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REVIEW

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Exploring genomic and molecular insights in enhancing endometrial cancer treatment: A comprehensive review and future directions

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ABSTRACT

This paper demonstrated the various aspects of treating endometrial cancer (EC), with a focus on its genomic and molecular intricacies. It starts by outlining the epidemiology, risk factors, and classification of the disease, differentiating between Type I and Type II EC. Genetic changes, particularly mutations in genes like PTEN, TP53, and KRAS, play a significant role in the progression of the disease and help guide treatment decisions. Precision medicine, tailored to a patient's genomic profile, is becoming more important to identify targeted therapies and predict treatment responses. Immune checkpoint inhibitors, notably immune therapy, is emerging as a promising treatment option for specific EC subtypes. Hormone therapy is explored for its mechanisms of action, particularly for estrogen receptor-positive cancers. To refine therapeutic strategies, resistance mechanisms, both genomic and adaptive, require exploration. Emerging biomarkers, such as liquid biopsies, offer dynamic disease monitoring capabilities. By integrating multiple treatment modalities, including surgery, radiation, chemotherapy, targeted therapy, and immunotherapy, patient outcomes can be enhanced. Ongoing research, particularly in areas like CRISPR-Cas9 and CAR-T cell therapy, promises transformative impacts. Challenges encompass drug resistance, side effects, and equitable access to genomic testing and targeted therapies. A patient-centric approach that emphasizes shared decision-making and robust supportive care is essential. Ethical considerations regarding patient privacy and data sharing in the genomic era are crucial. Overall, the review navigates the complex treatment landscape of EC, unraveling its genomic basis, and highlighting future research and clinical practice prospects.

KEYWORDS

Endometrial cancer; Hormone therapy; Liquid biopsies; CRISPR-Cas9; CAR-T cell therapy; Drug resistance

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Introduction

EC is a prevalent gynecological malignancy in developed countries and is among the leading causes of cancer-related deaths in women. There were approximately 417,000 new cases of EC diagnosed worldwide in 2020, demonstrating the significant health concern it poses. The incidence of EC is increasing and can be attributed to risk factors such as obesity and aging [1,2]. The current gold standard for treating EC involves a comprehensive approach that usually begins with a hysterectomy and bilateral salpingo-oophorectomy. Additional treatment modalities such as chemotherapy, radiotherapy, and brachytherapy may be recommended based on the individual's risk of disease recurrence. Recent advances in medical practice have led to the identification and removal of the sentinel lymph node as an essential advancement in the management and treatment of EC [3,4]. Molecular classification and traditional clinicopathological prognostic factors play a significant role in stratifying patients based on their risk profile. This approach is crucial in tailoring patient-specific therapies and has far-reaching implications for the management of patients suffering from various diseases. In the field of cancer therapeutics, a concerted effort has been made over the last few decades to develop treatments that target the molecular abnormalities driving carcinogenesis [3,5,6]. Targeted therapies have emerged as some of the most promising options for achieving favorable treatment outcomes in patients [7,8]. Recent advances in preclinical research have yielded encouraging results, and clinical trials are underway to evaluate the effectiveness of novel biological agents in the treatment of EC [9,10].

The goal of this review is to discuss the current state of EC classification, with a focus on advancements in molecular classification methodologies. The review will highlight how these classifications have made significant contributions to medical research and have revolutionized the clinical management of EC. Additionally, the review will assess the impact of molecular and genomic profiling on EC and provide insights into the current implications of these developments. Finally, potential future directions in the field will be discussed. Molecular classification involves the detailed examination of genetic and molecular characteristics of diseases, with a particular emphasis on the unique genotypic features of affected cells [11-13].

Molecular classification is crucial in understanding the differences in breast cancer, such as hormone receptor positivity, HER2 amplification, and triple-negative phenotypes, which each require a unique treatment approach [2,12,13]. Traditional clinicopathological prognostic determinants include a combination of clinical and histopathological metrics that have been used for a long time to assess the severity of the disease and anticipate prognosis [14]. These parameters include disease

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stage, which indicates the progression of the disease, tumor size, a histologic grade that defines cellular characteristics, and the presence of metastatic dissemination to other anatomical locations. These metrics are vital in helping clinicians understand the extent of the disease and form the basis for making informed decisions about treatment options [2,15,16].

