DOI:10.31557/APJCB.2024.9.2.201

REVIEW

Biomarker Panel for Early Detection in Uterine Cancer: A Review

N. Deepthi Priya, K. V. Nanda Kumar, M. Siva Charani, D. Bindu, K. Likhitha Reddy, Y. Gowthami

Krishna Teja Pharmacy College, Tirupathi, Andhra Pradesh, India.

Abstract

Uterine cancer is the numerous prevalent cancers of the female reproductive tract in industrialized as well as developing countries and its probability is arising annually. There is a total of approximated 90,000 mortality and 382,000 instances newly cases treated annually globally. The desire to create and define biological markers for the initial stages detection and therapy of uterine cancer is growing. We analyze the current state of biomarker utilization for early detection, including their sensitivity and specificity, paving the way for timely interventions. Several biomarkers, including P53, K-RAS, CA-125, HER2/neu, HE4, PTEN, MSI, ARID1A,Ki-67, microRNAs, DNA aneuploidy, estrogen and progesterone receptors are used for early detection, treatment, and prevention of uterine cancer. Oncogene biomarkers such as VEGF, Hypoxia-inducible factor-1α (HIF-1α), and PI3K-AKT-mTOR signalling pathways plays a crucial roles in cancer progression, offering promising targets for therapeutic intervention and prognostic assessment. Prognostic and emerging biomarkers L1CAM, MMR proteins, CTCs shed form primary tumors into the bloodstream, offer insights into tumour dissemination and treatment response. In conclusion, early detection through all biomarkers holds great promise for early diagnosis and treatment advancements, as well as providing hope for better results and a higher standard of living for individuals in future generations. This review aims to provide a holistic understanding of uterine cancer biology and its clinical implications.

Keywords: Endometrial cancer- Uterine Cancer- P53- VEGF- K-RAS- HE4- L1CAM- Prognostic Biomarker

Asian Pac J Cancer Biol, **9 (2)**, 201-208

Submission Date: 02/22/2024 Acceptance Date: 03/27/2023

Introduction

Uterine malignancy ranks as the fourth most prevalent cause of gynecological cancer-related deaths among women worldwide, resulting in 13,030 deaths anually [1]. Uterine cancer, it is a malignancy highly arising from the endometrium called as endometrial carcinoma [2]. Unusual bleeding from the uterus is the primary cause of the early identification of most uterine malignancies. About 10% of endometrial cancers are caused by an inherited mutations [3]. Endometrioid adenocarcinoma accounting for about 80-90% of cases and uterine sarcoma are rare and aggressive cancer and accounting for only about 1-3% of cases [4]. Uterine cancer appears to become more common in postmenopausal women with substantial hazards, including a higher age, being overweight, metabolic syndromes [2].

Uterine Cancer Frequency: Global Burden and Incidence patterns

According to WHO, a total number of 123,907 estimated cases and 9.1% deaths was reported for 2020 in India [1]. According to the American cancer society's estimates, there will be 65,620 new cases of uterus region tumors in 2020, 12,590 related to fatalities, and 90% of cases will be caused by EC [4]. In 73% of all EC cases, the female patients are elder than 54 years, despite the fact that 75% of cases are detected at stage I. By 2025, there will likely be a 20.3% and 17.4% increase in new cases and deaths, respectively [5].

Corresponding Author:
Dr. N. Deepthi Priya
Krishna Teja Pharmacy College, Tirupathi, Andhra Pradesh, India.
Email: nemalideepthi37@gmail.com

Various uterine cancer indicators were used to identify the early detection of tumors including P53 gene, HER2/neu, (PTEN), CA-125, MSI , HE4, VEGF, microRNAs, (HIF-1α) [6]. Prognostic biomarkers such as L1CAM, CTCs, MMR proteins. These biomarkers play multifaceted roles in uterine cancer by informing prognostic assessments, predicting treatment response, monitoring disease progression and identifying targets [7]. As we conclude, emphasizing its prevalence, and significance of early detection with the help of different biomarkers. By araising awareness, encouraging routine screenings, and supporting ongoing research, to improve diagnosis, treatment options and preventive efforts [8].

Exploring Biomarkers in Uterine Cancer: A Comprehensive Analysis of Diagnostic and Prognostic Indicators

1.Tissue biomarkers:

1.1 P53

It is a cruicial biomarker for uterine cancer. Tumors in the uterus can develop due to unchecked cell development caused by mutations in the P53 gene [9]. P53 gene like the Rb gene (Retinoblastoma protein), and it is a tumour suppressor gene [10]. Nuclear measurement of P53 antigen and P53 gene variants are present in 7-43% of endometrial carcinomas. These characteristics are commonly associated with tumours with lymphatic node distant metastases, profound myometrial spread, higher carcinoma level, advanced phase, and non-endometrioid pathology [6]. P53 controls the differentiation, apoptosis, and the cell cycle [6]. It can identify the presence of p53 mutations or abnormal expression levels and dangerous malignancies which facilitates surgery, prophylactic therapy, and enrollment plannings easier [11]. Based on their p53 mutation status, approximately 15.9% of the individuals have been classified to the highly hazardous category requiring drug therapy and adjuvant radiotherapy substantially increased survival10. It occurs in stages I-II disease [6]. IHC to assess the somatic P53 mutations to diagnose the endometrial biopsies in uterine malignancy.

