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Novel molecular classification of endometrial cancer – current and future clinical implications

Nova molekulska klasifikacija karcinoma endometrijuma – sadašnje i buduće kliničke implikacije

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Introduction

Endometrial cancer (EC) is the fourth most common female cancer in Serbia, with a peak incidence between 60 and 70 years of age. It is the most common gynecological disease in our country [1–3]. Conditions that drive excess estrogen production, such as obesity, metabolic syndrome, and estrogen therapy without progesterone, are thought to be the main causes of this disease [4–6]. Selective estrogen receptor modulators, drugs used for managing infertility, breast cancer, ovulatory dysfunction, and postmenopausal osteoporosis, multiply the risk of EC [7, 8]. Other conditions that lead to an increase in relative risk of EC are polycystic ovary syndrome, nulliparity, late menopause, Lynch syndrome, Cowden syndrome, and others [9, 10].

Surgery is the cornerstone for the initial management of EC. Most commonly, minimally invasive removal of the uterus, ovaries, and fallopian tubes, along with occasional sentinel lymph node mapping, provide the basis for adequate staging [11].

The major challenge for clinicians who care for patients with EC is distinguishing between those who can be treated with surgery alone and those in need of adjuvant therapy.

Current tools for risk stratification are insufficient in differentiating patients who are at risk for recurrent or metastatic disease. That is due to a subjective and, therefore, inconsistent histological categorization [12–15].

Data from The Cancer Genome Atlas (TCGA) has helped us gain a better understanding of EC. It is a diverse set of diseases, with genomic differences driving different treatment outcomes. New patient subsets have been defined, and new questions have emerged. The main question is which patients benefit the most from adjuvant treatment [16, 17]?

Classification of EC – histological approach

EC may come in the form of multiple neoplasms with very different characteristics and clinical outcomes. Histopathological (HP) evaluation, along with grading and subtyping, has traditionally been the cornerstone of EC classification. Over 25 different tumors have been described – ranging from epithelial hyperplasia to mesenchymal neuroectodermal tumors [18].

The other vital histological characteristic is grade. ECs are graded using the Federation of Gynecology and Obstetrics (FIGO) classification system on a scale from 1 to 3, according to the relative proportions of the glandular and solid-tumor components [19].

Tumor grade has a massive impact on prognosis. Grade 1 and 2 tumors are considered low grade and are associated with a better prognosis compared to grade 3 tumors, which are considered high grade.

In 1983, Bokhman [20] defined two types of EC based on clinical and histological characteristics. Type 1 tumors are mostly estrogen-dependent, commonly endometrioid, and have a more favorable prognosis. On the other hand, type 2 tumors are more diverse and more aggressive, leading to a less favorable prognosis. This classification system was a big step in the quest for a better understanding of EC.

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As mentioned, the major challenge is identifying subsets of patients in need of adjuvant therapy. For patients with an advanced stage of EC, there is no dilemma – all such patients will benefit considerably from adjuvant therapy. However, for stage I of the disease, identifying where patients lie on the spectrum of risk for recurrent disease – low, intermediate, or high – is still a great challenge. This challenge has led to the development of multiple risk stratification systems [20–24] based on data from landmark clinical trials such as PORTEC-2 [24] and PORTEC-3 [25]. Sadly, none can reliably predict disease recurrence or lymph node involvement [12, 26]. The reason for these limitations is unclear, but presumably, it is due to the limitations of HP and clinical data. Interobserver variability is high even among expert pathologists. EC grade assignment is subject to significant variation. One-third of cases with high-grade EC lacks a diagnostic consensus on the exact histologic type [27–30]. This data indicates that a more precise risk stratification model is needed.

Molecular classification of EC

An enormous change in the way we see EC subgroups has been introduced by TCGA [16].

The use of genomics, transcriptomics, and proteomics identified four molecular subgroups and several (we show four) predictive biomarkers based on genetic characteristics.

Ultramutated/DNA polymerase epsilon (POLE) mutated group

Pathogenic variants of the DNA polymerase epsilon, catalytic subunit *(POLE)* gene comprise approximately 10% of all endometrioid EC. *POLE* encodes a catalytic subunit of DNA polymerase epsilon, which is responsible for maintaining fidelity during DNA replication [31]. Mutations in these proofreading domains cause increased replication errors and result in an ultramutated phenotype. These tumors have an exceptionally high frequency of somatic mutations and a high occurrence of tumor-infiltrating lymphocytes (TILs). Typical features of this group include a presentation at a relatively young age and early stage, high tumor grade with scattered tumor, and rich in TILs and/or peritumoral (Crohn's-like) lymphocytes. As shown in Figure 1 [32], this group has very favorable outcomes (> 96% five-year survival) despite common aggressive pathologic features – for instance, high-grade or present lymphovascular space invasion [33, 34]. With the pronounced presence of TILs in this group, immunotherapy (IT) with immune checkpoint inhibitors (CIs) such as nivolumab may be an option for these patients [35, 36].