Molecular classification and traditional clinicopathological factors play a vital role in assessing the potential dangers of a patient's illness. These factors, when combined, provide a comprehensive picture of the disease attributes, allowing healthcare providers to better gauge the associated risks with greater accuracy [9,16]. The ability to predict the course and consequences of a disease, also known as prognostication, is closely tied to both molecular classification and conventional clinicopathological determinants. These facets enable healthcare practitioners to formulate more precise prognostic forecasts regarding the evolution of the disease and the likely outcomes for the patient [7,9]. These stratification techniques go beyond just prognostic capabilities and become critical tools in clinical governance and the development of customized therapeutic protocols. Molecular classification reveals therapeutic targets within a patient's illness, which is then used to design treatments tailored to the patient's unique genetic makeup. For example, certain cancer therapies target specific genetic mutations within a patient's tumor, resulting in a more effective and less harmful treatment approach [11]. Such therapies have been developed over several decades, and today, treatments that focus on molecular aberrations of malignant tumors are considered one of the best options for promising outcomes. Recent preclinical studies focusing on disease biology have shown satisfactory results, leading to the start of clinical trials to test the potential of new biological agents in the treatment of EC. In this review, we aim to discuss the current classification of EC and the recent advancements in molecular classifications. We will also evaluate their impact on medical research and clinical management. We will critically assess the effects of molecular/genomic profiling in EC, focusing on current implications and future perspectives.

A Watershed Moment in EC Understanding

In medical history, 1983 marks a seminal milestone in our comprehension of EC. This pivotal moment unfolded with the introduction of a groundbreaking pathogenetic classification by Bokhman. His innovation stratified EC into two distinct archetypes, colloquially known as type I and type II [17].

Type I ECs, constituting 70-80% of cases

Within this framework, type I ECs emerge as the predominant subset, encompassing approximately 70-80% of all cases. These tumors predominantly manifest as moderately or well-differentiated endometrioid tumors. Notably, they exhibit a distinctive feature—positive hormone receptors. Type I ECs find greater prevalence among women grappling with obesity.

Type I ECs: Prognostic significance

Type I endometrial cancers (ECs) show promise with a relatively favorable prognosis in the domain of endometrial cancer. This optimism predominantly arises among women exhibiting specific risk factors, including smoking habits, early onset of menstruation, delayed menopause, nulliparity, and lack of breastfeeding. Additionally, type I ECs commonly present as localized diseases, thereby enhancing the prospects for localized treatments.

Type II ECs: A divergent path

In contrast, type II ECs, though constituting a smaller share, occupy a distinct and divergent path, accounting for 20-30% of cases. They stand apart with their non-endometrioid histology, marked by poor differentiation. Notably, type II ECs lack the hormone receptors that typify type I cases.

Type II ECs: Independent of traditional risk factors

Type II ECs defy the influence of the 'traditional' risk factors associated with type I ECs. They select a different demographic, often afflicting older women. Most significantly, type II ECs carry the ominous burden of heightened metastatic potential and a less promising prognosis [18].

Historical EC Risk Stratification and Its Limitations

The historical paradigm for EC risk stratification leaned heavily on the assessment of histopathological characteristics, encompassing parameters like tumor gradation, histotype, depth of myometrial invasion, and involvement of neighboring structures such as the cervix and annexes.

The Paradigm Shift: The ascendance of the cancer genome profile (TCGA)

However, this historical stratification model bore intrinsic limitations, as it failed to grasp the nuanced molecular intricacies underpinning EC's heterogeneity. Consequently, it remained unable to offer a comprehensive insight into the manifold clinical presentations and behaviors of the disease. The Cancer Genome Atlas (TCGA) Research Network spearheaded a transformative shift in 2013. The TCGA transcended the shackles of conventional histopathological categorization by embracing the integration of molecular and genomic profiling [19,20].

TCGA's Legacy: Molecular precision and personalized medicine

The TCGA's initiative has left a lasting impact on the field of endometrial cancer (EC) by employing advanced molecular techniques to investigate genetic and genomic alterations. This comprehensive analysis provided profound insights into the fundamental biology of the disease at the molecular level. As a result, it facilitated advancements in precision diagnostics, prognostics, and therapeutic approaches, ushering in an era of personalized medicine.

Molecular and Genomic Profiling of EC

The assimilation of molecular and genomic data has since emerged as the vanguard of EC management, fostering the refinement of risk stratification. It empowers clinicians to craft therapeutic strategies tailored to the unique molecular profiles of individual patients. This paradigm shift has not only reshaped the landscape of EC research but has also cast a transformative light on clinical governance and patient care.

In summation, the introduction of molecular and genomic profiling into the study of EC signifies a monumental advancement. It has enriched our comprehension of the disease's intrinsic heterogeneity, redefined risk stratification,

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and elevated patient management. This paradigm shift from conventional histopathological classification to molecular characterization holds immense potential for elevating the standards of diagnosis and treatment outcomes in EC.

The contemporary delineation of EC represents a triumph in oncological sophistication, finely stratifying this disease into four prognostically significant groups. These distinctions are meticulously illuminated through cutting-edge techniques such as genome and exome sequencing, as well as the microsatellite instability (MSI) assay [12]. Each of these groups stands as a testament to the power of molecular precision and holds profound implications for prognosis and recurrence risk:

Polymerase epsilon (POLE) ultramutated

This subgroup emerges as a paragon of molecular refinement, characterized by somatic mutations within the exonuclease domain of polymerase epsilon DNA. Intriguingly, it envelops a spectrum ranging from low-grade to high-grade EC instances. Its predilection is often observed in a cohort of younger women distinguished by their lower body mass indexes.

