptive cellular response to hypoxia and is associated with poor clinical outcome in EC. Therefore, HIF-1 could be an attractive therapeutic target. Selective HIF-1 inhibitors have not been identified. A number of nonselective inhibitors which target signaling pathways upstream or downstream HIF-1 are known to decrease HIF-1α protein levels. In clinical trials for the treatment of advanced and/or recurrent EC are the topoisomerase I inhibitor Topotecan, mTOR-inhibitor Rapamycin, and angiogenesis inhibitor Bevacizumab. Preliminary data shows encouraging results for these agents. Further work is needed to identify selective HIF-1 inhibitors and to translate these into clinical trials.

1. Introduction

Endometrial cancer is the most common malignant tumour of the female genital tract. The American Cancer Society estimates that 42.160 women will have been diagnosed with, and 7780 women will have died of cancer of endometrial cancer in 2009 in the US [1]. Ninety percent of endometrial cancer cases are sporadic, while the remaining are deemed hereditary. In the endometrium, different adenocarcinoma subtypes can develop. Endometrioid endometrial carcinoma (EEC), or Type 1 cancer, accounts for approximately 75% of cases. These tumours are usually oestrogen dependent, tend to be of lower grade, and have fewer recurrences and a better survival. They often develop in a background of adenomatous hyperplasia and are characterized by mutations in PTEN and defects in DNA mismatch repair—as manifested by microsatellite instability. Type 2 tumours, of which serous endometrial carcinoma (USPC) is the most common subtype, arise from atrophic endometrium. Type 2 tumours often show p53 and are usually nondiploid. USPCs are often poorly differentiated and have a greater propensity for early spreading. They have worse prognosis than that of EEC.

A developing solid tumour will outgrow its own vasculature beyond the size of several cubic millimetres, resulting in hypoxia (defined as an oxygen tension below the physiological level, <2% pO_2) [2]. Hypoxia has been found to be an important event in carcinogenesis as it renders a more aggressive phenotype with increased invasiveness and proliferation, formation of metastases, and poorer survival in several types of cancer [3, 4]. Furthermore, it has been shown that hypoxia-induces resistance to radiotherapy and chemotherapy [5–7]. The key survival gene for cells in a hypoxic environment is hypoxia inducible factor-1 (HIF-1) (see Figure 1.).

The unsatisfactory results obtained with conventional pharmacological treatment encourage further biological and clinical investigations addressed to a better understanding of specific cell targets and signalling transduction pathways involved in endometrial carcinogenesis and to the identification of novel molecular therapeutic targets. As hypoxia, and thus HIF-1, leads to resistance to radiotherapy and

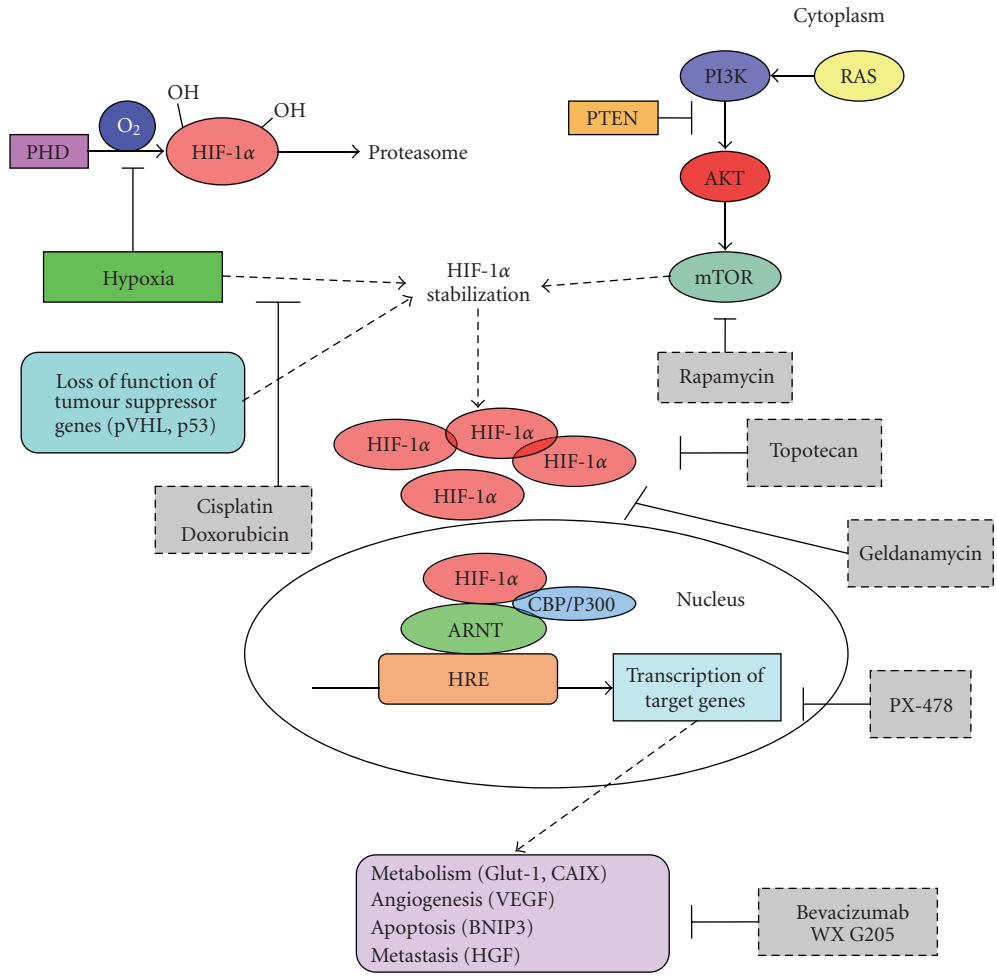


Figure 1: Mechanisms of HIF activation in cancer.

chemotherapy in solid tumours [5–8], targeting HIF-1 could be an attractive treatment strategy, with the potential for disrupting multiple pathways crucial for tumour growth. In this review, we will describe the current status of HIF-1 (upstream and downstream) inhibitors in the treatment of endometrial cancer.

2. Hypoxia-Inducible Factor-1α

HIF-1 is a transcription factor composed of the subunits HIF-1α and HIF-1β, which are basic helix-loop-helix DNA binding proteins. Both HIF-1α and HIF-1β genes are ubiquitously expressed and heterodimerize to form the active HIF-1 that activates gene transcription by binding to the consensus HIF Responsive Element (HRE): 5′-RCGTG-3′ in promoters and enhancers of target genes [9]. The activity of HIF-1 is predominantly regulated at the post-translational level by regulating HIF- 1α protein stability. At normal oxygen tension, HIF-1α is hydroxylated by prolyl hydroxylases (PHD) in the oxygen dependent degradation domain (ODDD). Hydroxylated HIF-1α is recognized by the Von Hippel-Lindau (VHL) protein, ubiquitinated and destined for degradation by proteasomes. This process is inhibited during hypoxia [10]. Under hypoxia, stabilized HIF-1α subunits heterodimerize with β subunits (also known as ARNT) to transactivate target genes after nuclear translocation. Among these are genes involved in adaptation to low glucose levels like the glucose transporter Glut-1, carboanhydrase IX (CAIX) that regulates pH [11], and vascular endothelial growth factor (VEGF) that is one of the most potent inducers of angiogenesis [12]. Although HIF-1α usually induces prosurvival (CAIX, Glut-1, VEGF) genes, a role of HIF-1α in regulation of apoptosis has also been described. HIF-1α promotes cell death through an increase in p53 or other proapoptotic proteins like BNIP3 [13]. As a result of this dual function of HIF-1α, a "stop-and-go" strategy as a dynamic balance to maintain overall cell growth and survival has been proposed [14]. Hypoxia induced HIF-1α also affects the expression of genes involved in metastasis formation. Hepatocyte growth factor (HGF), for example, is a cytokine which stimulates proliferation and invasion through its receptor, the protooncogene c-MET [15]. Invasive cell growth is promoted by HIF-1α -induced c-Met transcription and sensitizing of cells to HGF stimulation [16–18]. Taken together, the adaptive response to hypoxia

in primary tumours resembles in many ways the so-called metastatic phenotype which explains the poor prognosis of hypoxic cancers [19].