1.2 PTEN (Phosphatase and Tensin Homolog)

The mutation, which inhibits growth of malignancies and serves as a cruicial biomarker for uterine cancer [12]. The genes PTEN abnormalities was associated with a reduced risk of P53 amplification, the initial stages carcinoma, and prolonged patient life for uterine carcinomas [6]. PTEN role is regulating cell growth, preventing the formation of tumors, and maintaining genomic stability. The patients with wild-type PTEN mutations exhibited significantly better 8-year overall survival who had endometrioid-type endometrial cancer. A carcinoma samples from women with EC that had been preserved in beeswax and used for antigen-antibody were examined for PTEN [6]. Tumor marker PTEN is involved in the pathophysiology of endometrial cancer due to its changes of the P13-AKT activating chain1 [2]. Phase-2 studies for female patients with EC that are invasive or recurrence and evaluated the efficacy of letrozole, erlotinib, and temserolimus respectively [12]. It is advanced or recurrent and occurred stage I-II [6]. These targeted therapies can be tailored to inhibit the abnormal signalling caused by PTEN mutations [13].

2. Protein based biomarkers:

2.1 HER2 (Human Epidermal Growth factor receptor 2)/neu

Approximately 30% of endometrial squamous cancers exhibit high HER2 or neu binding protein and overexpression tests [14]. Neu is a kind of brain tumor that was created from a rodent tumor of the brain gene cell. The HER2 protein may contribute to the growth of cancer cells [15]. Certain cases of uterine serous carcinoma may include HER2 gene amplifications, which may lead to the cancer behaving more aggressively. HER2 testing is used to find advanced or recurrent endometrial malignancies that may respond to drugs that target the HER2 protein [4]. HER2 amplification and overexpression is a predictive biomarker for a poor response to EGFR inhibitor therapy [16]. HER2 positive endometrial serous carcinomas may respond to targeted therapies, such as trastuzumab which specifically target cells with HER2 amplifications [14].

2.2 Estrogen and Progesterone Receptors

Estrogen, if unopposed, can rapidly induce high endometrial and promote the growth of EC [17]. As a precursor of estrogen, progesterone inhibits the levels of the ER, prevents breakdown of cells, and stimulates the growth of cells to PR [17]. Estrogen stimulates epithelial proliferation by binding to its receptors, while progesterone inhibits growth and promotes cell differentiation [18]. Remarkably, women who ovulate and produce progesterone have a significantly lower risk of developing endometrial cancer [18]. These hormones work by controlling the uterine synthesis of certain genomes [19]. The hormonal therapy in EC is additionally related to uterine and PR positive energy [20].

2.3 Ki-67

Ki-67 expression serves as a widely utilized marker for cellular proliferation, and it is increasingly employed in pre-surgical window studies for endometrial cancer as a primary measure of outcome. Its expression is specific to the cell cycle and effectively reflects the level of cell proliferation, making it a valuable tool for evaluating tumour proliferation activity and biological behaviour [13, 19]. Immunohistochemistry allows for the observation of Ki-67 expression. It is considered an indicator of biological aggressiveness and is associated with tumour progression. When combined with the enzyme activity of Cyclin-dependent kinase 4/6 (CDK4/6SA), high CDK4/6SA and high ki-67 expression (>15%) are linked to progression-free survival (PFS) and can serve as independent prognostic factors for individuals with early endometrial cancers who do not require adjuvant therapy based on standard clinicopathological classification [18]. In stages II-IV disease, high CDK4/6SA appears to be associated with a more favourable prognosis and increased

sensitivity to chemotherapy [6, 20].

2.4 ARID1A

ARID1A, or AT-rich interactive domain 1 A, is a gene that has been identified as a potential tumour suppressor gene due to its frequent mutations [6]. This gene codes for a protein involved in chromatin remodelling, which is crucial for regulating gene expression. Mutations or loss of expression in the ARID1A gene have been detected in various cancers, particularly in uterine cancer where alterations are associated with specific subtypes like endometrioid and clear cell carcinomas [6, 13]. These alterations are believed to impact tumour initiation and progression by affecting key cellular processes such as cell cycle regulation, DNA repair, and cell differentiation. A study involving 535 primary endometrial cancers revealed that the loss of ARID1A expression was significantly linked to endometrioid and clear-cell histology, as well as to younger age, lower tumour grade, and diploid cancer cells. Despite its association with deep myometrial invasion, the loss of ARID1A expression did not result in a significant decrease in disease-specific survival [13].

3.Gene based biomarkers:

3.1 K-RAS (Kristen rat sarcoma viral oncogene homolog)

It is a predictive marker linked to numerous cancer detection and therapy [21]. The proto-oncogene k-RAS generates a GTPase it plays a role in the cell signalling system. Genetic variations in the K-RAS gene can result in unregulated growing and are commonly connected to a number of cancers [22]. K-RAS encodes a 21-Kda transmitting molecule that K-RAS expresses connects the MAPK and PI3K/AKT pathways to the stimulated transmembrane reeptor [22]. K-RAS abnormalities occur arise early in the pathway leading to endometrial carcinoma [6]. K-RAS mutations promotes down regulations, increased cell division, and finally cancer. 6% of samples with high endometrial have these K-RAS alterations. K-RAS mutations may response to chemotherapy and a high risk of recurrence [23].