MSI hypermutated group

Within the domain of EC, the MSI hypermutated subgroup emerges as a distinctive entity, rooted in the intricate intricacies of DNA mismatch repair (MMR) systems. At its core lies microsatellite instability (MSI), a genetic hallmark prevalent in approximately 10–15% of colon cancers and centrally implicated in Lynch syndrome, a hereditary predisposition to various malignancies, including EC.

Silencing of key genes

At the core of this subgroup's genetic profile lies a pivotal mechanism: the hypermethylation of the promoter region of MutL protein homolog 1 (MLH1), leading to its transcriptional silencing. This genetic event serves as a linchpin in the complex cascade of genetic anomalies.

Grade variability

The MSI hypermutated cohort transcends the conventional boundaries of EC grade, enveloping the full spectrum, from Grades I to III. However, in stark contrast to the POLE subgroup, its prognostic compass points toward the intermediate range, punctuated by distinctive hallmarks. Notably, lymphovascular space invasion (LVSI) frequently graces the histopathological landscape of this subgroup.

Prominent genetic alterations

This subgroup presents a unique genetic profile characterized by recurrent mutations in genes such as phosphatase and tensin homolog (PTEN), phosphatidylinositol-3-kinase catalytic subunit alpha (PIK3CA), phosphoinositide-3-kinase regulatory subunit 1 (PIK3RI), and AT-Rich interactive domain-containing protein 5B (ARID5B). These mutations define the distinct molecular signature of this EC subgroup [4,14,17,18].

Copy-number (CN) low group

In contrast to MSI hypermutated tumors, the CN low group consists of low-grade endometrioid tumors lacking specific genetic aberrations, including intact tumor protein 53 (TP53) and polymerase epsilon (POLE).

Microsatellite stability and hormone receptors

This subgroup exhibits microsatellite stability and is commonly referred to as 'microsatellite stable.' It demonstrates a significant presence of estrogen and progesterone receptors (ER/PR). Intriguingly, it navigates genetic composition, characterized by a relatively low number of somatic alterations.

Superior prognosis amid variability

The prognosis associated with the CN low group reveals its intricacies, intertwining variables such as tumor stage and histomorphology. Yet, in the majority of instances, this subgroup signifies a favorable prognosis, emblematic of the languid nature characterizing these neoplasms [4,14,19,20].

Copy-number (CN) high group

In contrast, the CN high group crafts a somber narrative, with a grievous mortality rate and the most dismal prognosis witnessed among the EC subgroups. Its defining genetic feature lies in the omnipresence of P53 abnormalities, accompanied by a profusion of somatic alterations.

Serous and mixed carcinomas

This subgroup predominantly plays host to serous and mixed carcinoma subtypes, with a preponderance of high-grade tumors. However, it is noteworthy that even low-grade tumors can carve their niche within this enigmatic domain.

Incidence and prevalence

The CN high subgroup represents a minority, accounting for a modest 8–24% of all EC cases. The intricate tapestry of characteristics and distinctions enveloping these molecular subgroups is meticulously outlined, providing an exhaustive panorama of their genetic underpinnings and clinical ramifications.

In essence, the classification of EC into these molecular subgroups marks a quantum leap in our comprehension of this intricate malignancy. It empowers clinicians with the prerogative to custom-tailor therapeutic strategies in alignment with the unique genetic imprints of individual patients, with each subgroup unveiling its own trove of challenges and opportunities in the relentless quest for enhanced patient outcomes.

Innovations and limitations of the TCGA study

The TCGA study represents a significant milestone in EC research, offering an unprecedented level of precision in characterizing EC patients. However, its pioneering approach, while revolutionary in its precision, was not without its complexities, financial constraints, and challenges concerning its practical integration into routine clinical practice. While laying essential groundwork for molecular understanding of EC, its translation into real-world clinical settings remained elusive.

ProMisE Emerges: A Practical Molecular Model

Over time, the need for a more practical and clinically applicable approach to molecular risk classification in EC became evident. In response to this pressing demand, the ProMisE model emerged, embodying the acronym Proactive Molecular Risk Classifier for EC. This model was meticulously

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crafted in adherence to the stringent guidelines established by the Institute of Medicine (IOM), representing a significant stride toward bridging the chasm between cutting-edge research and pragmatic clinical utility.

The intricacies of the ProMisE molecular decision tree analysis ProMisE's molecular decision tree analysis is a systematic and methodical process, meticulously designed to offer a streamlined and clinically viable method for EC classification.

Immunohistochemistry (IHC) assessment of mismatch repair (MMR) proteins

The journey commences with a precise assessment of the presence or absence of two pivotal MMR proteins, namely mutS homolog 6 (MSH6) and PMS2, accomplished through the intricate technique of immunohistochemistry (IHC). If the results of this IHC analysis fail to detect these critical proteins, the EC sample is promptly categorized within the MMR-deficient (dMMR) subgroup. This classification bears profound implications, signifying a notable malfunction in the DNA repair mechanisms, a hallmark feature of specific EC cases.