HIF-1 stabilization may also occur under oxygen-independent conditions, including infection with oncogenic viruses, loss-of-function mutations in tumour suppressor genes such as Von Hippel-Lindau (VHL), or signaling by receptor tyrosine kinases, prostaglandin E2 receptor, or nitric oxide [20]. Furthermore, genetic alterations in the EGFR [21], RAS, and PI-3K/Akt [22–24] as well as loss of p53 function [25] have been shown to lead to increased nonhypoxic HIF activity. HIF-1α has also been shown to be regulated by mammalian target of Rapamycin (mTOR). mTOR promotes increased translation of HIF-1α mRNA into protein [26, 27]. Other possible mechanisms contributing to normoxic HIF-1 expression like oncogenic mutation or amplification of HIF-1α gene have rarely been reported in solid cancers [28, 29]. A polymorphism in HIF-1α (P582S) has been found associated with increased HIF activity and poor prognosis in prostate cancer, but its significance with cancer risk is still incompletely understood [30, 31]. The single nucleotide polymorphism (SNP) C1772T (also described as C1744T) in the HIF-1α gene coding region results in an amino acid change at position 582 changing a Proline to a Serine (i.e., P582>S) in the ODD domain (http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=11549465). Carriers of this SNP seemed to have an increased risk of developing cervical and endometrial cancer [32]. However, the proportion of allele carriers with the most common polymorphism in the control group was different from ratios described in other studies. We [31] examined whether the C1744T polymorphism increased the risk for endometrioid endometrial cancer. Although the C1744T polymorphism was associated with higher microvessel density and AKT activation, it did not lead to increased cancer risk. Interestingly we found that the P582S genotype variation in the ODDD of the HIF-1α protein may occur as a de novo mutation in endometrial cancer. Although the significance of this remains to be established, others have proposed that it may increase transactivation of HIF-1α [30].

3. Endometrial Cancer

3.1. HIF-1α and Endometrial Carcinogenesis. It has been postulated that menstruation results from vasoconstriction of spiral arterioles, causing hypoxia which leads to necrosis [33]. This focal hypoxia in perimenstrual endometrium could result in locally increased HIF-1α. However, in premenopausal women, HIF-1α was undetectable in the majority of samples. In the HIF-1α positive cases, expression was only seen in a small focus within the tissue, suggesting that if hypoxia does occur at this time, then it is not widespread. There seemed to be no correlation of HIF-1α expression and the menstrual cycle [34]. In postmenopausal women, HIF-1α was increasingly overexpressed from inactive endometrium through hyperplasia to endometrioid carcinoma, paralleled by activation of its downstream genes such as CAIX, Glut-1, VEGF, and increased angiogenesis. Low HIF-1α expression was associated with negative/low VEGF staining in the total group [35]. These results highlight the potential importance of hypoxia and its key regulator HIF-1α in endometrial carcinogenesis and progression of disease [36].

Perinecrotic, chronic hypoxia-associated HIF-1α expression was absent in inactive endometrium, rare in endometrial hyperplasia, and frequent in endometrioid carcinoma. These results could point to the importance of hypoxia and the subsequent stabilization of HIF-1α in endometrial carcinogenesis [35–38]. Loss of PTEN tumour suppressor gene (also known as MMAC1) is often seen in endometrial carcinogenesis and is thought to cause nonhypoxia-mediated HIF-1α expression via activation of the PI3K/AKT and mTOR signaling pathway [39–42]. Horrée et al. (unpublished data) showed that although over 60% of the carcinomas showed extensive loss of PTEN by immunohistochemistry, this was not correlated to increased HIF-1α expression. Thus, diffuse nonhypoxia-related expression of HIF-1α seemed not to be related to PTEN mutation in endometrial cancer. Correlation of HIF-1α with tumour stage, tumour grade, or myometrial invasion is still under discussion [35, 43, 44].

The mechanism of tumourigenesis of USPC differs from that of EEC. More expression of HIF-1α was observed in USPC than in EEC [44, 45]. In USPC, HIF-1α expression was not correlated to clinical stage or depth of myometrial invasion. p53 mutations are a common event in USPC carcinogenesis and aberrant p53 accumulation has been associated with HIF-1α overexpression in different human tumours [46]. In contrast, p53 expression was not associated with HIF-1α expression in type II endometrial carcinomas [44, 45].

3.2. HIF-1α and Prognosis in Endometrial Cancer. Contradictory results have been described as to the prognostic value of HIF-1α overexpression in endometrial carcinoma. HIF-1α showed significantly higher expression in recurrent endometrial carcinomas when compared with their primary tumours; it was, however, not an independent predictor for recurrent endometrial carcinoma [43, 44]. In stage 1 endometrial cancers, HIF-1α was associated with a worse prognosis [37]. However, others did not find prognostic impact of HIF-1α expression [38]. Besides the limitation of relatively small numbers of patients in these studies, immunohistochemical studies are difficult to compare because of a variation in definition of HIF-1α positivity. In some studies, both nuclear and cytoplasmic staining was scored. The significance of cytoplasmic HIF-1α, however, is still not clear as stable HIF-1α is thought to rapidly translocate to the nucleus. Expression patterns that can be observed in endometrial tumours are the diffuse, perinecrotic, and mixed (both perinecrotic and diffuse) patterns [35]. Perinecrotic HIF-1α expression is thought to be hypoxia driven, whereas diffuse HIF-1α expression may rather be due to nonhypoxic stimuli [47]. Our experience shows that once authors take into account nuclear staining only and HIF-1α expression pattern, the results can change dramatically. Figure 2 shows an example of nuclear HIF-1α in a diffuse and perinecrotic expression pattern.

Table 1: Clinical trials on HIF-1α targeted therapies in endometrial cancer.

Class	Inhibitor	Mechanism	Clinical trials in endometrial cancer
Small molecule inhibitors of HIF-1			
Topoisomerase inhibitor	Topotecan (topo-I)	Inhibits hypoxic induction of HIF-1α protein and DNA binding activity	Miller et al. [48] Triana et al. [49] Wadler et al. [50]
HSP90 inhibitor	Geldanamycin	Induces degradation of HIF-1α protein and inhibition of DNA binding of HIF-1	—
Other	PX-478	Inhibition of HIF-1α transcription activity	—
Inhibitors of signal transduction pathways			
mTOR inhibitor	Temsirolimus (CCI-779)	Downregulation of HIF-1α by inhibing mTor	Oza et al. [51]
	Everolimus (RAD001)		Slomovitz et al. [52]
Inhibitors of HIF-1 target genes			
VEGF inhibitor	Bevacizumab	Monoclonal antibody against VEGF	Aghajanian et al. [53]
CAIX inhibitor	Rencarex (WX G250)	Monoclonal antibody against CAIX	—

As HIF-1α expression is associated with treatment failure and/or patient mortality, targeting HIF-1α could be an attractive treatment strategy, with the potential for disrupting multiple pathways crucial for tumour growth.

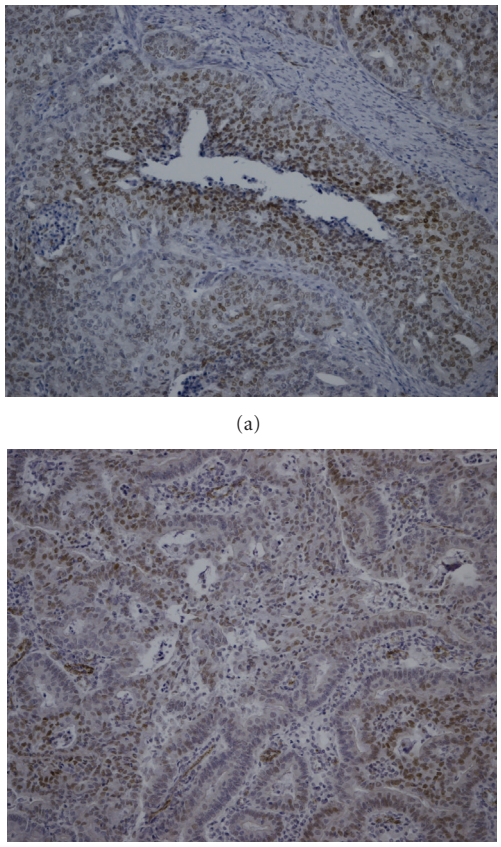
4. HIF-1α and Hypoxia as a Target for Cancer Therapy

The unsatisfactory results obtained with conventional pharmacological treatment encourage further biological and clinical investigations addressed to a better understanding of specific cell targets and signaling transduction pathways involved in endometrial carcinogenesis and to the identification of novel molecular targeted therapies. A new and more effective treatment for metastatic endometrial carcinoma is urgently needed.

There are different areas of research in hypoxia-related drug therapy including (1) designing drugs that directly inhibit HIF-1 signaling and (2) influencing other signaling cascades that indirectly alter HIF signaling.

Inhibition of HIF-1α would, of course, hit multiple targets but because of its bifunctional effects, for example, proapoptotic genes induced by hypoxia, outcome will be difficult to predict. Thus far, selective HIF-1 inhibitors have not been identified. A number of nonselective inhibitors, which indirectly target signaling pathways upstream or downstream HIF-1 are known to decrease HIF-1α protein levels. Antisense therapy against HIF-1α has been shown to reduce HIF-1α expression and transcriptional activity; however, at present it is not clinically applicable. Therefore, the potential of HIF-1α as a target for cancer therapy lies in the small molecule inhibitors of HIF-1. Several small molecular inhibitors of the HIF-1 transcriptional activation pathway have been identified (Table 1). Although none of these has been shown to directly and specifically target HIF-1 [54, 55], they do decrease HIF-1α protein levels. Some of these HIF-1 inhibitors are subject of clinical trials at present.

