Review article

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Biomarker panel for early detection in uterine cancer: a review

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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 are used for early detection, treatment, and prevention of uterine cancer. Prognostic biomarkers in uterine cancer have emerged as indispensable tools for predicting disease progression and patient outcomes. Endometrial biopsy, CT scan, MRI Scan, Dilation and Curettage, Transvaginal ultrasound are vital for diagnosing and staging of uterine cancer and provide essential information about the cancer's presence, size, and spread, guiding proper treatment decisions. Various treatments modalities, including surgery, Chemotherapy, targeted therapies are examined. In conclusion, early detection through biomarkers like P53, K-RAS, HER2/neu, PTEN, Serum CA-125 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.

Keywords: Endometrial cancer, Uterine Cancer, P53, PTEN, K-RAS, HE4, Prognostic Biomarker, Early diagnosis.

INTRODUCTION:

Uterine malignancy is the most frequently detected the gynecological malignancy in worldwide[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. Post menopausal women are highly affected this this type of cancer[2]. 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. Clear cell carcinoma and papillary serous carcinomas these types of cancers are occurred very less common and more aggressive. The two main signs for all uterine malignancies have been shown to include abnormal bleeding and lower abdominal pain. Uterine cancer appears to become more common in postmenopausal women with substantial hazards, including a higher age, being overweight, metabolic syndromes[2]. 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]. EC mortality has been rising, in contrast to many other cancers. 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]. Various uterine cancer indicators were discovered, which involves genetic variations in the P53 gene, HER2/neu, phosphatase and tensin homolog (PTEN), CA-125, MSI (Microsatellite instability), HE4. Biomarker tests may be used to select specific treatments and diagnose to the patients[6]. HE4 as a predictive indicator, and it appears to function as a helpful instrument for EC prognostic determination[7]. Due to its low response, Carbohydrate antigen (CA)-125 isn't a useful marker for the detection of carcinoma of the endometrium. It is elevated in only 24.6% of patients and in only 10% of instances in the initial stages (I and II) cases[7]. The combination of MR imaging with intraoperative hysteroscopic testing has produced results in terms of both efficacy and specificity for detecting risk-free illness[8]. 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.

"EXPLORING BIOMARKERS IN UTERINE CANCER: A COMPREHENSIVE ANALYSIS OF DIAGNOSTIC AND PROGNOSTIC INDICATORS"

Tissue biomarkers:

- 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[11].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[10]. 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 survival[10]. It occurs in stages I-II disease[6]. IHC to assess the somatic P53 mutations to diagnose the endometrial biopsies in uterine malignancy.
- 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 chain[12]. 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].

Protein based biomarkers:

➢ 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].

➢ 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].

Gene based biomarkers:

➢ 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].

➢ 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].

Serum Biomarkers:

➢ 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 patients[6]. 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[27].

➢ HE4(Human epididymis protein 4): HE4, an overexpressed glycoprotein in EC patient's serum, and it serves a valuable treatment and outlook biomarker[32]. 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[30]. Cancer biomarkers with high efficacy and specificity are essential the accurate detection of recurrent endometrial cancer[31]. The threshold point for EC was 52.40 mmol/L, having an accuracy 57.35% and an affinity of 76.38%[33]. Elevated HE4 levels are consistent across all stages of EC and exhibit higher sensitivity for detecting early-stage cases compared to CA-125[31].

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

➢ L1 cell adhesion molecule (L1CAM): L1CAM transcription was a significant predictive indicator in early-phase EECs, but lower in advanced-stage EECs and NEECs[34]. Aggressive uterine malignancies are linked to elevated L1CAM protein with a higher chance of recurrence[34,35]. Cell membrane protein L1CAM is a member of the antibody (Ig) supergene group and is found in 200-220KDA[35]. 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[35]. 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[36,35]. 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[36]. 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[36]. 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[35,36].

➢ 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[37]. Faulty MMR-induced higher frequency of mutations raises the chances that a tumor inhibitor change may become ineffective and cause cancer[38]. 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[39,38]. The immunoassay examination of MMR molecules (MLH1, MSH2, MSH6) any defects may be evaluated with PCR-based MSI assays[39,40].

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[39].

➢ 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[41,42]. 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.[41,42].

"Advances in Early detection and diagnosis in uterine cancer: A comprehensive review".

They are different assays used for determining the presence of endometrial cancer. When deciding on a diagnostic test, your doctor may consider these factors[44]:

- The diagnosed kind of malignancy.
- Your illness and indicators.
- Your overall quality of life and aging.
- The outcomes of earlier medical examinations[44].

➢ Pelvic Examination: A living test of the pelvis to

check for any abnormalities[43,45]. It is a common part of the diagnostic process for uterine cancer. During the examination, a healthcare provider will visually and manually examine the pelvic area, including the uterus to confirm the cancer[43,44]. A pelvic examination and pap test are often ordered together with the main objective of the test being to check for cervical carcinoma. Sometimes, a smear tests may occasionally reveal aberrant gland cells, which are the result of tumors in the uterus. [44,45].