PCR analysis to unveil POLE exonuclease domain mutation (POLE EDM)

In the event that the MMR proteins are perceptibly expressed within the sample, the analytical journey advances to its subsequent phase. Here, the polymerase chain reaction (PCR) technique comes to the forefront, orchestrating an intricate dance of genetic analysis to unveil mutations within the POLE exonuclease domain, succinctly referred to as "POLE EDM." The mere presence of these discernible mutations guides the unequivocal classification of the EC sample into the esteemed POLE ultramutated group. This subgroup represents an exquisite rarity, marked by an exceptionally heightened mutation rate within the POLE gene.

Immunohistochemistry for P53 status

However, if neither the spectra of MMR deficiency nor the presence of POLE EDM mutations casts its shadow upon the genetic landscape, the journey culminates with the sophisticated application of immunohistochemistry (IHC). This analytical denouement is orchestrated to assess the p53 status residing within the tumor. This discerning assessment, a hallmark of precision oncology, unravels the enigma surrounding the p53 gene, identifying whether it resides in its pristine wild-type form or bears the hallmarks of null/missense mutations. The outcome of this nuanced analysis bestows clinicians the power of EC sample classification, offering invaluable insights into the underlying genetic tapestry and, by extension, the prognosis of the tumor.

In essence, ProMisE emerges as the bridge traversing the abyss between the intricate molecular labyrinth of EC and the pragmatic domains of clinical application. It empowers clinicians with the exceptional ability to categorize EC patients into discreet molecular subgroups, a distinction bearing profound implications for personalized treatment strategies and prognostic precision, all achieved within clinical practice that seamlessly aligns with the evolving paradigm of precision medicine.

The imperative of molecular analysis in endometrial carcinomas

In the current landscape, it is paramount to underscore the recommendation that molecular analysis be conducted on all cases of endometrial carcinomas, adhering to the algorithm delineated in existing guidelines. It is worth noting that the decision to embark upon molecular testing is contingent upon the resources and infrastructure available within each medical center's multidisciplinary team [4]. The overarching objective has perpetually been the development of a pragmatic and cost-effective molecular classification framework, one that is amenable to the analysis of endometrial biopsies or curettages.

Empowering therapeutic precision through biological and molecular insights

Indeed, the confluence of biological and molecular insights gleaned from the tumour's intricate profile has transformative potential. It serves as the linchpin in the establishment of tailored therapeutic regimens, underpinning decisions regarding the extensiveness of surgical intervention and the potential utility of adjuvant or molecular-based therapies. The application of the ProMise molecular classification on diagnostic specimens stands as a validated avenue, extensively scrutinized by a plethora of studies.

Validation through concordance

Crucially, these studies have ushered in a resounding affirmation of the utility of this molecular classification paradigm. They have underscored a remarkable concordance between molecular assessments conducted on diagnostic specimens and their counterparts derived from the ultimate gold standard: hysterectomy specimens [21-23].

A pinnacle validation study

One of the pinnacle validations hails from an exhaustive analysis encompassing 947 early-stage endometrial carcinoma patients. This rigorous investigation, conducted within the confines of two expansive randomized trials (PORTEC-1 and PORTEC-2), predominantly encompassed individuals positioned at the high/intermediate risk stratum. Its primary objective was to corroborate and authenticate the profound prognostic significance conferred by molecular classification. Furthermore, it aspired to augment the granularity of risk assessment by forging connections between molecular subgroups, other genetic mutations, and the intricate domain of lymphovascular space invasion [24].

In endometrial carcinomas, an extensive genetic analysis was undertaken, analyzing mutations in a diverse array of genes including BRAF, CDKNA2, CTNNB1, FBXW7, FGFR2, FGFR3, FOXL2, HRAS, KRAS, NRAS, PIK3CA, PPP2R1A, and PTEN, alongside a study of the expression profiles of ER, PR, β-catenin, ARID1A, and L1CAM. These meticulous investigations unveiled stark disparities among four distinct molecular subgroups, differentiating themselves through clinicopathological and molecular attributes that distinctly reflect clinical outcomes. Tumors bearing P53 mutations signaled an unfavorable prognosis, entailing a complex interplay of factors including over 10% L1CAM expression, PPP2R1A, and FBXW7 mutations, histologic grade 3, and the

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absence of hormone receptor expression. In contrast, MSI tumors and those in the no specific molecular profile (NSMP) category followed an intermediate prognostic trajectory. The former exhibited a higher propensity for lymphovascular space invasion (LVSI) and ARID1A abnormalities, while the latter trended towards grade 1 tumors with a predilection for CTNNB1 mutations. In contrast, the POLE mutation-bearing subgroup consistently bore a favorable prognosis, even when coexisting with grade 3 tumors and PTEN mutations. Robust prognostic factors encompassed P53 mutations, substantial LVSI, and L1CAM expression surpassing 10%, correlating with heightened recurrence risk and diminished overall survival. Furthermore, CTNNB1 exon 3 mutations marked an increased risk of distant recurrence. ER positivity, PI3K/AKT pathway mutations, PR positivity, and L1CAM positivity coalesced as molecular hallmarks indicative of a bleaker prognosis, while mutations in FBXW7 and FGFR2 exhibited lower prevalence. These meticulously defined molecular subtypes offer invaluable insights into G3 endometrial carcinomas and all high-risk ECs, ushering in precision and personalized therapeutic avenues [25-29].