4.1. Topotecan. Topotecan, a topoisomerase I inhibitor that has been used as a second-line therapy for ovarian cancer, is one such small molecule inhibitor of HIF-1 [56, 57]. Topotecan inhibits hypoxic induction of HIF-1α protein and DNA binding activity [58]. In a GOG phase II trial of Topotecan in pretreated patients with advanced, persistent, or recurrent endometrial carcinoma, the total response rate was 9%, with 1 patient achieving a complete response and 1 experiencing a partial response. Twelve (55%) patients maintained stable disease [48]. The eastern Cooperative Oncology Group subsequently performed a phase II trial of Topotecan for metastatic or recurrent endometrial carcinoma. The overall response was 20%. Although single-agent Topotecan treatment has shown activity in chemonaïve [50] and previously treated patients [48, 49], severe (grade 4 neutropenia) and unexpected (primarily sepsis) toxicities were encountered [48, 50]. However, at modified doses,



(a)

(b)

Figure 2: Immunohistochemical staining of HIF-1α in endometrioid endometrial carcinoma. Typical patterns are shown: (a) perinecrotic HIF-1α expression (10× magnification) and (b) diffuse HIF-1α expression (10× magnification).

toxicity was acceptable and clinical activity was preserved [50].

Despite the different carcinogenesis of EEC and USPC, but probably due to the rareness of the latter, clinical trials including only USPC patients are rare. A pilot study of Topotecan for the treatment of USPC demonstrated clinical activity in this patient group [59]. However, because survival outcomes continue to be disappointing, combining Topotecan with other active drugs may lead to improved outcomes.

4.2. mTOR Inhibitors. HIF-1α has also been shown to be regulated by mammalian target of Rapamycin (mTOR). mTOR promotes increased translation of HIF-1α mRNA into protein [26, 27]. Rapamycin is a specific inhibitor of mTOR and inhibits both the stabilization and the transcriptional activity of HIF-1α in hypoxic cancer cells [60]. This effect is directly related to the disruption of mTOR-dependent signaling functions. The current hypothesis is that mTOR inhibitors could be effective inhibitors of hypoxic adaptation in developing tumours. These effects could be especially relevant in tumours with loss of PTEN function as is often the case in endometrioid endometrial cancer [61]. Loss of PTEN leads to constitutive activation of AKT, which leads to up-regulation of mTOR. Potential therapies targeting the mTOR pathway include mTOR inhibitors (Rapamycin derivates) Temsirolimus (CCI-779), and Everolimus (RAD001) [62]. Demonstrated activity in preclinical studies has led to numerous phase I and phase II trials. A phase II trial of Temsirolimus in patients with chemotherapy treated, recurrent, or metastatic endometrial cancer showed modest activity of Temsirolimus. Two patients (7.4%) showed partial response and twelve patients (44%) had stable disease [51]. A 44% clinical benefit response rate was found in a phase II study of Everolimus in 29 patients with recurrent endometrial cancer [52]. Clinical Benefit was defined as complete or partial response or prolonged stable disease. In this trial, loss of PTEN expression was predicative of response rate. The different mTOR inhibitors show encouraging single agent clinical benefit. A phase I trial of Temsirolimus with Topotecan (NCT00523432) in patients with gynaecological malignancies, including endometrial cancer, has just finished recruiting patients. Other trials of Temsirolimus are underway.

4.3. Bevacizumab. An HIF-1 inhibitor that targets a pathway activated by HIF-1 is Bevacizumab. Bevacizumab is a monoclonal antibody that targets VEGF, a potent endothelial cell mitogen that has been associated with increased angiogenesis in malignancies. Different studies showed that an increase in VEGF expression was linked to increased angiogenesis in endometrial carcinomas. High VEGF mRNA levels were correlated significantly with highly vascularized tumours [63, 64]. Early results of a phase II study of Bevacizumab in the treatment of recurrent or persistent endometrial cancer in 53 patients showed a 15% response rate. Nearly 36% of the patients were progression free at 6 months [53]. In conclusion, Bevacizumab appears to be active in women with recurrent or persistent endometrial cancer.

4.4. Cisplatin and Doxorubicin. Some conventional anticancer agents targeting signal transduction pathways have also been shown to inhibit HIF-1 [65]. Duyndam et al. [66] showed in human ovarian cancer cell lines that the conventional anticancer agents cisplatin and doxorubicin can negatively influence HIF-1 activity with a concomitant reduction of VEGF expression. A recent phase III trial demonstrated improved progression-free and overall survival for the three-drug regimen of cisplatin, doxorubicin and paclitaxel compared with a two-drug combination (cisplatin and doxorubicin) in advanced or recurrent endometrial carcinoma. However, toxicity problems often make the three-drug regimen less acceptable [67].

4.5. New Promising Drugs. Small molecule inhibitors of HIF-1 activity currently investigated in clinical trials are PX-478, an inhibitor of HIF-1 transcription factor activity [68], and geldanamycin, an HSP90 (heat shock protein 90) inhibitor [69]. HSP90 is involved in the folding of HIF-1α and Geldanamycin induces degradation of HIF-1α [70]. Both are being evaluated in advanced solid tumours. WX G250,

a CAIX antibody (http://www.wilex.com), is another HIF-1 inhibitor that targets a different pathway activated by HIF-1. WX G250 is currently in phase III clinical trials in renal cell cancers. These new drugs may find their way into clinical trials in endometrial cancer in the future.

5. Summary

Hypoxic tumours are usually resistant to radiotherapy and conventional chemotherapy, rendering them highly aggressive and metastatic. Response to hypoxic stress is largely mediated by the HIF pathway. HIF-1α expression is correlated with a poor prognosis in endometrial cancer. Therefore, targeting the HIF pathway provides an attractive strategy to treat hypoxic and highly angiogenic tumours. Thus far, selective HIF-1 inhibitors have not been identified. A number of nonselective inhibitors, which indirectly target signaling pathways upstream or downstream of HIF-1, are known to decrease the key regulating HIF-1α protein levels. Different (indirect) HIF-1α inhibitors that are in clinical trial for the treatment of advanced/recurrent endometrial carcinoma are Topotecan, Rapamycin derivates, and Bevacizumab. Preliminary results show encouraging results for these single-agent treatments with partial response and stable disease in the patients. However, lack of specificity increases the difficulty in attributing any antitumorigenic effects of these drugs specifically to inhibition of HIF-1. The combination of HIF inhibitors with conventional treatment may prove to be clinically useful. Further work is needed to identify more selective HIF-1 inhibitors, to determine their mechanism of action, and to translate these developments into clinical trials.

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Review Article

The LH/hCG Axis in Endometrial Cancer: A New Target in the Treatment of Recurrent or Metastatic Disease

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Endometrial cancer (EC) is a hormone-dependent cancer that currently represents the most frequent malignancy of the female reproductive tract. The involvement of steroid hormones in EC etiology and progression has been reported. More recently, gonadotropins, and, in particular LH/hCG, are emerging as novel regulators of tumor progression. In the present review, we discuss the role of the LH/hCG axis (i.e. LH/hCG and its receptors, LH/hCG-R) in both gonadal and nongonadal tissues, in physiological and neoplastic conditions. In cancer cells, LH/hCG mainly controls cell proliferation and apoptosis. In particular, in EC LH/hCG improves cell invasiveness, through a mechanism which involves the LH/hCG-R, which in turn activate protein kinase A and modulate integrin adhesion receptors. Indeed, the LH/hCG-R mRNA is expressed in primary ECs and this expression correlates with LH/hCG-induced cell invasiveness in vitro. These results lead to hypothesize that recurrent and metastatic ECs, which express LH/hCG-R, could benefit from therapies aimed at decreasing LH levels, through Gn-RH analogues. Hence, the LH/hCG axis could represent a prognostic factor and a new therapeutic target in EC.

1. Introduction

Endometrial cancer (EC) is currently the most frequent malignancy of the female reproductive tract [1] with a tendency to increase its incidence during the last decade [2, 3]. Approximately 75% of EC cases are diagnosed with the tumor confined to the uterine corpus [2, 3], but after primary surgery 15% to 20% of these tumors recur and have limited response to systemic therapy. The most common basis for determining risk of recurrent disease has been the categorization of EC into 2 subtypes: type I EC is associated with good prognosis, low stage and grade, and endometrioid histology; type II EC is, in contrast, characterized by high stage and grade, nonendometrioid histology and poor prognosis. The prognostic value of this distinction is limited, however, because up to 20% of type I cancer recur, and half of type II cancers do not [3]. Moreover, the molecular basis of the distinction between type I and II cancer is understood only partially. Type I cancer is associated with hyperestrogenic risk factors, is more often estrogen and progesterone receptor positive, microsatellite unstable, and displays mutations in KRAS or PTEN. Conversely, type II cancer is more often aneuploid and harbors alterations in CDKN2A, TP53, and ERBB2 [4]. Such molecular alterations, despite of prognostic value, have not provided a basis for improved therapy [5].