Hypermutated/microsatellite instability (MSI) group

About a third of all ECs belong to this group, characterized by a dysfunction in the DNA mismatch repair (MMR) system involved in an MMR of DNA postreplication. These tumors are most commonly endometrioid ECs, along with some non-endometrioid subtypes such as clear cell ECs [37, 38]. These ECs are also characterized by the presence of TILs, which makes them good targets for CIs. Pembrolizumab was approved by the United States Food and Drug Administration (FDA) in 2017 for a subset of these patients with progressive disease. Notably, this is the first FDA tissue/site agnostic drug approval [39]. Multiple clinical trials are ongoing in this patient population, targeting PI3K/AKT/mTOR pathways. Drugs like temsirolimus have failed to produce a robust benefit, but these pathway mutations continue to be targets of ongoing clinical trials [40, 41].

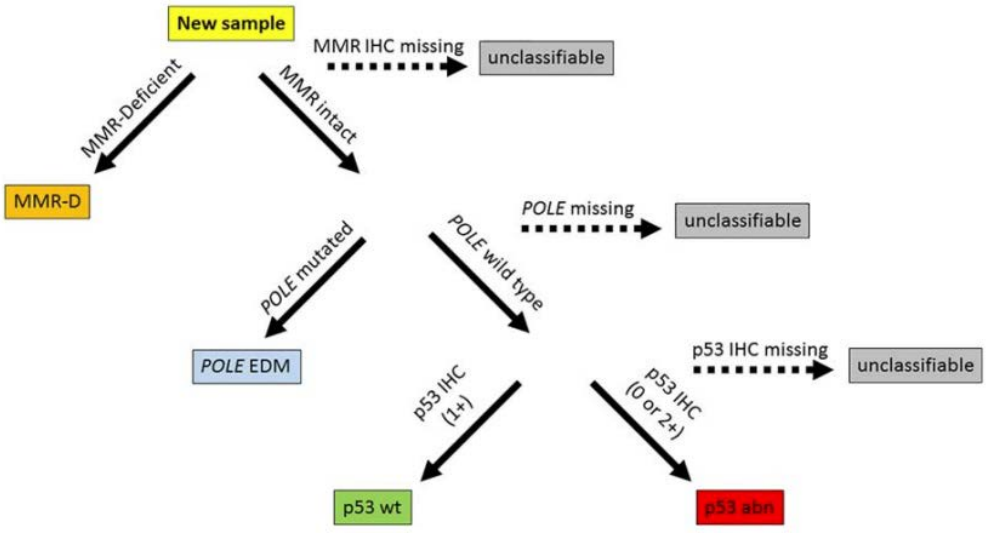

Fig. 1 – Steps in molecular classification with Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE).
MMR – mismatch repair; MMRd – MMR-deficient; IHC – immunohistochemical; *POLE* – DNA polymerase epsilon; *POLE* EDM – *POLE* exonuclease domain mutations; p53wt – p53-wild type; p53abn – p53-abnormal. Figure taken from Talhouk et al. [32].

Copy number low group/microsatellite stable group

A third group encompasses most of the low-grade (grade 1 and 2) ECs in the TCGA analysis. This group is characterized as genomically stable tumors with moderate mutational load ECs that are also not MMR deficient [16]. These are mostly endometrioid ECs, with good response rates to hormonal therapy due to the high presence of estrogen receptors and progesterone receptors.

Copy number high/serous-like group

This group includes mostly serous endometrial tumors and around a quarter of high-grade endometrioid tumors. These feature prominent somatic copy number alterations and often have *TP53* mutations (92% of cases) – similar to high-grade ovarian and basal-like breast carcinomas. Other amplified oncogenes are *MYC*, *ERBB2* (*HER2*), and *CCNE1*, all of which influence cell-cycle regulation [16, 17]. The prognosis was generally poor, and significantly worse progression-free survival (PFS) was noted compared to other groups, as shown in Figure 2. It has been well documented that tumor suppressor p53 leads to rapid tumor progression and invasion [42].

Molecular analysis of patient data from the landmark PORTEC-3 trial suggests that patients with p53 abnormalities have superior outcomes when treated with chemotherapy in addition to radiation, compared to radiation alone [42]. Trials are ongoing on therapeutic modalities, such as trastuzumab, that exploit molecular features of this subclass, such as *HER 2* [43].