High-risk ECs form a complex and diverse category of tumors, encompassing various non-endometrioid histotypes that exhibit distinct molecular profiles and clinical prognoses. Beyond the delineation of these tumors into the four molecular subgroups, it becomes imperative to discern additional alterations within potentially targetable pathways, notably the PI3K-AKT or FBXW7-FGFR2 pathways. This becomes particularly relevant for cases characterized by the most unfavorable prognoses, such as those bearing p53 mutations or falling within the NSMP category, as well as those manifesting non-endometrioid histological features. To shed light on the clinical-therapeutic significance of these supplementary target pathways and their potential to enhance survival outcomes, extensive investigations involving substantial cohorts of patients are warranted, thus representing a promising avenue for future research and therapeutic advancements in this intricate domain [30,31].

A subject that continues to elicit ongoing debate centers around the impact of mutations in the breast cancer genes, BRCA1 and BRCA2, on the development of EC (EC). Notably, women harboring pathogenic variants in these genes confront a lifetime risk spectrum encompassing a 40–80% susceptibility to breast cancer and an 11–40% vulnerability to ovarian cancer [32]. In scientific literature, there exists a compelling body of data that delves into the comparative analysis of uterine cancer, particularly serous EC, and serous ovarian cancer. These investigations hint at shared pathogenetic underpinnings and hereditary etiologies, intriguingly linking these two tumor classifications [33]. Both BRCA1 and BRCA2 assume the role of tumor-suppressor genes, intricately entwined with the homologous recombination (HR) system, a linchpin in DNA damage repair preceding cell replication. Notably, BRCA1 and BRCA2 mutations are frequently concomitant with homologous recombination deficiency (HRD), involving a cadre of auxiliary genes indirectly entangled in this pathway, among them ARID1A, ATM, p53, and PTEN [7,34,35]. Yet, the landscape remains marked by conflicting data pertaining to molecular alterations in EC and HRD. Within a comprehensive molecular analysis of 5540 EC cases, HRD emerged with a prevalence of 34%, accompanied by mutations in ARID1A, ATM, and BRCA2, registered at rates of 27%, 4.6%, and 3.05%, respectively [36]. Regrettably, a dearth of data obscures our ability to comprehensively scrutinize the outcomes among EC patients harbouring BRCA mutations. In a retrospective, multicenter study, encompassing 64 EC patients, no discernible disparities surfaced in median overall survival, progression-free survival, or disease-specific survival between the cohort bearing BRCA mutations and their BRCA wild-type counterparts. However, a noteworthy observation emerges, hinting at more advanced disease presentation at the time of diagnosis among those with BRCA mutations.

Therapeutic considerations

In recent years, the landscape of EC therapy has undergone a transformative shift, embracing the tenets of personalized medicine tailored to distinct subclasses. Robust scientific evidence now informs our therapeutic approaches. Notably, a pivotal phase III study has delineated precise therapeutic trajectories for diverse risk categories among EC patients. Those classified within the low-risk category, characterized by POLE mutations and early-stage disease (FIGO stage I–II), are, intriguingly, found to eschew the necessity for adjuvant treatment, a testament to their notably low recurrence rates [25,37-40]. Meanwhile, for patients occupying the intermediate-risk stratum, the role of brachytherapy assumes significance, although its application demands scrupulous evaluation on a case-by-case basis. Distinct considerations emerge for high-intermediate risk patients, contingent upon their lymph node status. Those with negative loco-regional lymph nodes, particularly in cases featuring LVSI positivity and stage II, may derive benefit from external beam radiation therapy (EBRT). Conversely, in instances characterized by high-grade features and/or substantial LVSI, the therapeutic pendulum swings towards chemotherapy. For patients with an enigmatic lymph node status, LVSI positivity and/or Stage II scenarios prompt a recommendation of EBRT. Simultaneously, high-grade and/or substantial LVSI positivity instances advocate for the integration of adjuvant chemotherapy.

Notably, high-grade LVSI-negative cases, conjoined with stage II endometrioid carcinomas, discern a therapeutic niche in adjuvant brachytherapy alone. Finally, high-risk patients necessitate systemic adjuvant therapy, orchestrating a symphony of external beam radiation therapy (EBRT) in tandem with concurrent and adjuvant chemotherapy, a multifaceted approach that underpins the evolving landscape of EC management [41,42].