Hormone (estrogen and progesterone) receptor status influences the choice of treatment especially in metastatic disease. Indeed estrogen secretion, especially when occurring without progesterone secretion, is apparently one of the most relevant etiologic factors in EC [6]. In fact, unopposed and prolonged exposure to estrogens can exert potent mitogenic effects on the endometrial surface epithelium, thus contributing to the malignant transformation of the latter [7]. However, as stated above, most aggressive tumors are often receptor negative [2]. In particular, those cancers arising in the postmenopause, which are often more aggressive, are also apparently unlinked to estrogen secretion [8]. It

was hypothesized that the latter types of EC might be sensitive to the elevated levels of luteinizing hormone/human chorionic gonadotropin (LH/hCG) that characterize the post-menopause.

The present review aims at updating the reader about some current trends in the field. In particular, we will focus on a brief overview of the single elements of the LH/hCG axis and its relevance in nongonadal tissues in physiological conditions. Moreover, we will briefly review the role of the LH/hCG axis in human cancers, with particular emphasis to EC. Finally, we will provide new perspectives for treatment of EC based on the targeting of the LH/hCG axis.

2. The LH /hCG Axis: LH/hCG, LH/hCG-R, and Intracellular Signalling

LH and hCG are structurally related glycoprotein hormones (GPH) produced by the pituitary gland and placenta, respectively. Both LH and hCG are heterodimers of noncovalently bound α and β subunits; hCG has a higher molecular mass and is the most heavily glycosylated among the GPH, resulting in a longer circulating half-life [9]. LH, secreted by anterior pituitary gland, is present in all mammalian species. On the other hand, hCG, which is secreted by placental trophoblasts, is present exclusively in primates although its occurrence in other species, as a modified form, has not been completely ruled out [10]. These two hormones bind the same receptors and have similar biological functions, although hCG is more potent because of its higher receptor binding affinity and its longer circulatory half life. LH and hCG are considered the most potent gonadal regulating hormones, even though there are reports demonstrating their effects in nongonadal tissues (see below).

The receptor for LH/hCG is encoded by a gene, located on chromosome 2, position 2p21 [11, 12]. The genomic sequence of the gene consists of 11 exons separated by 10 introns; the transcription of the LH/hCG-R gene can produce 7 different protein-coding mRNAs [12–14]. Recently, three more alternative splice variants have been found in corpus luteum and luteinized granulosa cells [14].

The LH/hCG-R is a member of the G-protein coupled receptor (GPCR) family and its functional activity is mediated by G proteins [6, 15]. The amino acids chain of the mature LH/hCG-R protein is composed by 699 residues with a molecular mass of about 78 kDa [12, 13]. The protein consists of a long extracellular N-terminal domain, a region containing seven transmembrane-spanning sequences connected by alternating extra and intracellular loops, and a short C-terminal cytoplasmatic tail [13, 16]. The extracellular domain is characterized by the presence of a structural motif rich in leucine repeats (LRR) which is involved in modulating ligand-receptor(s) binding [16].

Such binding determines conformational changes in the protein structure that in turn induces the activation of intracellular signalling. In particular, both LH and hCG stimulate adenylate cyclase on the internal membrane, which in turn converts adenosine triphosphate (ATP) into cyclic adenosine monophosphate (cAMP). Cyclic AMP stimulates the activation of an inactive Protein Kinase A (PKA), which, besides other actions, stimulates steroidogenesis in the mitochondria of the target cell by transforming cholesterol into pregnenolone. Other actions of LH/hCG include the induction of proteolytic enzymes, prostaglandin synthesis, inhibin production, induction of 17 beta-hydroxysteroid dehydrogenase, and changes in gene metabolism [17]. LH and hCG can also trigger the PLC/inositide tris-phosphate transduction pathway [18, 19]; the cell type and the amount of the receptor on the plasma membrane can influence the prevalent activation of either the signalling pathways [20]. In porcine endometrial cells, the LH hormone activates both cAMP/PKA and PLC/inositide tris-phosphate pathways [21]. Moreover, LH acting through the Akt and Erk pathways on theca cells plays a relevant function *in vitro* and follicle growth and development [22].

3. Expression and Role of the LH/hCG Axis in Extragonadal Tissues

By acting through the transduction mechanisms described above, LH and hCG regulate ovarian steroidogenesis, but have also been shown to exert various effects on nongonadal tissues, such as endometrium, myometrium, and fallopian tubes.

In the ovary, the main function of GTs is well known. According to the "two cells-two gonadotropins" theory, LH is acting on theca cells during ovarian follicle growth. At first, the synthesis of androgens is induced, then androgens are transformed in estrogens in the compartment of granulosa cells through an enzymatic reaction which is dependent on FSH [23]. Besides ovary, receptors for both LH and FSH were identified in different organs of the female reproductive apparatus, and in particular in the endometrium [24]. The presence of LH/hCG-Rs was shown for the first time by Reshef et al. [24] in the uterus of nonpregnant women by immunohistochemistry, an observation subsequently confirmed using different techniques [25, 26]. Collectively, LH/hCG-Rs have been identified in epithelial and stromal cells of the endometrium as well in smooth muscle cells of myometrium and uterine vessel. The expression of LH/hGC-R varied during the women's cycle phase, with the maximal expression occurring during the luteal phase, and a main localization in the luminal and glandular epithelial cells of endometrium [27]. The attainment of the highest values of LH/hGC-R correlated, also on a time scale, with the triggering of cyclo-oxygenase-2 (COX-2) and placental growth factor (PlGF) production. This finding suggests the hypothesis that LH could play a pivotal role at the beginning of luteolysis [28]. Moreover, LH could regulate the local metabolism of estrogens and progestins, acting through the cAMP pathway [29].

Specific receptors for LH/hCG have also been identified in the myometrium of several animal species, including humans [24]. In this tissue, LH/hCG apparently acts through the LH/hCG-R-dependent activation of both the c-AMP and phospholipase C transduction pathways [20, 21]. It was proposed that the triggering of adenyl cyclase could determine an activation of COX-2, which in turn should induce an increase of the synthesis of either prostaglandin

(PG)E, with an ensuing muscle relaxation, or PGF, which determines the contraction of the uterine musculature [28]. Also in this case, the highest expression of the LH/hCG-R occurred during the luteal phase of the cycle, and paralleled an increased synthesis of PGE2.

The LH/hCG-R is also expressed in the internal mucosa and smooth muscle vascular cells of fallopian tubes [30]. *In vitro* studies performed on explanted fallopian tissues showed that LH addition produces a dramatic reduction of tube motility [31]. This suggests that LH/hCG-R stimulation could contribute to the quiescent state of tube's muscles after ovulation, in turn favouring both oocyte fertilization and embryo movements along the tube to reach the endometrial cavity.

4. Expression and Role of the LH/hCG Axis in EC

Increasing evidence suggests that the action of LH and hCG might also contribute to the malignant transformation of human cells, by promoting either promitogenic or anti-apoptotic effects. For example, LH/hCG-R may be involved in the progression of some ovarian and breast cancers [32]. In addition, the expression of LH/hCG-R has been demonstrated in endometriosis and has been shown to be increased in patients with adenomyosis [33–35].

Work from Lin et al. [6] showed that the LH/hCG-R mRNA is also expressed in human ECs, and a notion subsequently reinforced by the demonstration that the addition of LH/hCG regulates proliferation in EC cell lines [7, 36]. In particular, two isoforms of the LH/hCG-R, arising from alternative splicing of the corresponding gene are documented in EC samples [37], as well as in neoplastic ovarian tissues [38]. More recently, we confirmed not only that specific LH/hCG-Rs can be detected in human EC, but also that their expression is apparently related to the cancer grading [39]. On the basis of these findings, as well as of the fact that we determined the effects of LH/hCG in tumor progression of EC, by analyzing the effects of such GTs on the invasion potential of both EC cell lines and primary human EC cells. We showed that human recombinant (hr) LH (as well as hCG) induced a significant increase in cell invasiveness through Matrigel-coated porous membranes in the human EC cell line Hec1A, which expresses the LH/hCG-R. This effect turned out to depend on the hrLH binding to its specific receptor and on the following activation of the cAMP/PKA signaling pathway. Moreover, the hrLH-induced increase in Hec1A invasiveness was dependent upon the functional activation of β1 integrin receptors and the subsequent induction of MMP-2 secretion. Interestingly, these mechanisms were found to be also operative in primary EC cells transferred *in vitro*, because hrLH addition produced an increase in cells invasiveness only in those primary EC tumors that expressed the LH/hCG-R. Here again, this effect was dependent on PKA activity [40]. Subsequently, we also provided evidence that the LH/hCG-R mRNA is expressed in the great majority of a cohort of primary ECs and that cells obtained from primary ECs can be triggered to invade a Matrigel layer by LH addition. A good correlation was found between the level of LH/hCG-R mRNA expressed by primary EC and that of LH-induced cell invasiveness *in vitro*. The analysis of cell invasion *in vitro* in response to LH/hCG, allowed us to divide the EC samples into two groups, one with a null or very low response (non-responders = NR) and the other with a significant response to LH (responders = R). The two groups had significantly different levels of LH/hCG-R mRNA expression. These results may contribute to reconcile the conflicting results present in the literature, about the clinical effect of LH analogues in the treatment of recurrent or metastatic EC (see below).