3.2 Microsatellite instability (MSI)

11-45% of endometrioid uterine malignant tumors have MSI, a sign of abnormalities in the repair of mismatched DNA proteins. Five consensus markers are used to perform MSI (BAT genes25, BAT cells26, D2S123, D5S346, and D17S250) [6]. The MSI+ study indicates that aberrant methylation may be the first stage in the formation of the mutator profile during uterus carcinogenesis [24]. Tumor samples immunohistochemical profiling is carried out in NCIC-CGT Trials [6]. It is a predictive biomarker for cancer immunotherapy. A surgical therapy is no effective therapy for individuals suffering from progressed and occurring again EC. 30% of E.C patients (MSI) arises due to DNA mismatch repair gene dysfunction, contributing to the oncogenic mechanism of the disease [25]. This endometrioid endometrial carcinoma detected with MSI and treated with surgery and adjuvant radiotherapy [6, 25].

3.3 MicroRNAs

MicroRNAs, which are small non-coding RNAs, play a significant role in various transcriptional processes, including carcinogenesis [6, 13]. They can be detected in multiple bodily fluids. The expression of 138 miRNAs differs between normal and malignant endometrial tissues [6]. These regulatory RNA molecules have diverse cellular functions and pathological implications. They function by modulating gene expression after transcription, repressing genes, and are crucial in carcinogenesis [13]. They are encoded by genes in the human genome and target approximately 60% of mammalian genes. Specific miRNAs are expressed in different tissues, and their dysregulation has been observed in various diseases and carcinogenesis [13, 22]. In the case of carcinogenesis, they modulate oncogenes and tumour suppressor genes. Some miRNAs exhibit differential expression between different stages of the disease and could potentially be used to distinguish between early and advanced stages. Upregulation of miR-944 and miR-301 has been associated with less than 50% myometrial invasion and improved overall survival in early-stage endometrioid endometrial cancers [6, 24]. On the other hand, miR-149, miR-34b, miR-221, and miR-152 are downregulated in endometrial cancer. These miRNAs have also been identified as biomarkers in various body fluids such as plasma, saliva, breast milk, and urine. However, further validation of these findings in larger cohorts is necessary. Nonetheless, urine microRNAs hold promises as potential biomarkers in gynecological cancers [13, 25].

3.4 DNA aneuploidy

Aneuploidy, characterized by a high number of chromosomes, is a prevalent genetic mutation observed in cancer cells [6, 13]. Mutations in genes responsible for tumor suppression and the absence of mismatch repair genes have been associated with aneuploidy. DNA aneuploidy results from irregularities in cell division regulation and chromosome segregation processes, often caused by mutations in genes controlling the cell cycle, DNA repair mechanisms, and chromosomal stability [13]. The disruption of these processes can lead to the accumulation of cells with abnormal chromosome numbers, contributing to the development and progression of uterine cancer. Aneuploid tumours make up 16-28% of endometrial malignancies and are strongly correlated with lymph node involvement, non-endometrioid histology, high tumor grade, and age at diagnosis. Patients with aneuploid malignancies typically exhibit significantly lower survival rates when considering common clinical and pathological factors [6, 13].

4. Serum Biomarkers:

4.1 CA-125 (Cancer antigen-125)

A blood sample called the Cancer Antigen-125 test is used to measure the amount of the protein cancer antigen-125 within the blood [26]. Cancer Antigen-125 values that are higher than 35 u/ml were recently detected in 11-34% of uterine carcinoma patients6. Elevations of

CA-125 have been associated with endometriosis, uterine fibroids, and other malignancies [26]. Elevated levels CA-125 can also be caused by menstruation and pregnancy [26]. Preoperative serum antigen concentrations are all linked with lymphatic status, cancer grade, phase, depth of myometrial invasion [6]. Numerous research has looked into whether the serum CA-125 assay can give more data to help identify patients who require a lymphadenectomy because they have an elevated risk of developing preclinical extra-uterine distribution. A more accurate diagnostic to differentiate between abnormal uterine bleeding and endometrial carcinoma is CA-125 [19].

4.2 HE4(Human epididymis protein 4)

HE4, an overexpressed glycoprotein in EC patient's serum, and it serves a valuable treatment and outlook biomarker [27]. HE4 is linked with weak predictive indicators, like as phase, myometrial spread, and tumors in lymph nodes, and aiding in treatment decisions and predicting responses to progestin therapy and need adjuvant therapy in early-stage EC [28]. Serum the amount of CA-125 and the protein HE4 have been shown to be analytically effective in identifying uterine cancer and its connected dangerous characteristics in women who have either menstrual signs or a confirmed diagnosis [29]. The study emphasizes its utility in preoperative risk stratification, aiding the determination of individuals at increased risk among those with uncommon endometrioid uterine cancer, potentially guiding the decision for lymphadenectomy [27]. Cancer biomarkers with high efficacy and specificity are essential the accurate detection of recurrent endometrial cancer [30]. The threshold point for EC was 52.40 mmol/L, having an accuracy 57.35% and an affinity of 76.38% [31]. Elevated HE4 levels are consistent across all stages of EC and exhibit higher sensitivity for detecting early-stage cases compared to CA-125 [30].