Advanced approaches in therapeutic decision-making

Despite the ongoing proliferation of studies in this domain, the incorporation of mutational and genomic profiling into the selection of adjuvant treatments for patients with the early-stage disease remains unsupported by level A evidence. However, it's worth noting that the MSI status does carry significant implications when it comes to tailoring the most fitting therapies in the metastatic context [43,44].

One promising avenue within the therapeutic landscape hinges on the interplay between programmed death ligand 1

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(PD-L1) and programmed death-1 (PD-1), two pivotal immune checkpoint-associated proteins. These proteins, frequently found in abundance within the tumor microenvironment, play a pivotal role in enabling cancer cells to evade immunosurveillance. Immune checkpoint inhibitors targeting these proteins have emerged as transformative agents in various cancer types. By obstructing PD-1 and PD-L1 interactions, these drugs render cancer cells vulnerable to immune system-mediated attacks [45].

A notable illustration of this paradigm shift unfolds in the form of the Phase II study KEYNOTE-158. This investigation delves into the efficacy of Pembrolizumab, a humanized anti-PD-1 monoclonal antibody, in patients with advanced MSI-H/dMMR tumors who have undergone prior treatments. The results were compelling enough to secure FDA approval in 2017 for the use of Pembrolizumab in patients diagnosed with non-resectable or metastatic solid tumors, marking a pivotal milestone in the realm of immunotherapy [46].

Advancements in immunotherapy: Illuminating insights

The pivotal KEYNOTE-028 study, along with subsequent research by Patrick et al. and O'Malley et al., has offered robust confirmation of the promising survival outcomes in this realm [46,47]. The exploration of single-agent immune checkpoint inhibitors has emerged as a pivotal avenue in the management of advanced or recurrent EC, particularly among patients who have previously undergone at least one line of platinum-based chemotherapy. Notably, nivolumab monotherapy has unveiled an impressive objective response rate (ORR) of 23% in advanced EC patients, irrespective of MSI status. Avelumab and Durvalumab, administered as monotherapies, have likewise demonstrated noteworthy ORRs of 26.7% and 43%, respectively, among individuals with advanced EC and dMMR tumors [48-50].

Pioneering insights continue to emerge from the ongoing phase I GARNET trial, as reported by Oakin et al. This trial meticulously probes the efficacy of Dostarlimab in a cohort comprising both dMMR/MSI-H and proficient/stable (MMRp/MSS) EC patients. The preliminary data paints a compelling picture, revealing an ORR of 43.1% coupled with a commendable duration of response (DCR), all underscored by a manageable safety profile [51]. These advancements underscore the transformative potential of immunotherapy in reshaping the landscape of EC treatment.

Innovations in treatment: A paradigm shift

Remarkable strides have been made in the therapeutic landscape, especially in immune checkpoint inhibitors. Notably, Durvalumab monotherapy has displayed remarkable efficacy, transcending prior chemotherapy, and has proven to be remarkably safe for individuals with dMMR EC, boasting an impressive objective response rate (ORR) of 47.7%. However, its activity remains somewhat restricted in pMMR AEC cases, emphasizing the importance of personalized approaches [52].
A significant milestone was achieved with the FDA's expedited approval of the combination therapy of Lenvatinib and Pembrolizumab for advanced EC cases that did not exhibit MSI-H or dMMR status and had not progressed following previous treatments. Lenvatinib, a potent multikinase inhibitor targeting key players like vascular endothelial growth factor receptor (VEGFR), fibroblast growth factor receptor (FGFR), KIT, RET, and platelet-derived growth factor receptor (PDGFR), induces immune activation, complementing the immune-enhancing effects of Pembrolizumab [53,54].

This collaborative approach was corroborated by a 2019 phase II study, elucidating the treatment's efficacy in patients with primary advanced or recurrent EC, even after prior platinum-based chemotherapy, irrespective of MMR status [55]. A subsequent analysis in 2020, the single-arm trial KEYNOTE-146/Study 111, underscored the safety and efficacy of this regimen, boasting an overall ORR of 38%, median progression-free survival (PFS) of 7.5 months, and a median overall survival (OS) of 16.7 months [56]. Further validation emerged in the KEYNOTE-775/Study 309 trial, wherein Pembrolizumab in tandem with Lenvatinib outperformed paclitaxel or doxorubicin chemotherapy, showcasing PFS, OS, and ORR rates of 6.6 months, 17.4 months, and 30.3%, respectively, and significantly elevating patient outcomes in the first arm [57].

As of now, the combination therapy of Pembrolizumab plus Lenvatinib is considered the standard second-line treatment for advanced or metastatic EC that has progressed despite platinum-based chemotherapy. In the United States, this treatment is approved exclusively for MSS EC, whereas in Europe, it is granted approval in the second line without discrimination based on MSI-H/MSS status, marking a significant advancement in EC management [53].

