Clinicopathological Determinants of Prognosis and Survival in Uterine Cancer: A Comprehensive Review

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Abstract

Background: Uterine cancer represents the most common gynecologic malignancy in developed countries, with incidence rates steadily rising due to increased obesity, metabolic disorders, and aging populations. Despite advancements in diagnostic and therapeutic modalities, survival outcomes remain variable, largely influenced by a range of clinicopathological determinants. This review explores the critical clinicopathological factors influencing prognosis and survival in uterine cancer, integrating traditional histopathological and staging parameters with emerging molecular classifications.

The review examines classical prognostic indicators, including FIGO stage, histologic subtype, grade, depth of myometrial invasion, and lymphovascular space invasion (LVSI), all of which remain fundamental determinants of recurrence and survival. Furthermore, molecular and genetic insights—such as mutations in PTEN, TP53, and POLE, along with mismatch repair (MMR) deficiencies—have revolutionized risk stratification and therapeutic approaches. Hormone receptor expression, particularly of estrogen and progesterone receptors, continues to provide valuable prognostic and therapeutic guidance. Additionally, patient-related factors such as age, obesity, diabetes, and comorbidities modulate outcomes, emphasizing the need for individualized risk assessment.

By integrating molecular features with traditional pathological parameters, precision prognostication and tailored therapeutic decision-making are becoming increasingly feasible. The review highlights the significance of combining clinicopathological data with genomic profiling to refine treatment algorithms and improve survival outcomes. Ultimately, understanding the interplay of these factors supports personalized management strategies, reduces recurrence risk, and optimizes long-term survival for patients with uterine cancer.

Keywords: *uterine cancer, clinicopathological factors, prognosis, survival, molecular classification, endometrial carcinoma.*

Introduction

Uterine cancer, encompassing primarily endometrial carcinoma, constitutes a major public health concern due to its increasing incidence worldwide. The global burden is estimated to exceed 400,000 new cases annually, with a substantial proportion occurring in postmenopausal women. The disease demonstrates marked heterogeneity in clinical behavior and treatment response, largely driven by underlying clinicopathological and molecular differences. Despite improved surgical and adjuvant treatment strategies, recurrence and mortality remain significant challenges in high-risk subgroups [1].

Traditional prognostic evaluation has long relied on clinicopathological features such as tumor stage, grade, histological subtype, depth of myometrial invasion, and lymphovascular invasion. However, these parameters alone often fail to capture the biological complexity of uterine cancers. Recent molecular classifications, particularly those derived from The Cancer Genome Atlas (TCGA), have provided novel insights into tumor biology, offering opportunities for more accurate prognostication and therapeutic stratification [2].

The aim of this review is to comprehensively analyze the clinicopathological determinants influencing prognosis and survival in uterine cancer, integrating classical and molecular perspectives. The research gap addressed here is the limited integration of traditional histopathologic features with emerging molecular markers in clinical prognostication. By bridging this gap, this review provides an updated synthesis of evidence to enhance risk assessment, guide individualized treatment, and improve patient outcomes [3].

1. Epidemiology and Global Burden of Uterine Cancer

Uterine cancer is the sixth most commonly diagnosed malignancy in women globally, with substantial geographic variability in incidence and mortality rates. The highest rates are observed in North America and Europe, correlating with the prevalence of obesity, diabetes, and low parity. The disease predominantly affects postmenopausal women, with a median age at diagnosis of approximately 60 years. However, an increasing number of cases are being reported among younger women, partly attributed to lifestyle changes and rising metabolic risk factors [4]. Mortality disparities persist, particularly among racial and socioeconomic groups, emphasizing the need for equitable prevention and management strategies [5].

Clinicopathological Classification of Uterine Cancer

Uterine cancers are broadly classified into two major types according to Bokhman's dualistic model. Type I tumors, comprising endometrioid histology, are typically estrogen-dependent, low-grade, and associated with a favorable prognosis. Type II tumors, including serous and clear cell carcinomas, are estrogen-independent, high-grade, and exhibit aggressive clinical behavior [6]. Although this classification remains clinically useful, it oversimplifies the molecular and biological diversity within uterine tumors. Subsequent refinements incorporating molecular markers have demonstrated significant overlap between these categories, underscoring the need for integrated diagnostic models [7].

[6][7]

Histopathological Subtypes and Grading Systems

Histopathological subtype and grade are among the most powerful determinants of outcome in uterine cancer. Endometrioid carcinomas account for approximately 80% of cases and generally exhibit a more favorable prognosis compared to non-endometrioid subtypes such as serous, clear cell, and carcinosarcoma. Tumor grade, reflecting architectural and nuclear atypia, directly correlates with risk of recurrence and survival [8]. The revised FIGO grading system simplifies categorization but interobserver variability remains a limitation. Integrating histopathological assessment with molecular subtyping enhances prognostic accuracy and treatment planning [9].