5. Oncogenes

Oncogenes possess the capacity to expedite the progression of the cell cycle and induce the expression of various factors that promote tumour growth [13, 26]. These proteins undergo significant mutations and are overexpressed in numerous cancer types. Oncogenes originate from proto-oncogenes, which play a crucial role in regulating cell growth and differentiation. These genes play roles in cell growth, proliferation, and differentiation, and their dysregulation can contribute to the development and progression of uterine cancer [13, 20].

5.1 Vascular endothelial growth factor

VEGF, a homodimeric protein with molecular weight of 40-45 kDa, is secreted by a diverse range of cells in both physiological and pathological circumstances [6]. Tumour growth and the formation of metastases heavily rely on angiogenesis. This biological process is modulated by pro-angiogenic and anti-angiogenic factors [6, 13]. VEGF, an essential mitogen for endothelial cells, exerts its effects through specific receptors, namely flt-1 and flk-1/KDR receptors. In endometrial carcinoma, elevated VEGF expression is often linked to advanced tumour stage, high tumour grade, deep myometrial invasion, lymph vascular space involvement and lymph node metastases. Elevated levels of VEGF and other angiogenic markers are connected to reduced survival rates in EmCa [21]. Therapeutic interventions targeting VEGF, such as bevacizumab, hold promise for inhibiting tumour growth in EmCa. VEGF plays a key role in stimulating the formation of new blood vessels from pre-existing ones, providing oxygen and nutrients to the growing tumour. This process facilitates tumour growth, invasion into surrounding tissues, and ultimately metastasis to distant sites [6, 13, 15].

5.2 Hypoxia-inducible factor-1α

HIF-α, also known as hypoxia- inducible factor 1, plays a crucial role in regulating cellular processes in responses to hypoxic conditions. When oxygen levels are low, HIF-α is synthesized and builds up within cells and translocate to the nucleus where it acts as a transcription factor, regulating the expression of genes involved in various processes including angiogenesis, glucose metabolism, cell proliferation, and metastasis [13, 25]. Numerous HIF-1α downstream genes, totalling more than one hundred, have been pinpointed with diverse roles including erythropoiesis/iron metabolism, angiogenesis, vascular tone, matrix and glucose metabolism, cell proliferation/survival, and apoptosis. A study revealed that HIF-α expression was present in close to 49% of EmCa. In uterine cancer, upregulation of HIF-α contributes to tumour progression by promoting angiogenesis, allowing the tumour to obtain the necessary oxygen and nutrients for growth, as well as enhancing metastatic potential [13, 19].

5.3 PI3K-AKT-mTOR signalling pathway

Endometrial carcinoma often exhibits alterations in the PI3K-PTEN-AKT signalling pathway, which is the pathway most frequently affected in this type of cancer [6, 13]. The PTEN-PIK3-mammalian target of rapamycin [mTOR] signalling pathway is involved in the control of various biological functions such as cell growth, proliferation, apoptosis, and angiogenesis. Changes in this pathway are prevalent in endometrioid endometrial carcinoma [13]. The PTEN gene product acts as a lipid phosphatase, eliminating phosphate groups from key intracellular phospho-inositide signalling molecules, thereby inhibiting the activity of the PI3K-AKT-mTOR pathway [5, 6]. The malfunction of PTEN results in an excessive activation of this pathway. Alterations in these pathways are commonly seen in endometrioid endometrial cancer, with about 80% of cases showing these changes. In endometrial cancer, the most prevalent mutations involve the PIK3CA gene, with PTEN mutations present in 24-36% of cases and associated with a poor prognosis. The identification of mTOR, a serine/threonine kinase, as a promising target for cancer treatment has arisen from pharmacological research aimed at exploring the effects of the natural antibiotic rapamycin, known for its

immunosuppressive and anti-cancer properties6,13,18.

6. Empowering Early Detection: Unveiling Current and Emerging Prognostic Biomarkers in Uterine Cancer Research

6.1 L1 cell adhesion molecule (L1CAM)

L1CAM transcription was a significant predictive indicator in early-phase EECs, but lower in advanced-stage EECs and NEECs [32]. Aggressive uterine malignancies are linked to elevated L1CAM protein with a higher chance of recurrence [32, 33]. Cell membrane protein L1CAM is a member of the antibody (Ig) supergene group and is found in 200-220KDA [33]. The cellular adhesive a compound is vital for the growth of the central nervous system, as well as for neural movement and invasion of tumor cells [33]. In various malignancies, including endometrial cancer, increased L1CAM levels in cancerous cells speeds up the course of many malignancies, including endometrial cancer, by improving mobility of cells, spread, and metastasis [33, 34]. Recent studies have identified L1CAM positivity in 7-18% of early-stage endometrial cancers, indicating an increased chance of cancer relapse within a little -risk patient group [34]. L1CAM protein has been linked to stage 3 histology tests, non-endometrioid histopathology, nodular illness, and an increased likelihood of metastatic tumor growth. This has the potential to improve surgical choice of elevated risk malignancies and their response to adjuvant chemotherapy in clinical practice [34]. In the L1CAM plus category, 50% of recurrent illness occurred as isolated in uterine recurrences, while the other 50% resulted in distant metastasis and 1% of L1CAM negative group [33, 34].