Continuing quest: Cutting-edge clinical trials

In EC management, an imperative unmet need persists—deciphering the optimal adjuvant strategy for EC patients, particularly those grappling with positive nodes and low-volume disease [58-60]. To address this crucial gap in knowledge, several prospective studies are currently underway, exploring a diverse array of adjuvant strategies tailored to these patient populations [60,61].

Foremost among these groundbreaking clinical trials is the RAINBO umbrella program, a trailblazing initiative meticulously designed to investigate novel adjuvant therapies for EC patients. Within this transformative program, EC patients are thoughtfully assigned to one of the four distinct RAINBO trials, contingent upon the molecular profile of their cancer.

The p53abn-RED trial (international, multicenter, phase III randomized study focuses on patients harboring p53-mutant EC and delves into the efficacy of adjuvant chemoradiation coupled with two years of Olaparib versus adjuvant chemoradiation alone, representing a profound leap forward in personalized therapeutic strategies.

On a parallel front, the MMRd-GREEN trial, another international, multicenter, phase III randomized study, unfolds its significance for MMRd EC patients. This trial scrutinizes the potential benefits of adjuvant pelvic external beam radiotherapy when combined with Durvalumab for one year, offering a tantalizing alternative to adjuvant pelvic external beam radiotherapy alone. These ongoing trials, propelled by a steadfast commitment to precision medicine, herald a promising era in EC management, where tailored therapeutic

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approaches based on molecular insights stand poised to revolutionize patient care and outcomes [15,61].

Pioneering the Way: Advancements in Clinical Trials

The NSMP-ORANGE trial is designed for patients with EC who do not exhibit a specific molecular profile. These individuals are subjected to adjuvant pelvic external beam radiotherapy, followed by a two-year regimen of oral progestins, such as medroxyprogesterone acetate or megestrol acetate. Meanwhile, the POLEmut-BLUE trial, which caters to POLE mutant EC patients, represents an international, multicenter, single-arm, phase II investigation focused on assessing the safety of de-escalating adjuvant therapy. Specifically, patients with stage I and II receive no adjuvant therapy, whereas those at stage III are either administered pelvic external beam radiotherapy or remain without adjuvant therapy. The overarching goal of the comprehensive RAINBO research endeavor is to consolidate data and tumor material gleaned from the four RAINBO clinical trials. This consolidation facilitates translational research, enabling a comprehensive comparison between molecular profile-based adjuvant therapy and standard adjuvant therapy in terms of effectiveness, toxicity, quality of life, and cost-utility [62].

Furthermore, the PORTEC-4a initiative is actively exploring diverse treatment modalities for Stage I–II high-intermediate risk EC patients, tailoring interventions based on their specific molecular profiles [63]. Beyond these endeavors, a spectrum of prospective studies continues to explore novel strategies in both adjuvant and metastatic settings, ushering in a new era of personalized EC care.

Discussion

Endometrial carcinoma generally boasts a favorable prognosis, with the choice of surgical intervention contingent upon factors like tumor extent and the patient's preoperative assessment. The surgical approach stands as the cornerstone of early EC treatment [63,64]. Nevertheless, the realm of adjuvant therapy necessitates a meticulous, personalized approach. This is particularly crucial since EC predominantly afflicts elderly patients beset with comorbidities like hypertension and diabetes. Therefore, every endeavor is dedicated to minimizing morbidity and enhancing treatment outcomes. In the wake of the TCGA's groundbreaking revelations, significant strides have been made in fusing histological assessments with molecular tests. The overarching objective is to attain an even more precise staging for each unique patient, cementing the path toward tailored and effective therapeutic strategies.

This burgeoning fusion of molecular insights and histological assessments has ushered in a more profound comprehension of tumor biology, amplifying the potential to enhance disease diagnosis and prognosis. Additionally, the integration of molecular classification has furnished a substantial advantage by facilitating the precise identification of patients poised to derive maximal benefit from systemic treatments like chemotherapy, radiotherapy, and immunotherapy. In recent years, the realm of medical imaging has witnessed a significant evolution, with radiomic analysis emerging as a pivotal tool for risk stratification in individuals grappling with endometrial carcinoma. This innovative approach empowers clinicians with the ability to unearth intricate details beyond the scope of the human eye.

In a noteworthy study, Bi Cong et al. leveraged preoperative magnetic resonance imaging (MRI) data from a substantial cohort of 717 EC patients to devise a radiomic model. Impressively, this model exhibited commendable performance in predicting high-risk cases, boasting an area under the curve (AUC) of 0.845 in the validation group. Intriguingly, when coupled with clinical features, its accuracy surged to nearly exceptional levels, boasting an AUC of 0.919 [64]. Subsequent investigations buttressed these findings, encompassing preoperative MRI and other advanced imaging modalities [15,65,66].

