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A new perspective on Endometrial Carcinoma classification and management strategies in context of molecular subtypes

Pohľad na klasifikáciu a manažment endometriálneho karcinómu v kontexte molekulárnych subtypov

Z. Ballová, P. Gašparová, M. Sitáš, E. Dosedla

Department of Gynaecology and Obstetrics, Faculty of Medicine, University P. J. Safarik in Košice, Hospital AGEL Košice-Šaca Inc., Slovak Republic

Summary: Endometrial cancer is the most common gynecological cancer and the second most prevalent female malignancy in the developed world. It is typically diagnosed in postmenopausal women, presenting with the characteristic clinical symptom of uterine abnormal bleeding. In the past, only two histological types were considered. However, it has become increasingly evident that endometrial cancer is a clinically heterogeneous disease, and this heterogeneity is closely associated with the diversity of underlying molecular alterations. The Cancer Genome Atlas classification has significantly advanced the diagnosis, risk stratification, and management of endometrial cancer by categorizing it into four molecular subgroups, each characterized by distinct mutational burdens and copy number alterations.

Key words: endometrial cancer – molecular classification – POLE mutation – The Cancer Genome Atlas Research Network – hysterectomy – targeted therapy – mismatch-repair – p53

Súhrn: Karcinóm endometria je najčastejším gynekologickým karcinómom a druhým najčastejším ženským zhubným nádorom v rozvinutom svete. Zvyčajne sa diagnostikovaný u žien po menopauze s typickým klinickým obrazom abnormálneho krvácania z maternice. V minulosti sa na základe histologického hodnotenia zvažovali iba dva typy. Endometriálny karcinóm je však klinicky heterogénne ochorenie a je čoraz jasnejšie, že táto heterogenita môže byť hybnou silou pri určení rôznorodosti na základe molekulárnych zmien. The Cancer Genome Atlas klasifikačný systémy zlepšil diagnostiku, stratifikáciu rizika a manažment endometriálneho karcinómu popisom štyroch molekulárnych podskupín s rôznou mutačnou záťažou a zmenami v počte kópií.

Kľúčové slová: endometriálny karcinóm – molekulárna klasifikácia – POLE mutácia – The Cancer Genome Atlas Research Network – hysterektómia – cielená terapia – mismatch-repair – p53

Introduction

Endometrial cancer (EC) is a malignancy that originates in the epithelial lining of the uterus [1]. It stands as the most prevalent gynecological cancer and ranks as the second most common malignancy affecting women in the developed world. Notably, EC incidence has shown a rapid and consistent increase worldwide in recent years [2], with disparities in its prevalence influenced by geographic, socioeconomic, and racial factors [1]. As projections anticipate a continued rise in EC incidence [2], the associated burden of this disease is poised to surge. This burden encompasses not only the sheer number of patients diagnosed annually, but it also encompasses their age, risk profiles, and concurrent medical conditions, all of which warrant significant attention in the pursuit of optimal prevention and therapeutic strategies [3].

Historically, EC was classified into two types primarily based on its association with estrogen stimulation [1,4]. However, this traditional classification now falls short in providing a comprehensive understanding of this complex disease. Recent molecular discoveries and novel histopathological parameters have ushered in a fresh perspective on risk stratification. The Cancer Genome Atlas Research Network (TCGA),

Tab. 1. Features of the four molecular subtypes. Adapted and modified from Alexa et al. [22].
Tab. 1. Vlastnosti štyroch molekulárnych podtypov. Upravené podľa Alexa et al. [22].

Subtype	POLE mut	MMRd/MIS	p53 wt/NSMP	p53abn
Top five recurrent gene mutations (%)	POLE (100%)	PTEN (84%)	PTEN (77%)	TP53 (92%)
	DMD (100%)	PIK3CA (54%)	PIK3CA (53%)	PIK3CA (47%)
	SMD1 (100%)	PIK3R1 (42%)	CTNNB1 (52%)	FBXW7 (22%)
	FAT4 (100%)	RPL22 (37%)	ARID1A (42%)	PPP2R1A (22%)
	PTEN (100%)	ARID1A (37%)	PIK3R1 (33%)	PTEN (10%)
Associated histological feature	endometroid	endometroid	endometrioid	serous
	grade 3	grade 3	grade 1–2	grade 3
	ambigious morphology	LVSI substantial MELF type invasion	squamous differentiation	destructive invasion
	broad front invasion		ER/PR expression	slit-like spaces
	tumorinfiltrating/peritumoral Ly	tumorinfiltrating Ly		high cytonuclear atypia
	giant tumoral cells	lower uterine segment involment		giant tumoral cells
Associated clinical feature	lower BMI	higher BMI	higher BMI	lower BMI
	early stage (IA/IB)	Lynch syndrome		advanced stage
	early onset			late onset
Prognosis in early stage	excellent	intermediate	excellent/intermediate/ poor	poor
Diagnostic test	sanger	MSI assay		p53-IHC
	NGS	MMR-IHC		NGS
	tumor mutation burden	tumor mutation burden		somatic copy-number aberrations