6.2 Mismatch Repair Proteins (MLH1, MSH2, MSH6, PMS2)

Approximately 20-30% of individuals with tumours of the uterus, exhibit imperfect MMR technique in their tumors, with research relying on hysterectomy samples, while clinical diagnostics typically utilize preoperative biopsies [35]. Faulty MMR-induced higher frequency of mutations raises the chances that a tumor inhibitor change may become ineffective and cause cancer [36]. Damage to the MMR system, which removes genetic abnormalities created during differentiation of cells, causes MSI, which is characterized by a build-up of incorrect matches in repeated patterns, leading to hypermutated tumors [36, 37]. The immunoassay examination of MMR molecules (MLH1, MSH2, MSH6) any defects may be evaluated with PCR-based MSI assays [37, 38].

Does the response to adjuvant treatment in uterine cancer depend on the MMR status?

When additional treatment is administered to women with MMR-deficient uterine malignancies, the chance of recurrence rate declines than that of women with MMR-proficient tumors. The MMR status is no longer linked to variations in advancement in progression-free survival or overall survival on multivariable analysis [37].

6.3 CTCs (circulating Tumor Cells)

The existence of circulating malignant cells in the bloodstream has been studied in a potentially non-invasive biomarker for cancer prognosis and predicting therapeutic response, including in uterine cancer [39, 40]. They detect both genetic and epigenetic mutations [13]. According to following surgery unhealthy outcomes, individuals with a prior identification of dangerous EC were further separated into two groups: high-intermediate probability (grade2-3, endometrioid, myometrial spread, and phase I-II) and highly hazardous (grade 3, non-endometrioid, myometrial damage in phase III-IV). In examining highly hazardous EC individuals, the evaluation of CTCs is important because preliminary uterine cancer people who have identifiable CTCs may benefit from further adjunct treatments [39,40].

7. Future Prospects of Biomarkers in Uterine cancer:

Revolutionizing Early Detection and Personalized Therapies.

7.1 Liquid Biopsies

The ability of Blood-based biomarkers, which include tumor cells in circulation (CTCs) along with circulation tumor genomes (ctDNA), to identify tumors in uterine cancer is being researched at an early stage and monitor treatment response more effectively than present methods [41, 42]. These non-invasive tests involve the anlysis of various biomarkers, such as circulating tumor DNA (ctDNA), and microRNAs, in bodily fluids like blood or urine [42]. Liquid biopsies may detect tumor-specific molecular alterations in blood samples before clinical symptoms manifest, enabling earlier diagnosis and intervention. Liquid biopsies may help identify residual disease or recurrence after primary treatment, allowing for prompt intervention and surveillance [41].

7.2 Genomic and Proteomic Profiling

Advances in genomic and proteomic technologies allow for comprehensive analysis of tumors. Identifying specific genetic mutations, epigenetic changes, and protein markers can aid in personalized treatments strategies and targeted therapies [43]. Genomic profiling involves analysing the genetic alterations, such as mutations, chromosomal rearrangements, present in the tumours DNA. Genomic profiling can identify mutations in genes like PTEN, TP53, PIK3CA, and CTNNB1 which can inform prognosis and treatment. Proteomic profiling examines the expression levels and modifications of proteins within the tumor tissue or body fluids [41, 44]. Proteomic analysis may reveal overexpression or activation of proteins like HER2/neu oestrogen and Progesterone receptor [40, 45].

7.3 Metabolomic Markers

Metabolomic profiling can reveal unique metabolic signatures associated with uterine cancer. Analysing metabolites in tissues or body fluids may offer valuable diagnostic and prognostic information [41, 44]. Alterations

in lipid metabolism, such as changes in fatty acid composition or lipid signalling molecules, have been associated with uterine cancer development and progression. Dysregulation of energy metabolism pathways, such as glycolysis, tricarboxylic acid (TCA) cycle, and oxidative phosphorylation, is common in cancer cells. Abnormalities in nucleotide metabolism, including purine and pyrimidine biosynthesis pathways, can influence cancer cell proliferation and DNA synthesis [41, 45, 46].

7.4 Exosomal Biomarkers

Exosomes are small vesicles released by cancer cells containing biomolecules. Analysing exosomal content, including proteins, nucleic acids, and lipids, can provide information about tumor progression, metastasis, and drug resistance [41, 47, 48]. Exosomes play a role in cell-to-cell communication and can carry various biomolecules, including proteins, nucleic acids (such as DNA, RNA, and microRNAs), lipids, and metabolites [41, 49].