On the whole, these results open the possibility that GTs could directly regulate tumor progression of EC by regulating tumor invasiveness through the binding to specific receptors exposed on the plasma membrane of EC. This finding opens new therapeutic prospective of recurrent EC.

5. Therapeutical Perspectives

Some clinical trials were performed with the aim of treating patients affected by EC with Gonadotropin releasing hormone (Gn-RH) analogues, in order to decrease LH levels. Conflicting results emerged from these studies. In fact, Davies et al. [36], Lhommé et al. [41], and Jeyarajah et al. [42] showed evidence of efficacy in long-term treatments, with response rate ranging from 9% to 57%. On the other hand, Covens et al. [43], Markman et al. [44], and Asbury et al. [45] observed insufficient activity. We provided a contribution in this controversy, reporting a case of a patient affected by EC, primarily treated with a Gn-RH analogue. In fact, in this case, surgical treatment was unfeasible, due to the compromised health of the patient [46]. The therapy was carried out for 6 years and no progression of the disease was observed throughout this period.

Our recent data, reported in the previous paragraph, on the role of LH/hCG in EC invasiveness could contribute to reconcile the conflicting results present in the literature, about the clinical effect of LH analogues in the treatment of recurrent or metastatic EC. In fact we showed that only 35% of patients showed a high expression of LH/hCG mRNA and only these patients responded to exogenous recombinant LH addition by increasing the cell invasion through Matrigel [39]. This could in turn imply that only patients highly positive for LH/hCG-R expression could receive benefits from a therapy aimed at decreasing LH levels, through Gn-RH analogues. On the whole, based on available data, we suggest that therapies, employing Gn-RH analogues, could produce benefits in the treatment of recurrent or metastatic EC, especially in those patients where cancer tissue displays high LH/hCG-R levels. We prospect to analyze herein all the IV stage patients (whose five-year survival is less than 10%) for the expression of LH/hCG mRNA and treat only the high expressors with Gn-RH analogues.

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Review Article

Endometrial Cancer: What Is New in Adjuvant and Molecularly Targeted Therapy?

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Endometrial cancer is the most common gynaecological cancer in western countries. Radiotherapy remains the mainstay of postoperative management, but accumulating data show that adjuvant chemotherapy may display promising results after staging surgery. The prognosis of patients with metastatic disease remains disappointing with only one-year survival. Progestins represent an effective option, especially for those patients with low-grade estrogen and/or progesterone receptor positive disease. Chemotherapy using the combination of paclitaxel, doxorubicin, and cisplatin is beneficial for patients with advanced or metastatic disease after staging surgery and potentially for patients with early-stage disease and high-risk factors. Toxicity is a point in question; however, the combination of paclitaxel with carboplatin may diminish these concerns. In women with multiple medical comorbidities, single-agent chemotherapy may be better tolerated with acceptable results. Our increased knowledge of the molecular aspects of endometrial cancer biology has paved the way for clinical research to develop novel targeted antineoplastic agents (everolimus, temsirolimus, gefitinib, erlotinib, cetuximab, trastuzumab, bevacizumab, sorafenib) as more effective and less toxic options. Continued investigation into the molecular pathways of endometrial cancer development and progression will increase our knowledge of this disease leading to the discovery of novel, superior agents.

1. Introduction

Endometrial cancer is the most prevalent gynecological cancer in the Western World representing the third commonest cancer affecting women. By contrast, the incidence in the non-Western World is approximately tenfold lower [1]. The excellent prognosis of early-stage endometrial cancer renders it one of the most curable gynecological malignancies. Radiotherapy remains the mainstay of postoperative management, but accumulating data show that adjuvant chemotherapy may display promising results after staging surgery. The term staging surgery implies to hysterectomy, bilateral salpingoophorectomy, and pelvic and para-aortic node dissection with or without omentectomy. Unfortunately, the prognosis of patients with metastatic disease remains disappointing with only one-year survival commonly reported despite treatment efforts [2].

Systemic interventions play a key role in the treatment of advanced/metastatic and relapsed endometrial cancer. Progestins remain an effective option, especially for those patients with low-grade estrogen and/or progesterone receptor positive disease, some of whom achieve prolonged survival [3–14]. Platinum compounds, anthracyclines, and more recently taxanes have been developed in combination regimens, achieving response rates exceeding 50% and resulting in more than one-year survival in randomized trials [2, 15–40]. Today, the combination of doxorubicin 45 mg/m^2, cisplatin 50 mg/m^2, and paclitaxel 160 mg/m^2 (TAP) [29] is considered the most effective chemotherapy regimen for advanced or recurrent endometrial cancer. A large GOG trial which is currently evaluating TAP against paclitaxel and carboplatin may at last provide conclusive data on the comparative efficacy of the less toxic nonanthracycline combination [2]. It is worth mentioning that the GOG

209 trial has closed to accrual, although results are not yet available.

Adjuvant chemotherapy using the same agents is beneficial for patients with advanced disease after staging surgery and potentially for patients with early-stage disease and high-risk factors, such as high-grade or nonendometrioid histology. Their combination with radiotherapy is still under debate. Toxicity is a point in question for endometrial cancer patients treated with chemotherapy, given their often advanced age and multiple comorbidities. Hematologic toxicity, cardiac toxicity, and neurotoxicity probably present more cause for concern, as they can increase the risk of treatment-related death or long-term disabilities. The development of less toxic regimens such as the combination of paclitaxel with carboplatin may diminish these concerns.

Our increased knowledge of the molecular aspects of endometrial cancer biology has paved the way for clinical research to develop novel targeted antineoplastic agents as more effective and less toxic options. This review article aims to present the gathering evidence of current adjuvant systemic treatment of endometrial cancer in an attempt to direct ongoing clinical research.

2. Adjuvant Chemotherapy

Radiotherapy (vaginal brachytherapy and/or pelvic irradiation) remains the mainstay of postoperative management, decreasing the rate of pelvic recurrences. Moreover, it is the preferred sole method of treatment for patients with high-risk and may be intermediate-risk early-stage disease [41–43]. Additionally, it is worth mentioning that trials in early-stage disease have shown decreased locoregional recurrence but no improvement in survival with radiotherapy. The use of adjuvant systemic treatment in endometrial cancer is an individualised decision based on the assessment of prognostic factors which increase the potential for relapse and distant metastasis such as stage, age >70 years, and histological characteristics (grade, serous or clear cell type, lymphovascular space invasion) [42, 44]. The anticipated benefits and risks for toxicity are also taken into the equation. Grade 3 endometrioid tumours, as well as the serous and clear cell variants, display a more aggressive behaviour than grades 1 and 2 endometrioid cancers. These high-risk types are commonly diagnosed as advanced or metastatic disease but early-stage cancers can also result in similarly unfavourable outcomes [45]. Surgical staging procedures also play a significant role, since a recurrence risk for a proportion of patients with ostensible stage I disease and high-risk histology may be underestimated [45, 46].

Although current evidence does not support the use of progestins in the adjuvant treatment of endometrial cancer [47, 48], chemotherapy may prove beneficial in patients with high-risk features. Three randomised trials comparing chemotherapy with radiotherapy for high- and intermediate-risk endometrial cancer have produced somewhat equivocal but important results (Table 1).