BMI – body mass index, IHC – immunohistochemistry, LVSI – lymphovascular space invasion, Ly – lymphocytes, MMR – mismatch repair, MSI – microsatellite instability, NGS – next generation sequencing

through its comprehensive analysis of tumors, has shed new light on the management of endometrial cancer [5]. The identification of four distinct molecular subgroups holds significant prognostic value and offers a promising tool for guiding clinical decisions, particularly in the realm of adjuvant treatment [6].

In this review article, we aim to present an in-depth exploration of the evolving landscape of endometrial cancer classification and the therapeutic strategies, all within the context of these emerging molecular subtypes.

Endometrial cancer's general characteristics

Endometrial cancer, also referred to as corpus uterine cancer, is a malignancy that originates in the inner lining of the uterine body [1,7]. It is characterized by the invasive and abnormal proliferation of the endometrial lining of the uterus [8]. EC holds a significant position in women's health due to its associated mortality [7]. According to the GLOBOCAN database, in 2020, there were nearly half a million new cases detected and one hundred thousand deaths attributed to EC worldwide [9]. The 5-year survival rate in 2018 was estimated at 84% in the US Surveillance, Epidemiology, and End Results (SEER) database [4]. Data from the EUROCARE-5 study suggests a 5-year relative survival rate of approximately 76–80% for European women [10].

Endometrial cancer predominantly affects postmenopausal women, with the majority of cases occurring between the ages of 65 and 75. However, it's estimated that up to 14–25% of cases are diagnosed before menopause [1,9,11]. The American Cancer Society recommends that all women over the age of 65 be informed of the risks [12]. Nearly three-quarters of patients present with early-stage disease, with postmenopausal bleeding being the dominant symptom [13].

Risk factors for EC include non-genetic factors such as increased age, lower parity, tamoxifen use, metabolic syndrome, family history, and notably, genetic predisposition [1,2]. Over 50% of cases are associated with a higher body mass index (BMI), including obesity, while lower risk is linked to normal BMI, higher parity, and oral contraception use [1]. The primary risk factors for EC development remain tied to excessive, unopposed exposure of the endometrium to estrogen [12]. Over 90% of EC cases are sporadic, with 5–10% being hereditary, typically as part of the

hereditary non-polyposis colorectal cancer syndrome or Lynch syndrome [13]. Endometrial biopsy offers high sensitivity (90–100%) and specificity (98–100%) for detecting endometrial cancer and should be performed in primary care whenever possible [14].

Traditional classification system

Endometrial carcinomas are classified according to the World Health Organization (WHO) classification system. They are divided into several subgroups, including endometrioid (70%), serous, clear cell, mixed cell adenocarcinoma, and other relatively rare types such as mucinous adenocarcinoma, neuroendocrine tumors, dedifferentiated carcinoma, and undifferentiated carcinoma [11]. This classification has been in use since 1983, proposed by Bokhman, and is based on histological characteristics [11,13]. It relies on tumor morphology and grade, determined by glandular architecture and nuclear grade. Type I comprises of low-grade cells, is more common, has a favorable prognosis, and is estrogen-dependent, often consisting of grade I or grade II endometrioid adenocarcinomas histopathologically. Type II comprises of high-grade cells, is less common, and carries an unfavorable prognosis, including grade III endometrioid adenocarcinomas, and serous, clear cell, and undifferentiated carcinosarcomas [4,9].

Advanced molecular classification system

The WHO classification, while useful in determining surgical and adjuvant therapy, has limitations due to a lack of reproducibility and significant inter-observer variability [11,13]. Over the past decade, it has become evident that endometrial cancers are a diverse group of tumors, not only in terms of biology, histology, and clinical features, but also in terms of their genetic makeup [15]. Therefore, a more specific classification system was needed. Genomic analysis in 2013 and subsequent studies employing immunohistochemistry have led to the current molecular classification of EC. Initially, TCGA divided serous and endometrioid EC into four molecular subgroups based on mutational burden and copy number alterations. This approach resulted in molecular stratification of EC into four distinct molecular groups: MMR-deficient (MMR-d), p53 mutation (p53mut)-type, POLE mutation (POLEmut)-type, and cases with no specific molecular profile (NSMP) [9,16]. Next-generation sequencing (NGS) has become a standard procedure for cancer genomic analysis [13].