In conclusion, Biomarkers including p53, PTEN, HER2, Ki-67, kras, MSI, VEGF and HE4 collectively offer a comprehensive profile for diagnosing and monitoring uterine cancers. These biomarkers provide valuable insights into tumor characteristics, molecular pathways, and prognosis, aiding in personalized treatment strategies and improving patient outcomes. The emerging biomarkers L1CAM, MMR proteins and CTCs integrating into clinical practice holds potential for improving early detection, risk stratification, and therapeutic decision-making in uterine cancers. These advancements signify a research and personalized medicine in the battle against this disease.

Acknowledgments

Statement of Transparency and Principals:

• Author declares no conflict of interest

• Study was approved by Research Ethic Committee of author affiliated Institute .

• Study's data is available upon a reasonable request.

• All authors have contributed to implementation of this research.

References

1. Leslie KK, Thiel KW, Goodheart MJ, De Geest K, Jia Y, Yang S. Endometrial cancer. Obstetrics and Gynecology Clinics of North America. 2012 06;39(2):255-268. https://doi.org/10.1016/j.ogc.2012.04.001
2. Boeckstaens S, Dewalheyns S, Heremans R, Vikram R, Timmerman D, Van den Bosch T, Verbakel JY. Signs and symptoms associated with uterine cancer in pre- and postmenopausal women. Heliyon. 2020 Nov;6(11):e05372. https://doi.org/10.1016/j.heliyon.2020.e05372
3. Gu B, Shang X, Yan M, Li X, Wang W, Wang Q, Zhang C. Variations in incidence and mortality rates of endometrial cancer at the global, regional, and national levels, 1990-2019. Gynecologic Oncology. 2021 05;161(2):573-580. https://doi.org/10.1016/j.ygyno.2021.01.036
4. Socha MW, Malinowski B, Puk O, Wartęga M, Bernard P, Nowaczyk M, Wolski B, Wiciński M. C-reactive protein as a diagnostic and prognostic factor of endometrial cancer. Critical Reviews in Oncology/Hematology. 2021 08;164:103419. https://doi.org/10.1016/j.critrevonc.2021.103419
5. Coll-de la Rubia E, Martinez-Garcia E, Dittmar G, Gil-Moreno A, Cabrera S, Colas E. Prognostic Biomarkers in Endometrial Cancer: A Systematic Review and Meta-Analysis. Journal of Clinical Medicine. 2020 06 17;9(6):1900. https://doi.org/10.3390/jcm9061900
6. Gadducci A, Cosio S, Genazzani AR. Tissue and serum biomarkers as prognostic variables in endometrioid-type endometrial cancer. Critical Reviews in Oncology/Hematology. 2011 Nov;80(2):181-192. https://doi.org/10.1016/j.critrevonc.2010.11.005
7. Degez M, Caillon H, Chauviré-Drouard A, Leroy M, Lair D, Winer N, Thubert T, Dochez V. Endometrial cancer: A systematic review of HE4, REM and REM-B. Clinica Chimica Acta; International Journal of Clinical Chemistry. 2021 04;515:27-36. https://doi.org/10.1016/j.cca.2020.12.029
8. Kozar N, Kruusmaa K, Dovnik A, Bitenc M, Argamasilla R, Adsuar A, Goswami N, Takač I, Arko D. Identification of novel diagnostic biomarkers in endometrial cancer using targeted metabolomic profiling. Advances in Medical Sciences. 2021 03;66(1):46-51. https://doi.org/10.1016/j.advms.2020.12.001
9. Banno K, Kisu I, Tominaga M, Masuda K, Nomura K, Ueki A, et al. Biomarkers in endometrial cancer: Possible clinical applications (Review). Oncology Letters. 2012 06;3(6):1175-1180. https://doi.org/10.3892/ol.2012.654
10. Tashiro H, Isacson C, Levine R, Kurman RJ, Cho KR, Hedrick L. p53 gene mutations are common in uterine serous carcinoma and occur early in their pathogenesis. The American Journal of Pathology. 1997 01;150(1):177-185.
11. Tresa A, Sambasivan S, Rema P, Dinesh D, Sivaranjith J, Nair SP, Mathew A, Ammu JV, Kumar A. Clinical Profile and Survival Outcome of Endometrial Cancer with p53 Mutation. Indian Journal of Surgical Oncology. 2022 09;13(3):580-586. https://doi.org/10.1007/s13193-022-01523-9
12. Djordjevic B, Hennessy BT, Li J, Barkoh BA, Luthra R, Mills GB, Broaddus RR. Clinical assessment of PTEN loss in endometrial carcinoma: immunohistochemistry outperforms gene sequencing. Modern Pathology: An Official Journal of the United States and Canadian Academy of Pathology, Inc. 2012 05;25(5):699-708. https://doi.org/10.1038/modpathol.2011.208
13. Hutt S, Tailor A, Ellis P, Michael A, Butler-Manuel S, Chatterjee J. The role of biomarkers in endometrial cancer and hyperplasia: a literature review. Acta Oncologica (Stockholm, Sweden). 2019 03;58(3):342-352. https://doi.org/10.1080/0284186X.2018.1540886
14. Alrhmoun S, Sennikov S. The Role of Tumor-Associated Antigen HER2/neu in Tumor Development and the Different Approaches for Using It in Treatment: Many Choices and Future Directions. Cancers. 2022 Dec 14;14(24):6173. https://doi.org/10.3390/cancers14246173
15. Zhao D, Wang L, Chen Z, Zhang L, Xu L. KRAS is a prognostic biomarker associated with diagnosis and treatment in multiple cancers. Frontiers in Genetics. 2022 Oct 18;13:1024920. https://doi.org/10.3389/fgene.2022.1024920
16. Sideris M, Emin EI, Abdullah Z, Hanrahan J, Stefatou KM, Sevas V, Emin E, et al. The Role of KRAS in Endometrial Cancer: A Mini-Review. Anticancer Research. 2019 02;39(2):533-539. https://doi.org/10.21873/anticanres.13145
17. Wang C, Tran DA, Fu MZ, Chen W, Fu SW, Li X. Estrogen Receptor, Progesterone Receptor, and HER2 Receptor Markers in Endometrial Cancer. Journal of Cancer. 2020 01 16;11(7):1693-1701. https://doi.org/10.7150/jca.41943