Randall et al. reported the results of the GOG protocol 122 which randomized 396 women with stage III and optimally debulked stage IV endometrial cancer to postoperatively receive either whole abdominal irradiation (WAI) or chemotherapy with cisplatin and doxorubicin (Figure 1). This study favoured chemotherapy with a hazard ratio for progression of 0.71 and 0.68 for death, and five-year survival rate of 55% versus 42%, respectively [49]. Another trial included 345 intermediate- and high-risk patients (stage IC grade 3, stage II grade 3 with >50% myometrial invasion, and stage III) who were randomized to receive adjuvant chemotherapy with cisplatin, doxorubicin, and cyclosphosphamide (CAP) or external beam radiotherapy (pelvic and paraortic). Similar results in overall and disease-free survival were reported for both arms. The authors noted that radiotherapy did improve local relapse rates, while chemotherapy improved the risk for distance metastases [50]. The latest published study comparing chemotherapy with radiotherapy randomized 385 patients with >50% myometrial invasion, 61% of whom had stage I disease, to receive either CAP or external beam pelvic radiotherapy. Although the 5-year OS and PFS rates were similar in both arms, a significant improvement of PFS (HR = 0.44) and OS (HR = 0.24) was observed with chemotherapy in a subgroup comprising patients with stage IC and >70 years old, stage IC and grade 3 endometrioid tumors, stage II, and stage IIIA (positive cytology) [51]. Interestingly, no significant increase in adverse effects was observed in the CAP group versus the radiotherapy group.

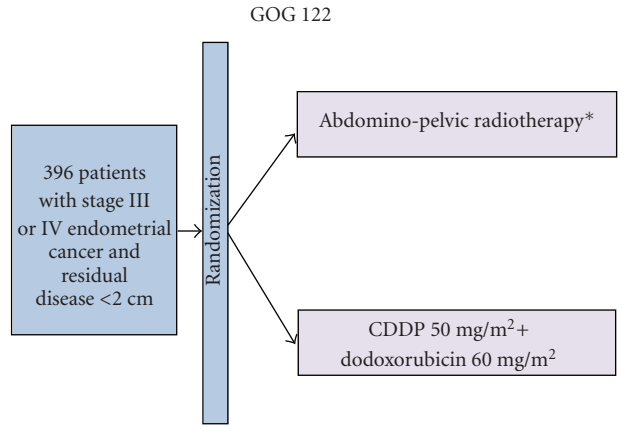

Figure 1: Postoperative whole abdominal radiotherapy versus combination doxorubicin-cisplatin chemotherapy in advanced endometrial carcinoma. *30-Gy in fractions with a 15-Gy boost.

Single modality adjuvant treatment with chemotherapy entails a high risk of local relapse. Indeed, 36% of the initial recurrences were limited to the pelvis in the GOG 122 study [49]. This presents a strong argument for the implementation of combined modality treatments. Nevertheless, salvage external beam radiotherapy in previously nonirradiated patients with locoregional recurrence has resulted in five-year local control rate of 54%, disease specific survival of 51%, and overall survival of 44% [42]. Consequently, radiotherapy could be considered in later stages of management rather than postoperatively with less risk for combined toxicities. In the RTOG 9708 study, 46 patients

Table 1: Trials on adjuvant treatment for endometrial cancer.

Author(s)	Setting (Stage)	Pts (No.)	Treatment arms	5-year PFS[1] (%)	5-year OS[2] (%)	Comments
Randall et al. [49]	III-IV (optimally debulked)	396	WAI[3]	38	42	Treatment related deaths AP: 8 (4%), WAI: 5 (2%)
			AP[4]	50	55	
Maggi et al. [50]	ICG3-III	345	External beam XRT[5]	63	69	
			CAP[6]	63	66	
Susumu et al. [52]	>50% myometrial invasion	385	Pelvic XRT	83.5	85.3	Superiority of CAP in high/intermediate risk (stICG3-IIIA) patients
			CAP	81.8	86.7	
Hogberg et al. [53]	IC-IIIC (confined to pelvis)	367	Relvic XRT +/− BT[7]	75	NR[8]	
			Pelvic RT +/− BT + Cx[9]	82	NR	
Kuoppala et al. [51]	IAG3-IIIA	156	Pelvic XRT	18+ months	84.7	Intestinal complications demanding surgery
			Pelvic XRT + CEP[10]	25+ months	82.1	XRT: 2 (2.7%), Pelvic XRT + CEP: 8 (9.5%)

[1]PFS, progression-free survival; [2]OS, overall survival; [3]WAI, whole abdominal irradiation; [4]AP, doxorubicin and cisplatin; [5]XRT, irradiation; [6]CAP, cyclophosphamide, doxorubicin and cisplatin; [7]BT, vaginal brachytherapy; [8]NR, not reported; [9]Cx, chemotherapy with AP or paclitaxel, epirubicin and carboplatin or paclitaxel and carboplatin; [10]CEP, cyclophosphamide, epirubicin and cisplatin.

with endometrial cancer confined to the pelvis (stage I to IIIC) displaying adverse histological prognostic factors were treated with chemo-radiotherapy followed by chemotherapy with cisplatin and paclitaxel. The 5-year DFS and OS rates for stage III patients were 72% and 77%, respectively, and no relapses in stage I or II patients were recorded. However, a grade 4 long-term toxicity was reported in 4% of patients [54]. The NSGO-EC-9501/EORTC 55991 study randomized 372 patients with high-risk endometrial cancer (grade 3, deep myometrial invasion, DNA nondiploidy, serous, clear-cell, or anaplastic histology) of surgical stages I to IIIC and without paraortic lymph node involvement to receive either external beam irradiation with or without vaginal brachytherapy, or radiotherapy plus platinum-based chemotherapy. The results favoured the combined modality treatment with an HR of 0.58 for PFS [53]. Nevertheless, another recently published study of sequential chemo-radiotherapy (cyclophosphamide, cisplatin, epirubicin) versus radiotherapy alone in 157 patients, with stage IA/B, grade 3 and stages IC to IIIA of any grade, failed to show a statistically significant improvement in survival outcomes. Furthermore, chemotherapy seemed to increase intestinal toxicity requiring surgery [51].

It has become clear that questions surrounding adjuvant chemotherapy in endometrial cancer and its optimal application are far from being settled and hence form an active field of clinical research. The use of newer agents, such as paclitaxel, appears promising. Its combination with carboplatin has shown favourable efficacy and toxicity as adjuvant treatment of endometrial cancer [55] and may prove to be a valid and less toxic option to anthracycline-platinum combinations. GOG protocol 184 (Figure 2) deals with advanced stage patients randomized after surgery with optimal debulking (diameter ≤2 cm) and tumor-directed

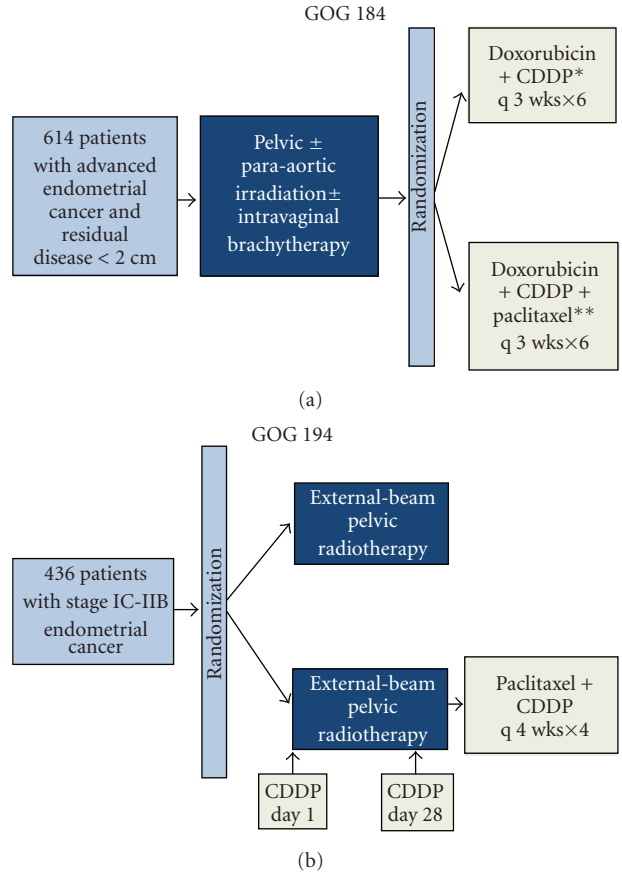

Figure 2: Recent randomized GOG trials of postoperative radiotherapy and/or combination chemotherapy in endometrial cancer. *Both arms received G-CSF. **Paclitaxel was administrated on day 2.