Predictive biomarkers – L1 Cell Adhesion Molecule

L1 Cell Adhesion Molecule (L1CAM) is a transmembrane protein first identified on postmitotic mice neurons by M. Schachner in 1984. These immunoglobulins are thought to drive invasion and metastasis by promoting aggressive cell behavior. L1CAM overexpression has been reported in various malignancies, while Zeimet et al. [44] were the first to report that ECs positive for this biomarker have worse outcomes.

Positive L1CAM was a powerful driver of unfavorable outcomes in low-grade and early-stage ECs – the 5-year disease-specific survival rate dropped from 100% to 71% for L1CAM-positive patients [45].

Incorporation of molecular characteristics into everyday clinical usage

The TCGA classification is impractical in a clinical setting due to considerable cost and time requirements driven by genome sequencing. That has prompted research teams to develop pragmatic molecular classification systems that can be performed on standard HP samples. These serve as surrogates for the diagnosis of the four molecular subtypes described by the TCGA classification. Molecular classification systems have been developed by two groups in Vancouver and the Netherlands. The Dutch team retrospectively analyzed bio-banks from the PORTEC-1 and -2 (postoperative radiation therapy for endometrial carcinoma) trials, identified four molecular subgroups, and validated their prognostic value [46]. The Canadian team developed a tool for molecular

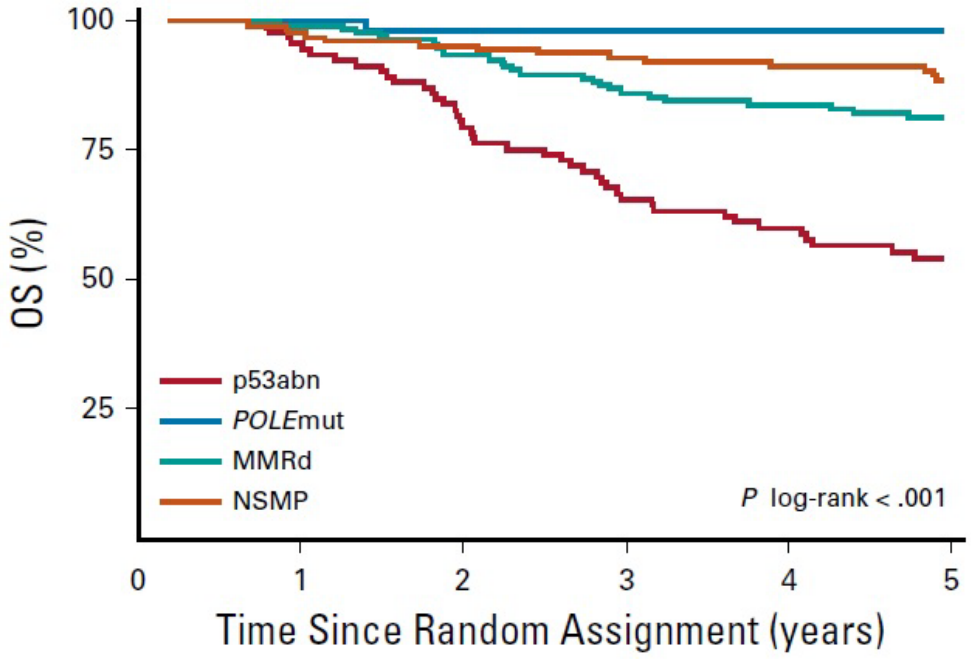

Fig. 2 – Kaplan-Meier survival curve for 5-year OS in patients with p53abn EC (54.0%), *POLE*mut EC (98.0%), MMRd (81.3%), or NSMP EC (88.5%).
OS – overall survival; EC – endometrial cancer; *POLE* – DNA polymerase epsilon; MMRd – mismatch repair deficient; NSMP – no specific molecular profile; p53abn – p53-abnormal; *POLE*mut – *POLE*-mutated. Figure taken from León-Castillo et al. [42].

classification named Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE). It was developed in agreement with strict National Academy of Medicine guidelines for biomarker tests based on omics [32]. These groups use three immunohistochemical (IHC) stains and sequencing for POLE exonuclease domain mutations (POLE EDMs) as surrogate markers corresponding to TCGA molecular subtypes. The results were four molecular subtypes, as shown in Figure 1. They were termed *p53* wild type (corresponding to TCGA copy-number – CN low), *p53* abnormal (corresponding to CN high), MMR defective (corresponding to MSI-H), and *POLE* EDM (corresponding to *POLE*-mutated group).

This simpler molecular classification system is advantageous when compared to the complexity of the TCGA classification. As mentioned, it works on standard formalin-fixed HP samples. With IHC stains for *p53* and MMR being readily available, the barrier to clinical implementation remains only *POLE* hotspot sequencing.