POLE ultramutated (POLE mut)

This subtype is characterized by ultramutation caused by POLE mutations [15]. These mutations typically occur in the exonuclease domain of the POLE gene, which encodes DNA polymerase epsilon involved in DNA replication and repair [6,17]. POLE encodes the catalytic subunit of DNA polymerase, responsible for leading strand DNA replication [18]. It recognizes and removes mispaired nucleotides through its exonuclease activity, ensuring high fidelity DNA replication [19,20]. ECs harboring POLE exonuclease domain mutations make up 5–15% of all EC cases and often affect young women with low BMI [21]. These tumors typically present at earlier stages and exhibit a high survival rate, around 96% at 5 years, despite their aggressive histological appearance (high-grade endometrioid histotype with intense tumor-infiltrating lymphocytes) [21]. The potential relationship between POLE mutations and the prognosis of endometrial cancer patients remains unclear [17].

p53 mutation (p53 mut/abn)

The tumor suppressor gene *TP53*, which encodes the p53 protein, is one of the most common mutations in human tumors. The p53 subgroup accounts for 8–24% of EC cases. This subgroup was initially defined by a high number of somatic copy-number alterations and a low mutational yield [22]. The p53 category is associated with older age and lower BMI, as well as more advanced stage and poorer prognosis, contributing to 50–70% of EC mortality [6]. p53-mutant ECs are typically high-grade and morphologically ambiguous [23]. Histologically, the proportion of p53 abnormalities is high in serous EC (93%), carcinosarcoma (85%), clear cell EC (38%), and grade 3 endometrioid EC (22%). Recent studies have consistently demonstrated a poor prognosis associated with p53 mutations in EC [22,23].

Mismatch repair deficient (MMRd)

Defective DNA mismatch repair (dMMR) leads to elevated tumor mutational burden (TMB) and microsatellite instability (MSI) in multiple cancer types [24]. The MMR-deficient molecular group represents 20–30% of EC cases [6,22]. Analysis of EC from the TCGA series revealed significant variation in proportions of tumor-infiltrating lymphocytes, CD8+, CD4+, NK cells, and immune checkpoint expression in MMR-deficient ECs [24]. MMR-deficient ECs show an intermediate prognosis and may benefit from immunotherapy [23]. Studies have evaluated the efficacy of immunotherapy, with pembrolizumab and avelumab being preferred due to their favorable toxicity profiles [25–27]. NCCN guidelines recommend pembrolizumab and nivolumab for treating patients with advanced or recurrent microsatellite instability-high/mismatch repair-deficient EC [28]. It is important to realize that mismatch repair-deficient cancers have varied responses to an immune-check-point blockade [29].

The "non-specific molecular profile" (NSMP)

The category of EC that did not exhibit any of the previously described features was classified as "p53 wt" or "no specific molecular profile" (NSMP) [22]. The

NSMP group is the most common in the TCGA dataset [23], accounting for approximately 40–50% of EC cases. This group primarily includes endometrioid ECs with estrogen and progesterone receptor positivity, and these tumors often exhibit high response rates to hormonal therapy [6]. Patients with "p53 wt" tumors tend to have a higher BMI [22]. The prognosis for this group is highly variable and influenced by clinicopathological and molecular factors, many of which are still under evaluation [23].

Discussion

Endometrial cancer ranks among the most prevalent female malignancies. Typically, primary treatment involves a combination of surgical procedures, vaginal brachytherapy, external beam radiation therapy, and adjuvant chemotherapy [22]. The surgical approach typically includes a hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymph node dissection/biopsy, often extended to para-aortic lymph nodes [30,31]. Surgery may be the sole treatment option for early-stage, low-grade tumors, while advanced stages often necessitate a combination of adjuvant therapies, such as chemotherapy, radiotherapy, chemoradiotherapy, antiangiogenesis agents, immune checkpoint inhibitors, and multi-target agents [31]. Treatment decisions are primarily guided by the tumor stage and pathological findings. Historically, Bokhman's 1983 classification system described two types of EC. The WHO has further categorized EC into four histological types: low-grade endometrioid, high-grade endometrioid, serous, and clear cell EC [22].

Endometrial cancer is a clinically heterogeneous disease, and it is increasingly evident that this heterogeneity arises from the diversity of underlying molecular alterations [32]. Understanding these molecular alterations offers the potential to enhance the current histologic classification system, improve diagnostic testing methods, and personalize treatments by incorporating targeted therapies [11,33].

Multiple studies have demonstrated discrepancies between pathologists in approximately 30% of cases. The Cancer Genome Atlas conducted a genome-wide analysis of 373 cases, encompassing exome sequencing, mRNA expression, protein expression, miRNA expression, and DNA methylation evaluation. This comprehensive analysis identified four distinct groups: Polymerase Epsilon ultra-mutated, microsatellite instability hypermutated, copy-number-low, and copy number high EC [22].