18. Sinreih M, Knific T, Thomas P, Frković Grazio S, Rižner TL. Membrane progesterone receptors β and γ have potential as prognostic biomarkers of endometrial cancer. The Journal of Steroid Biochemistry and Molecular Biology. 2018 04;178:303-311. https://doi.org/10.1016/j.jsbmb.2018.01.011
19. Zengin T, Çakir A. Tumor Markers in Endometrial Cancer. Current Obstetrics and Gynecology Reports. 2020 03 01;9. https://doi.org/10.1007/s13669-020-00279-9
20. Shen F, Gao Y, Ding J, Chen Q. Is the positivity of estrogen receptor or progesterone receptor different between type 1 and type 2 endometrial cancer?. Oncotarget. 2016 Nov 19;8(1):506-511. https://doi.org/10.18632/oncotarget.13471
21. Yang Y, Sang Z, Ma J, Zhu Y, Wu S. KRAS, YWHAE, SP1 and MSRA as biomarkers in endometrial cancer. Translational Cancer Research. 2021 03;10(3):1295-1312. https://doi.org/10.21037/tcr-20-2969
22. Jančík S, Drábek J, Radzioch D, Hajdúch M. Clinical Relevance of KRAS in Human Cancers. Journal of Biomedicine and Biotechnology. 2010;2010:150960. https://doi.org/10.1155/2010/150960
23. Rachmawati M, Yulianti H, Hernowo BS, Suryanti S, Wijaya I, Rahadiani N, Heriyanto DS, Irianiwati I. The Correlation of KRAS Gene Expression and P53 Immunoexpression in Colorectal Adenocarcinoma. Open Access Macedonian Journal of Medical Sciences. 2019 06 30;7(12):1940-1945. https://doi.org/10.3889/oamjms.2019.549
24. Li K, Luo H, Huang L, Luo H, Zhu X. Microsatellite instability: A review of what the oncologist should know. Cancer Cell International. 2020 01 13;20. https://doi.org/10.1186/s12935-019-1091-8
25. Kunitomi H, Banno K, Yanokura M, Takeda T, Iijima M, Nakamura K, Iida M, et al. New use of microsatellite instability analysis in endometrial cancer. Oncology Letters. 2017 09;14(3):3297-3301. https://doi.org/10.3892/ol.2017.6640
26. Nithin KU, Sridhar MG, Srilatha K, Habebullah S. CA 125 is a better marker to differentiate endometrial cancer and abnormal uterine bleeding. African Health Sciences. 2018 Dec;18(4):972-978. https://doi.org/10.4314/ahs.v18i4.17
27. Mutz-Dehbalaie I, Egle D, Fessler S, Hubalek M, Fiegl H, Marth C, Widschwendter A. HE4 is an independent prognostic marker in endometrial cancer patients. Gynecologic Oncology. 2012 08;126(2):186-191. https://doi.org/10.1016/j.ygyno.2012.04.022
28. Brennan DJ, Hackethal A, Metcalf AM, Coward J, Ferguson K, Oehler MK, Quinn MA, et al. Serum HE4 as a prognostic marker in endometrial cancer--a population based study. Gynecologic Oncology. 2014 01;132(1):159-165. https://doi.org/10.1016/j.ygyno.2013.10.036
29. Moore RG, Brown AK, Miller MC, Badgwell D, Lu Z, Allard WJ, Granai CO, Bast RC, Lu K. Utility of a novel serum tumor biomarker HE4 in patients with endometrioid adenocarcinoma of the uterus. Gynecologic Oncology. 2008 08;110(2):196-201. https://doi.org/10.1016/j.ygyno.2008.04.002
30. Simmons AR, Baggerly K, Bast RC. The emerging role of HE4 in the evaluation of epithelial ovarian and endometrial carcinomas. Oncology (Williston Park, N.Y.). 2013 06;27(6):548-556. https://doi.org/5555
31. Liu J, Han L, Jiao Z. The diagnostic value of human epididymis protein 4 for endometrial cancer is moderate. Scientific Reports. 2021 01 12;11(1):575. https://doi.org/10.1038/s41598-020-79960-1
32. Smogeli E, Davidson B, Cvancarova M, Holth A, Katz B, Risberg B, Kristensen G, Lindemann K. L1CAM as a prognostic marker in stage I endometrial cancer: a validation study. BMC Cancer. 2016 08 04;16:596. https://doi.org/10.1186/s12885-016-2631-4
33. Putten LJ, Visser NC, Vijver K, Santacana M, Bronsert P, Bulten J, Hirschfeld M, et al. L1CAM expression in endometrial carcinomas: an ENITEC collaboration study. British Journal of Cancer. 2016 09 06;115(6):716-724. https://doi.org/10.1038/bjc.2016.235