Future research and implementation – PORTEC-4a

PORTEC-4a is a randomized trial that aims to compare rates of vaginal recurrence in women with high-intermediate risk EC. The control arm received standard adjuvant treatment with vaginal brachytherapy. The experimental arm received observation, vaginal brachytherapy, or external pelvic beam radiotherapy after surgery based on a patient-specific molecular-integrated risk profile [47].

The rate of vaginal recurrence was chosen as the primary outcome. Added metrics such as adverse events (AEs), patient-reported symptoms and quality of life (QoL), pelvic and distant recurrence, and healthcare costs related to cancer treatment also need to be studied.

Utility in planning surgical treatment

Tissue samples gathered *via* endometrial curetting or pipelle biopsy will hopefully soon be available for molecular testing. Information obtained from these samples will most likely have an impact on surgical treatment and intraoperative decision management.

A hysterectomy and bilateral adnexectomy may suffice for patients burdened by *POLE* mutations, while more aggressive surgical treatment and lymph node dissection may be more suitable for *p53*-aberrant tumors.

Utility in guiding adjuvant treatment decisions

The area that will be most impacted by the adoption of molecular classification is the adjuvant treatment of ECs. Variables such as stage, histological type, grade, depth of invasion, and others are currently used to guide surgical management and adjuvant treatment decisions. As mentioned, these variables do not sufficiently predict patient outcomes. Molecular classification effectively identifies different diseases that all belong in the landscape of EC, and clinical practice is moving toward treating them as such. These four subtypes differ concerning histogenesis, risk factors, hereditary susceptibility syndromes, molecular abnormalities, response to treatment, and outcomes. For instance, there is an interest in de-escalating treatment for early-stage *POLE*-mutated EC. The first randomized clinical trial for the use of molecular characterization as an integral component of guiding adjuvant treatment decisions for patients with stage I–II high-intermediate risk EC is PORTEC-4a [47]. The clinical effectiveness of the integrated pathological/molecular risk profile will be prospectively measured.

Utility in guiding treatment decisions for progressive disease

In recent years, numerous novel therapeutic options for progressive EC have emerged – pembrolizumab, lenvatinib, bevacizumab, and others.

Bevacizumab, in combination with carboplatin/paclitaxel, is being evaluated for advanced EC in phase 2 trials such as GOG-86P and MITO END-2 [48, 49]. Based on National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN guidelines®), bevacizumab is offered in the advanced disease setting in combination with platinum-based treatments or as a single agent after progression [50].

Patient selection for IT options is crucial as not all patients will benefit. For example, around 90% of ECs express PD-L1, which can serve as a biomarker for some immune CIs in certain tumor types [51].

There are multiple CIs that have demonstrated efficacy as monotherapy in the setting of advanced EC that had progressed on or after platinum-based chemotherapy. Studies such as KEYNOTE-028, KEYNOTE-158, GARNET, and others have evaluated the place of CIs in certain molecular subsets of ECs and have reported durable responses [52–54].

Another therapeutic strategy is to add immune CIs to other ITs, targeted agents, or chemotherapy. The hypothesis asserts that targeted therapies may alter the immune system, leading to better effectiveness of IT [55].

Lenvatinib combined with pembrolizumab was recently granted accelerated FDA approval, based on the KEYNOTE-146 trial, for previously treated advanced EC that is not MSI-H or deficient MMR (MMR-d). Dose reductions were noted in 53% of cases, and dosing was interrupted in 74% of patients. Both the reduction and the interruption of the doses occurred due to treatment AEs. Given the toxicity of this regimen, the comorbidities and toxicities of prior regimens should be taken into account in patient selection [56].

Multiple trials continue to explore the combination of IT with chemotherapy – phase 3 RUBY trial and phase 3 AtTEnd trial. These trials evaluate carboplatin/paclitaxel in combination with dostarlimab or atezolizumab in the setting of advanced and/or recurrent disease.

Another area of interest is the combination of CIs with PARP inhibitors. Trials such as olaparib/durvalumab DOMEC and rucaparib/atezolizumab/bevacizumab (ENDOBARR) investigate these combinations in patient populations with recurrent or metastatic ECs.

Conclusion

Our understanding of EC has been changed fundamentally by genomics. Depending on institutional resources, implementation of the molecular-based classification will vary, but it may well prove to be cost-effective because unnecessary or ineffective adjuvant treatment can be avoided. Ongoing research efforts are focused on identifying additional prognostically relevant biomarkers and optimally integrating the molecular risk profile with conventional clinicopathological variables to treat patients best.

Molecular classification will become the basis for adjuvant therapy directed at molecular subgroups and provide the framework for new trial designs that will explore the effectiveness of targeted agents and combination approaches. Ongoing clinical trials will hopefully result in better clinical decisions, thus leading to improved survival and QoL for patients.

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