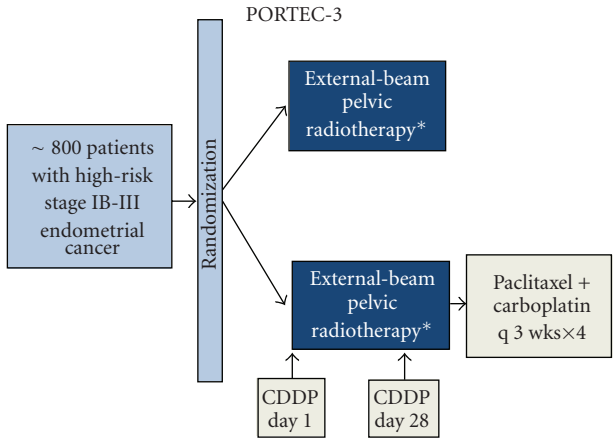

Figure 3: Chemotherapy and radiation therapy compared with radiation therapy alone in treating patients with high-risk stage I, stage II, or stage III endometrial cancer. *Patients with cervical involvement undergo vaginal brachytherapy.

radiation to cisplatin and doxorubicin with or without paclitaxel. There was no statistically significant improvement in recurrence free survival between the two regimens. Overall, the addition of paclitaxel had little impact on recurrence free survival and was associated with increased morbidity. Of note, subset analysis revealed a 50% reduction in the risk of recurrence or death for patients with gross residual disease in the triplet arm when compared to the doublet one [56]. The advantages of identifying early-stage patients who may benefit from adjuvant chemotherapy are the subject of GOG 194 (Figure 2) and PORTEC-3 (Figure 3) trials, evaluating the addition of paclitaxel and either cisplatin or carboplatin to adjuvant radiotherapy. Notably, the aggressive nature of serous and clear cell tumours and a wealth of data from nonrandomized studies [30–41, 54, 57–67] have led many institutions to standardize adjuvant chemotherapy for all early-stage patients with such histology. However, the small volume of patients belonging to these subgroups (2%–4% of stage I endometrial cancer) hampers the design of a phase III study to further clarify the merits of this approach.

3. Toxicity of Systemic Chemotherapy for Endometrial Cancer and Patient Selection

Patients with endometrial cancer often present cause for concern due to toxicity, given that they are often of advanced age, with poor performance status and multiple comorbidities. The significance of age and coexisting medical conditions in clinical decision-making can be extrapolated from the observation that 40% of deaths in patients participating in clinical trials are attributed to conditions other than endometrial cancer [41]. Whilst it is true that more intensive combination regimens achieved greater efficacy in advanced or recurrent endometrial cancer, toxicity was unfortunately increased. Even among selected populations of phase II or III trials, treatment-related deaths are not uncommon despite the use of G-CSF [25–27, 29, 35]. A meta-analysis of pooled toxicity data from five randomized trials [17–19, 29, 68] comparing less intensive with more intensive chemotherapy showed that treatment intensification resulted in higher rates of severe (grades 3 and 4) nausea and vomiting, gastrointestinal toxicity, thrombocytopenia, infection, renal toxicity, and neurotoxicity with odds ratios of 2.73, 2.48, 4.44, 4.36, 3.55, and 5.81, respectively [15].

Toxicity far outweighs any concerns in the adjuvant setting. In the phase III trial comparing WAI with AP chemotherapy for stage III/IV endometrial cancer after staging surgery, 13 treatment-related deaths were reported among 396 randomized patients, most of which involved the chemotherapy arm. Severe hematologic toxicity was documented in 88% of patients on AP as opposed to 14% of those on WAI arm [49]. Furthermore, 17% of patients receiving AP discontinued treatment due to toxicity, compared to only 3% treated with WAI. Maggi et al. [50] reported a rate of 35% for grades 3 and 4 neutropenia in stage IC-III patients receiving adjuvant CAP as opposed to a 16% rate of severe gastrointestinal toxicity in patients treated with radiotherapy [50]. Gastrointestinal toxicity may be more frequently observed in patients receiving both radiotherapy and chemotherapy, as reported by Kuoppala et al. [51], where the addition of the cyclophosphamide, epirubicin, and cisplatin (CEP) regimen to pelvic irradiation increased the rate of gastrointestinal complications requiring surgery from 2.7% to 9.5%.

Since previous pelvic irradiation depletes the hematopoietic stem cell pool and increases the potential for severe hematologic toxicity, such patients have habitually received lower doses of chemotherapy in phase III trials [17, 29, 35]. Albeit G-CSF support may improve the tolerability of doublet and triplet regimens, grade 4 neutropenia remains notably frequent at over 35% [29, 35].

Elderly patients with predisposing factors or preexisting cardiac disease about to be treated with anthracycline based chemotherapy are a source of concern for cardiotoxicity. Patients enrolled in studies are routinely screened for left ventricular function defects and those with preexisting dysfunction or active coronary heart disease are typically excluded [17–19, 23, 29]. Finally, patients with longstanding diabetes mellitus may be more prone to neurotoxicity, a debilitating condition commonly associated with combinations including cisplatin and/or paclitaxel [20–22, 26].

The use of prophylactic G-CSF, as well as the use of single-agent chemotherapy or less toxic regimens, such as the combination of carboplatin with paclitaxel or carboplatin with liposomal doxorubicin, is reasonable options to be considered for improved tolerability.

Overall, research data should be interpreted with caution. Populations treated in studies are very likely to differ from the average population encountered in common clinical practice; quality of life factors must be considered in the individualization of management decisions.

4. Targeted Therapy for Endometrial Cancer

4.1. Genetic Alterations in Endometrial Cancer. Nowadays, we have a better understanding of molecular characteristics of endometrial cancer which seem to concur with previously established clinical and histological disease types (Table 2) [69–79]. The importance of angiogenesis has been recognised in regard to the natural history of endometrial cancer and presents potential clinical and therapeutic implications. Tumor suppressor protein PTEN (phosphatase and tensin homolog deleted on chromosome ten), a lipid-protein phosphatase key to the regulation of normal cell function, has been reported to be altered in up to 83% of endometrioid carcinomas [76, 80, 81]. PTEN inactivation is most commonly caused by mutations in both alleles resulting in the complete loss of function (reviewed in [76, 80]). It principally targets and dephosphorylates 3, 4, 5-trisphosphoinositides resulting in the inhibition of the phosphatidylinositol-3 kinase (PI3K) pathway [82]. Total lack or impairment of PTEN protein from cancer cells causes hyperactivation of the PI3K pathway, leading to uncontrolled function of several kinases, including the serine/threonine kinase mTOR (mammalian target of rapamycin) (reviewed in [80]). PI3KCA mutation is seen in 36% of endometrioid endometrial cancers and is most common in tumors that also bear the PTEN mutation [83]. Additionally, the upregulation of proapoptotic mechanisms involving AKT-dependent mechanisms is mediated through PTEN, as is the downregulation of antiapoptotic mechanisms through Bcl-2 [84]. Since the protein phosphatase activity of PTEN is involved in the inhibition of focal adhesion formation, cell spread, and migration, as well as the inhibition of growth factor-stimulated MAPK signaling, a failed or altered PTEN expression can result in aberrant cell growth and apoptotic escape (reviewed in [76]).

Microsatellite instability (MSI) [85], specific mutations of K-ras [86], and β-catenin genes [87] are other genetic alterations in endometrioid endometrial cancer. Microsatellites are short segments of repetitive DNA bases scattered throughout the genome predominantly found in noncoding DNA. MSI, reported in 20% of sporadic endometrioid endometrial cancers, is caused by inactivation of any number of intranuclear proteins comprising the mismatch repair system, leading to an accumulation of structural changes in coding and noncoding repetitive elements of many genes [85]. Higher rates of mutations in the PTEN gene have been described in tumors displaying MSI as opposed to those that do not, suggesting that PTEN could be a target for mutations in a deficient DNA repair setting [88].

β-catenin, a component of the E-cadherin unit of proteins, plays an important role to cell differentiation, maintenance of normal tissue architecture, and to signal transduction. It also acts as a downstream transcriptional activator in the Wnt signal transduction pathway. These mutations result in stabilization of protein that resists degradation through the ubiquitin-proteasome pathway, leading to cytoplasmic and nuclear accumulation and constitutive target gene activity (reviewed in [76, 89, 90]).

Mutations in p53 are present in about 90% of tumors and constitute the most common genetic alterations in type 2 serous carcinomas [86]. After DNA damage, nuclear p53 accumulates and causes cell cycle arrest by inhibiting cyclin-D1 phosphorylation of the Rb gene, thereby promoting apoptosis [89]. Mutated p53 results in a nonfunctional protein that accumulates in the cell and acts as a double negative inhibitor of the wild-type p53, leading to propagation of aberrant cells. It has been suggested that mutation in one allele occurs during early development of serous carcinoma, and loss of the second normal allele occurs late in the progression to carcinoma. Other frequent genetic alterations in type 2 endometrial cancers include inactivation of p16 and overexpression of HER-2/neu [89]. Inactivation of p16 tumor suppressor gene, that encodes for a cell cycle regulatory protein, leads to uncontrolled cell growth and has been identified in 45% of serous carcinomas and some clear cell cancers (reviewed in [76]). HER-2/neu is an oncogene that codes for a transmembrane receptor tyrosine kinase involved in cell signaling. HER-2 overexpression and gene amplification have been found in 45% and 70% of serous carcinomas, respectively [91].