According to the recommendations for managing EC patients by the European Society of Gynecological Oncology (ESGO), the European Society for Radiotherapy and Oncology (ESTRO), and the European Society of Pathology (ESP), this classification holds strong prognostic value, particularly in high-risk endometrial cancer cases where adjuvant therapies are typically recommended. Additionally, the Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE) has been developed as an alternative classification system using immunohistochemical markers [6].

Epigenomics, genomics, transcriptomics, proteomics, and metabolomics have been subjects of extensive research. They provide valuable information on gene and protein expression, as well as the mechanisms involved in their regulation. These approaches offer the potential for a deeper understanding of the events occurring during cancer development, the molecular makeup of the tumor microenvironment, and the identification of new markers and therapeutic targets [6].

Conclusion

In conclusion, the TCGA classification has significantly improved the diagnosis, risk stratification, and management of EC. The utilization of next-generation sequencing techniques, including whole-genome sequencing, enables a comprehensive analysis of genetic material and uncovering critical genomic alterations that play a pivotal role in the understanding and treatment of this disease.

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ORCID authors

Z. Ballová 0000-0002-0605-948X
P. Gašparová 0000-0002-6354-6911
M. Sitáš 0000-0002-7273-1051
E. Dosedla 0000-0001-8319-9008

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Assoc. Prof. Erik Dosedla, MD, PhD, MBA
Department of Gynaecology and Obstetrics
Faculty of Medicine
University P. J. Safarik in Košice
Hospital AGEL Košice-Šaca Inc.
Lúčna 57
040 15 Košice-Šaca
Slovak Republic
erik.dosedla@nke.agel.sk

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drovelis

14,2 mg estetrolu + 3 mg drospirenonu
Režim 24/4[1]

PRVNÍ ANTIKONCEPCE S ESTETROLEM

GEDEON RICHTER

(1) SPC přípravku Drovelis

ZKRÁCENÉ SPC LÉČIVÉHO PŘÍPRAVKU DROVELIS ▼ Tento léčivý přípravek podléhá dalšímu sledování. **Složení:** Aktivní tableta obsahuje drospirenon 3 mg a estetrol 14,2 mg. Placebo tablety neobsahují léčivou látku. **Indikace:** Perorální antikoncepce. **Dávkování:** Užívá se jedna tableta denně po dobu 28 po sobě následujících dní. Každé následující balení se začíná užívat hned následující den po užití poslední tablety z předchozího balení. **Kontraindikace:** Protože nejsou dosud k dispozici žádné epidemiologické údaje o CHC s obsahem estetrolu, kontraindikace CHC s obsahem ethinylestradiolu jsou považovány za platné i pro použití přípravku Drovelis: Přítomnost rizikových faktorů pro žilní nebo arteriální tromboembolismus. Závažná jaterní onemocnění včetně tumorů. Těžká renální insuficience. Nádory ovlivnitelné pohlavními steroidy. Vaginální krvácení s nejasnou příčinou. Hypersenzitivita na složky přípravku. **Upozornění:** Užívání jakékoli CHC zvyšuje riziko VTE ve srovnání s jejím neužíváním. Nejvyšší riziko je v prvním roce užívání. V souvislosti s užíváním CHC bylo zaznamenáno zhoršení endogenní deprese, epilepsie, Crohnovy choroby a ulcerózní kolitidy. Diabetičky užívající CHC musí být pečlivě sledovány. **Interakce:** CHC může interagovat s induktory jaterních enzymů, což může vést až k selhání CHC. Souběžné podávání silných inhibitorů CYP3A4 může zvýšit koncentrace estrogenu nebo progestinu v plazmě. **Těhotenství a kojení:** Přípravek Drovelis není indikován během těhotenství. CHC se během kojení obecně nedoporučuje. **Nežádoucí účinky:** Mezi nejčastěji hlášené nežádoucí účinky patří metroragie (4,3 %), bolest hlavy (3,2 %), akné (3,2 %), vaginální krvácení (2,7 %) a dysmenorea (2,4 %). Mezi další časté NÚ patří: Poruchy nálady a libida, Abdominální bolest, Nauzea, Bolest prsů, Kolísání tělesné hmotnosti. **Velikosti balení:** 84 (3×28). **Držitel rozhodnutí o registraci:** Gedeon Richter Plc., Gyömrői út 19-21, 1103 Budapešť, Maďarsko. **Registrační čísla:** EU/1/21/1547/001-004. **Datum schválení:** 19.5.2021. Výdej přípravku je vázán na lékařský předpis. Přípravek není hrazen z veřejného zdravotního pojištění.

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