- Endometrial Biopsy: It is a cruicial diagnostic procedure when uterine cancer is suspected[44,53]. In order to check for the existence of cancer cells, a tiny amount of living tissue from the inner layer of the uterus had to be taken. Using an extremely fine tube, the physician removes a tiny number of tissues to perform a uterine sampling[44,45]. After inserting the pipe into the vagina to reach the endometrium by the lining of the cervix, the tissue is suctioned out[45,44]. It just takes a few minutes only. After that patients experience cramping and bleeding from the vagina. Diagnosing uterine cancer can often be done with high accuracy via endometrial biopsy[43,44].
- Dilation and curettage: It is a medical procedure that involves dilating the cervix and scrapping tissue away the lining of the uterus, which is analysed for cancer cells[43,46]. A thin, flexible tube with a light attached is inserted by the doctor into the cervical cavity and into the genital area and uterine, during a hysteroscopy. Following the removal of uterine tissue, while dilation and curettage[44,46]. It helps to determine the extent of cancer within the uterus[43,44].

Imaging Tests:

- Transvaginal Ultrasound: It is a valuable tool in the diagnosis and staging of uterine cancer[46]. It uses sound waves to create images of the uterus, helping to detect tumors. It allows healthcare providers to assess the thickness of the uterine lining & detect abnormalities such as tumours[44,46]. Additionally, it can help determine the extent of cancer within the uterus[43,45].
- Computed Tomography (CT) Scan: CT scan is commonly used in the evaluation of uterine cancer. A computed tomography (CT) test uses X-ray radiation taken at multiple directions to create images of the inner part of the body. angles[44,47]. They provide detailed cross-sectional images of the pelvis and abdomen that shows any abnormalities or tumors[43,47]. It can be used to measure the tumour's size[44].
- Magnetic resonance imaging (MRI): MRI yields highly refined pictures of the pelvis and abdomen without using ionizing radiation, by using magnetic fields and making it particularly valuable for certain aspects of uterine cancer diagnosis and staging[44,47].

Comprehensive Strategies for Uterine Cancer Care: Treatment and Management:

How is uterine cancer treated?

The majority of endometrial cancer patients require surgery. your particular treatment plan depends on the type of cancer and your general health[43].

Surgery: It is usually the primary treatment for endometrial cancer[43]. It involves major surgery is Hysterectomy, it means a surgical operation to remove all or part of the uterus[43]. They are four types of hysterectomy procedures.

Did Patients experience any side effects after undergoing uterine cancer treatment?

Yes, patients are mostly affected infertility, not being able to pregnant. Additionally, if the surgery involves removing ovaries in premenopausal women, it can trigger early menopause with symptoms like vaginal dryness and night sweats[43].

- Chemotherapy: some powerful drugs are used to destroy the cancer cells[43]. The most combinations of drugs include carboplatin/paclitaxel and cisplatin or doxorubicin may be used. sometimes caused side effects like nausea, fatigue[48].
- Radiation therapy: Which sends X-ray radiation or another extremely strong radiation beams to destroy malignant cells[43,49]. Interior radiation treatment, also known as brachytherapy treatment, involves injecting harmful substances into the human body. By utilizing a device, a type of similar to an x-Ray, concentrates radiation beams at the tumour is called as external beam radiation therapy[49].
- Hormone therapy: In this therapy Which gives hormones or blocks them to treat cancer[43]. The mostly commonly used progesterone hormone to treat stage 3 and 4 womb cancers[50].
- Immunotherapy: By adding immunotherapy to standard treatment for advanced endometrial cancer, to fight cancer and improve progression -free survival[51]. Some common side effects are occurred, include fatigue, rash, itching, diarrhoea[52].
- Targeted therapy: Which targets particular cancer cells with medications to prevent them for multiplying[43]. Larotrectinib and entrectinib are drugs to target

the TRK protein. These types of drugs are used to treat recurrent uterine sarcomas with NTRK gene changes[53].

Current Use and Future Prospects of Specific Biomarkers in Uterine Cancer Research:

Current Use of Biomarkers in Uterine Cancer: Enhancing Diagnosis and Treatment Strategies.

1. Estrogen Receptor (ER) and Progesterone Receptor (PR): These hormone receptors are often tested to determine if the cancer is hormone receptor-positive, which can influence treatment decisions[17,19].
2. HER2/neu expression: Human epidermal proliferation Factor Receptor 2 (HER2) its significant in uterine serous carcinoma[6,15]. Tumor cell growth may be aided by the protein HER2[16]. In some carcinoma cases HER2 gene[6]. Amplifications or overexpression causes the cancer more aggressively[14].
3. P53: P53 protein is expressed by the Tp53 genome, and variants in this gene are frequently seen in uterine malignancies among other cancers[6,9]. P53 testing can help predict prognosis and guide treatment choices[11].
4. Mismatch Repair (MMR) proteins: Deficiencies in MMR peptides, including MSH2, MSH6, and PSM2, can lead to microsatellite instability (MSI), which is found in some uterine cancers[38,39]. Testing for MMR protein expression or MSI helps identify patients who may benefit from immunotherapy[6].
5. Cancer Antigen 125 (CA-125): Increased quantities of CA-125 levels were found in uterine cancer. It is used for monitoring disease progression and recurrence[6].

Future Prospects of Biomarkers in Uterine cancer:

Revolutionizing Early Detection and Personalized Therapies.

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[54,55].
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[56].
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[57].
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[58].

Conclusion:

The most prevalent gynecological uterine cancer it is affected highly in a nowadays, biomarkers have revolutionized the diagnosis and treatment of uterine cancer, enabling early detection, personalized therapies, and improved outcomes. Ongoing research continues to enhance our understanding, offering the prospect of even more precise and effective approaches in the future. These advancements signify a research and personalized medicine in the battle against this disease.

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