4.2. Molecularly Targeted Therapy

4.2.1. mTOR Inhibitors. The activation of the PI3K/AKT/mTOR signalling pathway triggered by the loss of function of PTEN gene suggests a therapeutic role for the mammalian target of rapamycin (mTOR) inhibition. Chemotherapy-naïve endometrial cancer patients treated with temsirolimus, an mTOR inhibitor, achieved a preliminary response rate of 26% according to the National Cancer Institute of Canada; this result was not correlated to PTEN status as evaluated by immunohistochemistry [92]. Preliminary studies of other mTOR inhibitors, everolimus and AP2357, have shown clinical responses mainly in the form of stable disease (8 of 15 and 7 of 19 women, resp.) [93–95]. A phase II trial of temsirolimus in heavily pretreated patients with endometrial cancer, recently completed by the NCIC, reported a 7% partial response rate and a 44% stable disease rate [96]. It should be noted that the trials of everolimus and AP2357 were both in pretreated patients. Combinations of mTOR inhibitors with hormonal therapy, chemotherapy, or other targeted therapies such as epidermal growth factor receptor (EGFR) inhibitors and antiangiogenic agents have shown such promise, in the preclinical setting, that numerous trials are currently underway to develop and test such combinations; temsirolimus is being tested with topotecan, bevacizumab and progestin therapy (reviewed in [80]). It has been shown that exposure of endometrial cancer cell lines to an mTOR inhibitor increases progesterone mRNA expression and inhibits ER mRNA expression (reviewed in [80], [97]).

4.2.2. Human Epidermal Growth Factor Receptor (EGFR) or HER Family Inhibition

EGFR Inhibitors. EGFR is commonly expressed in normal endometrium, but its overexpression in endometrial cancer

Table 2: Types of endometrial cancer according to the Bokhman model and correlations with clinicopathological and molecular characteristics.

Characteristics	Type I tumors	Type II tumors
Clinicopathological		
Incidence	~80%	~20%
Age at initial diagnosis	Pre/peri-menopausal	Postmenopausal
Histology	Endometrioid	Non-endometrioid (predominantly serous and clear cell)
Grade	Usually low	Usually high
Premalignant phase	Atypical hyperplasia	Glandular dysplasia (for serous tumours)
Predisposing factors	Obesity, prolonged estrogen exposure	
ER, PgR	>90%	0–31%
Molecular		
HER-2/neu (overexpression)	3%	18%
EGFR expression	46%	34%
P53 mutations	5–10%	80–90%
Ploidy	67% diploid	45% diploid
PTEN (loss of function through deletion or mutation)	50–80%	10–11%
P16 inactivation	10%	40%
K-ras (mutational activation)	13–26%	0–10%
E-cadherin (reduced or non expression)	10–20%	62–87%
β-catenin CTNNB1 (gain of function mutation)	25–38%	Rare

is associated with advanced stage and poor prognosis [98–103]. Antagonists to EGFR include small molecule tyrosine kinase inhibitors (gefitinib, erlotinib, and lapatinib) and the anti-EGFR monoclonal antibody cetuximab. The use of erlotinib in women with recurrent and metastatic endometrial cancer was not promising with only 1 partial response among 27 women [104]. A phase II clinical trial of cetuximab in recurrent endometrial cancer is still ongoing. It is hoped that other new therapies will succeed in targeting specific known molecular defects in endometrial cancer, making significant headway in the prognosis of women with metastatic disease. Meanwhile, there is a need for an expedient second-line treatment, and clinical trials should be encouraged.

Trastuzumab. HER-2 amplification or overexpression has been demonstrated and linked to prognosis in endometrial cancer as well as in many other cancer types [105, 106]. HER-2/neu overexpression and gene amplification were found in about 20%–30% of serous carcinomas [91]. It is worth mentioning that in most series overexpression is more common than amplification. Trastuzumab is a monoclonal antibody to the extracellular domain of the HER-2 protein. Although HER-2 overexpression observed in serous carcinoma of the uterus provides a strong biologic rationale for the use of trastuzumab in the treatment of this malignancy, a GOG study examining the use of trastuzumab in women with HER-2 positive endometrial cancer did not report any activity [107].

4.2.3. Angiogenesis Inhibition. It has been recognised that VEGF is key to tumour angiogenesis and progression representing the cornerstone of successful antineoplastic treatments. Increased levels of VEGF in endometrial cancer have been correlated with poor outcome. Preclinical models demonstrate the effectiveness of bevacizumab in combination with chemotherapy against endometrial cancer cell lines [108, 109]. Bevacizumab, a recombinant humanized immunoglobulin monoclonal antibody to vascular endothelial growth factor (VEGF), has proved to be effective and well tolerated in a number of malignancies. A small, retrospective study reviewed 10 patients with recurrent uterine neoplasms treated with bevacizumab. Two patients responded to treatment and the disease was stabilized in three patients [110]. A GOG phase II trial of single-agent bevacizumab in metastatic endometrial cancer has recently been completed, the results of which should soon be announced (GOG 229-E). VEGF-Trap is a recombinantly produced fusion protein consisting of human VEGF receptor extracellular domains fused to the Fc portion of a human immunoglobulin γ (IgG). It functions as a decoy receptor preventing the VEGF ligand from interacting with its ligand. A GOG phase II trial of VEGF trap in metastatic endometrial cancer is still in progress (GOG 229-F) (reviewed in [80]). A phase II trial of sorafenib, a tyrosine kinase inhibitor with antiangiogenic activity, has been completed in the National Cancer Institute's phase II network (reviewed in [80]). Preliminary results were not encouraging. A phase II trial of a second antiangiogenic tyrosine kinase inhibitor, sunitinib, is underway [111].

4.2.4. Fibroblast Growth Factor Receptor 2 Inhibition. Fibroblast growth factor receptor 2 (FGFR2) is regulated on the basis of the balance of FGFs, heparan-sulfate proteoglycans, FGFR2 isoforms, endogenous inhibitors, and microRNAs [112]. The recent identification of activating mutations in FGFR2 in endometrial tumors has generated a new avenue for the development of targeted therapeutic agents [113, 114]. The majority of the mutations identified are identical to germline mutations in FGFR2 and FGFR3 that cause craniosynostosis and hypochondroplasia syndromes and result in both ligand-independent and ligand-dependent receptor activation [115]. Mutations that predominantly occur in the endometrioid subtype of endometrial cancer (16%) are mutually exclusive with KRAS mutation but occur in the presence of PTEN abrogation [116, 117]. In vitro studies have shown that endometrial cancer cell lines with activating FGFR2 mutations are selectively sensitive to a pan-FGFR inhibitor, PD173074 [113]. Oral administration of AZD2171 or Ki23057 inhibits in vivo proliferation of cancer cells with aberrant FGFR2 activation in rodent therapeutic models [112]. Several agents with activity against FGFRs are currently in clinical trials. Among PD173074, SU5402, and AZD2171 functioning as FGFR inhibitors, AZD2171 is the most promising anticancer drug [114]. Investigation of these agents in endometrial cancer patients with activating FGFR2 mutations is warranted [113].

5. Claudines

Epithelial receptors for clostridium perfringens enterotoxin (CPE), also known as claudines, may well prove to be the next target therapy for endometrial cancer, especially against aggressive disease variants. It has been shown that papillary-serous neoplasms overexpress claudines-1,-3 and -4 [118–120], while clear-cell ones overexpress claudines -3, and -4 [119]. Overexpression of claudines-3 and -4 could in part explain the aggressive behaviour of these histologies [119, 121] suggesting their potential as useful biomarkers or targets for type specific treatment.

6. Conclusion

Endometrial cancer is the most common gynaecological cancer in western countries. Although radiotherapy remains the cornerstone of postoperative management, accumulating data show that adjuvant chemotherapy may display promising results after staging surgery. Unfortunately, the prognosis of patients with metastatic disease remains disappointing with only-one year survival commonly reported despite treatment efforts. Progestins remain an effective option, especially for those patients with low-grade estrogen and/or progesterone receptor positive disease. Chemotherapy comprising paclitaxel, doxorubicin, and cisplatin is beneficial for patients with advanced or metastatic disease after radical surgery and potentially for patients with early-stage disease and high-risk factors. Toxicity is a concern, in which the development of less toxic regimens such as the combination of paclitaxel with carboplatin may diminish. In women with multiple medical comorbidities, single-agent chemotherapy may be better tolerated and still yield acceptable results. A better understanding of the molecular aspects of endometrial cancer biology has allowed clinical research to develop effective and targeted antineoplastic agents (everolimus, temsirolimus, gefitinib, erlotinib, cetuximab, trastuzumab, bevacizumab, sorafenib). Although targeted therapy is in general less toxic than chemotherapy, its use may be accompanied in some instances by considerable toxicity. Continued investigation into the molecular pathways of endometrial cancer development and progression will enhance existing knowledge of this disease process promoting the discovery of novel, superior treatment options for patients.

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