Moreover, Mor et al. conducted a multicenter retrospective study involving 498 EC patients, where they ventured into the realm of ultrasound imaging, a cost-effective and accessible first-line imaging investigation frequently employed in gynecology. Through the development and validation of a radiomic model based on ultrasound images, they achieved promising outcomes. In the validation test, the radiomics model showcased a sensitivity of 58.7% and specificity of 85.7% in effectively distinguishing high-risk EC from other malignancies [67]. This exemplifies the remarkable potential of radiomic analysis in refining risk stratification and patient care in the realm of endometrial carcinoma.

These compelling data underscore the potential of radiomic analysis to guide surgical management choices even prior to the availability of molecular analysis results. Given the elevated costs associated with genetic and molecular tumor assessments, a hybrid approach, aptly termed "radio-genomics," has been introduced. This innovative approach carries the dual promise of cost reduction in processing and analyzing histologic samples and expediting a more rapid and reproducible exploration of the intricate characteristics and behaviors of these complex diseases, all before the initiation of surgical interventions.

Regrettably, the landscape of radio-genomics remains somewhat nascent, with limited studies conducted thus far. For instance, radiomics models have been developed to predict PD1 expression and its potential association with Lynch Syndrome in a cohort of 100 EC patients. Another study involving 150 patients delves into the determination of DNA mismatch repair deficiency (MMR-D) [68,69].

As the realm of endometrial carcinoma evolves, it increasingly affects patients who are pre-menopausal, often delaying their first pregnancy. This shifting demographic has spurred interest in employing molecular analysis to tailor therapeutic strategies for the conservative management of lesions that foreshadow EC. Zhang et al. conducted a retrospective analysis involving 59 patients afflicted with EC and endometrial atypical hyperplasia/endometrial intraepithelial neoplasia (EAH/EIN). Their study investigated how molecular classification could predict responses to conservative treatment, with a specific focus on identifying subclasses at the highest risk of progression. This forward-looking approach holds great promise in safeguarding the well-being of a broader spectrum of patients [70].

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Intriguingly, the treatment landscape for EC reveals divergent responses based on molecular subgroups. The POLEmut group displayed an astonishing 100% complete response rate, while the copy number-low mutation (CNL) subgroup exhibited a commendable 71.43% rate, underscoring a favorable prognosis for these cohorts. In stark contrast, the copy number-high mutation (CNH) and MSI-H group faced significantly bleaker outcomes, registering complete response rates of 33.3% and 25%, respectively [70].

In a separate analysis involving 89 EC patients, the aim was to discern the predictive power of various clinicopathological indicators for treatment efficacy. Intriguingly, no discernible associations emerged between prognosis and the expression of ER, PAX2, PTEN, or Ki-67 in the initially untreated AH or EEC groups. However, a glimmer of hope emerged in the form of >50% PR expression, which exhibited the highest complete response rates in both the EEC and AH groups [71]. Furthermore, in a study involving 117 cases initially diagnosed as endometrial hyperplasia, histopathological reevaluation using the EIN diagnosis category was carried out. The objective was to establish the immunohistochemical expressions of PTEN and β-catenin. Results from this analysis hinted at the potential emergence of the combination of PTEN-negative/β-catenin-positive as a reliable marker for detecting EIN, bearing in mind that these markers could serve as predictors of disease progression [15,72]. While this review draws strength from the inclusion of the most recent studies available in prominent scientific databases, it also acknowledges inherent limitations. The paucity of data supporting these findings underscores the need for additional studies to validate this scientific evidence, which has the potential to revolutionize the management of endometrial disease [73,74].

Conclusion

In summary, molecular classification has ushered in a new era in the risk assessment and treatment of EC. Recent years have witnessed a surge in research exploring tailored therapies, encompassing chemotherapy, radiation therapy, immune checkpoint inhibitors, and molecular targeting agents, guided by clinical and molecular-genetic characteristics. Notably, immune checkpoint inhibitors have demonstrated remarkable response rates, particularly in patients with dMMR, positioning them as promising therapeutic agents. Ongoing studies are poised to potentially establish these agents as the new standard for first-line treatment in advanced or recurrent EC, potentially reshaping the landscape by comparing radiation therapy alone with radiation therapy combined with checkpoint inhibition.
The p53 subgroup, though representing a small percentage of cases, presents the bleakest prognosis among all EC subgroups. Nonetheless, novel therapeutic avenues are displaying promise. PARP inhibitors, targeting homologous recombination deficits, and specific antibodies tailored to tumours overexpressing human epidermal growth factor receptor 2 (HER2) hold particular potential. Ongoing investigations comparing chemoradiation with chemoradiation plus PARP inhibitors aim to delineate the efficacy of these therapeutic strategies.

Crucially, the ongoing PORTEC 4a and the RAINBO umbrella program stand as pioneering initiatives, marking significant strides toward overcoming current limitations in the management of EC subtypes. These endeavours aim to pave the way for personalized adjuvant treatments based on molecular profiling, marking a substantial leap toward the realm of precision medicine in EC [73-75].

Disclosure Statement

No potential conflict of interest was reported by the author.

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