34. Van Gool IC, Stelloo E, Nout RA, Nijman HW, Edmondson RJ, Church DN, MacKay HJ, et al. Prognostic significance of L1CAM expression and its association with mutant p53 expression in high-risk endometrial cancer. Modern Pathology: An Official Journal of the United States and Canadian Academy of Pathology, Inc. 2016 02;29(2):174-181. https://doi.org/10.1038/modpathol.2015.147
35. Fountzilas E, Kotoula V, Pentheroudakis G, Manousou K, Polychronidou G, Vrettou E, Poulios C, et al. Prognostic implications of mismatch repair deficiency in patients with nonmetastatic colorectal and endometrial cancer. ESMO open. 2019;4(2):e000474. https://doi.org/10.1136/esmoopen-2018-000474
36. Kim SR, Pina A, Albert A, McAlpine J, Wolber R, Blake Gilks C, Kwon JS. Does MMR status in endometrial cancer influence response to adjuvant therapy?. Gynecologic Oncology. 2018 Oct;151(1):76-81. https://doi.org/10.1016/j.ygyno.2018.08.020
37. Loukovaara M, Pasanen A, Bützow R. Mismatch Repair Deficiency as a Predictive and Prognostic Biomarker in Molecularly Classified Endometrial Carcinoma. Cancers. 2021 06 22;13(13):3124. https://doi.org/10.3390/cancers13133124
38. Berg HF, Engerud H, Myrvold M, Lien HE, Hjelmeland ME, Halle MK, Woie K, et al. Mismatch repair markers in preoperative and operative endometrial cancer samples; expression concordance and prognostic value. British Journal of Cancer. 2023 02;128(4):647-655. https://doi.org/10.1038/s41416-022-02063-3
39. Long Q, Peng Y, Tang Z, Wu C. Role of endometrial cancer abnormal MMR protein in screening Lynch-syndrome families. International Journal of Clinical and Experimental Pathology. 2014;7(10):7297-7303.
40. Barwick TD, Rockall AG, Barton DP, Sohaib SA. Imaging of endometrial adenocarcinoma. Clinical Radiology. 2006 07;61(7):545-555. https://doi.org/10.1016/j.crad.2006.03.011
41. Łukasiewicz M, Pastuszak K, Łapińska-Szumczyk S, Różański R, In 't Veld S, Bieńkowski M, Stokowy T, et al. Diagnostic Accuracy of Liquid Biopsy in Endometrial Cancer. Cancers. 2021 Nov 16;13:5731. https://doi.org/10.3390/cancers13225731
42. Habermann JK, Bündgen NK, Gemoll T, Hautaniemi S, Lundgren C, Wangsa D, Doering J, et al. Genomic instability influences the transcriptome and proteome in endometrial cancer subtypes. Molecular Cancer. 2011 Oct 31;10:132. https://doi.org/10.1186/1476-4598-10-132
43. Yang X, Wang J. The Role of Metabolic Syndrome in Endometrial Cancer: A Review. Frontiers in Oncology. 2019;9:744. https://doi.org/10.3389/fonc.2019.00744
44. Makler A, Asghar W. Exosomal biomarkers for cancer diagnosis and patient monitoring. Expert Review of Molecular Diagnostics. 2020 04;20(4):387-400. https://doi.org/10.1080/14737159.2020.1731308
45. Ni T, Sun X, Shan B, Wang J, Liu Y, Gu S, Wang Y. Detection of circulating tumour cells may add value in endometrial cancer management. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 2016 Dec;207:1-4. https://doi.org/10.1016/j.ejogrb.2016.09.031

46. Denschlag D, Ulrich U, Emons G. The diagnosis and treatment of endometrial cancer: progress and controversies. Deutsches Arzteblatt International. 2010 08;108(34-35):571-577. https://doi.org/10.3238/arztebl.2011.0571
47. Braun MM, Overbeek-Wager EA, Grumbo RJ. Diagnosis and Management of Endometrial Cancer. American Family Physician. 2016 03 15;93(6):468-474.
48. Shen Y, Yang W, Liu J, Zhang Y. Minimally invasive approaches for the early detection of endometrial cancer. Molecular Cancer. 2023 03 17;22:53. https://doi.org/10.1186/s12943-023-01757-3
49. Bipat S, Glas AS, Velden J, Zwinderman AH, Bossuyt PMM, Stoker J. Computed tomography and magnetic resonance imaging in staging of uterine cervical carcinoma: a systematic review. Gynecologic Oncology. 2003 Oct;91(1):59-66. https://doi.org/10.1016/s0090-8258(03)00409-8