Tumor Stage and Prognostic Relevance (FIGO Classification)

The International Federation of Gynecology and Obstetrics (FIGO) staging system remains the cornerstone for prognostic assessment and treatment planning in uterine cancer. Stage at diagnosis strongly correlates with overall and disease-free survival, with early-stage disease demonstrating 5-year survival exceeding 85%, compared to less than 20% in advanced stages [10]. The 2023 FIGO revision further emphasizes lymph node status and adnexal involvement, improving prognostic discrimination. Accurate surgical staging, including pelvic and para-aortic lymphadenectomy, is crucial for optimal classification and adjuvant therapy selection [11].

Depth of Myometrial Invasion and Lymphovascular Space Invasion (LVSI)

Depth of myometrial invasion is a pivotal pathological parameter reflecting tumor aggressiveness and metastatic potential. Tumors invading >50% of the myometrium are associated with a two-fold higher risk of nodal metastasis and recurrence [12]. Lymphovascular space invasion (LVSI) independently predicts poor prognosis regardless of stage or grade and serves as an indicator for adjuvant therapy. Quantitative assessment of LVSI, now recommended in pathology reports, enhances risk stratification, particularly for intermediate-risk endometrioid cancers [13].

Lymph Node Involvement and Metastatic Spread

Regional lymph node involvement represents one of the most powerful adverse prognostic factors in uterine cancer. Positive pelvic or para-aortic nodes reduce 5-year survival by up to 50% compared to node-negative cases [14]. Sentinel lymph node (SLN) mapping has emerged as a less morbid yet accurate alternative to full lymphadenectomy, allowing improved detection of micrometastases through ultrastaging techniques [15]. The presence of isolated tumor cells or micrometastases, although subtle, significantly influences adjuvant treatment decisions and survival expectations [16].

Molecular and Genetic Alterations in Uterine Cancer

Molecular profiling has transformed understanding of uterine carcinogenesis. The TCGA identified four major molecular subgroups: (1) POLE-ultramutated, (2) microsatellite-instable (MSI) hypermutated, (3) copy-number-low (endometrioid), and (4) copy-number-high (serous-like, TP53-mutant) [17]. These categories carry distinct prognostic and therapeutic implications—POLE-mutant tumors exhibit excellent outcomes, whereas TP53-mutant tumors show dismal survival [18]. Routine incorporation of molecular testing in pathology workflows now guides adjuvant therapy intensity and clinical trial stratification [19].

Hormone Receptor Status and Its Prognostic Role

Estrogen and progesterone receptor (ER/PR) expression plays both diagnostic and prognostic roles in uterine cancer. High receptor positivity correlates with low-grade, early-stage disease and favorable survival [20]. Loss of PR expression, particularly in high-grade endometrioid or serous tumors, indicates hormonal independence and therapeutic resistance. Hormonal therapy with progestins remains a valuable option in selected receptor-positive, low-grade tumors and for fertility-sparing management in young patients [21]. Quantitative immunohistochemical scoring has improved predictive precision and standardized reporting [22].

umor Microenvironment and Immune Infiltrates

The tumor microenvironment, comprising immune cells, stroma, and cytokine networks, critically modulates progression and therapy response. High densities of CD8+ tumor-infiltrating lymphocytes (TILs) and PD-L1 expression are associated with favorable outcomes, especially in MSI-high tumors [23]. Immunosuppressive cell populations, such as regulatory T cells and tumor-associated macrophages, promote invasion and metastasis [24]. Understanding these interactions has paved the way for immune-checkpoint inhibitors, which have demonstrated durable responses in MMR-deficient and POLE-mutant endometrial cancers [25].

Patient-Related Factors (Age, Comorbidities, Obesity, Diabetes)

Host factors significantly influence uterine cancer prognosis and treatment tolerance. Older age and multiple comorbidities correlate with poorer survival, partly due to limited therapeutic options [26]. Obesity and diabetes increase not only disease incidence but also recurrence risk through hyperinsulinemia, chronic inflammation, and altered steroid metabolism [27]. Lifestyle modification and metabolic control should therefore complement oncologic management to optimize outcomes and reduce mortality [28].

Surgical Factors and Extent of Resection

Total hysterectomy with bilateral salpingo-oophorectomy remains the mainstay of treatment for most cases. The extent of lymph node dissection continues to be debated, with sentinel node mapping offering equivalent staging accuracy and reduced morbidity [29]. Minimally invasive techniques, including

robotic and laparoscopic approaches, achieve comparable oncologic outcomes with shorter recovery and fewer complications [30]. Intraoperative frozen-section assessment of myometrial invasion aids in tailoring the extent of surgery and adjuvant planning [31].

Adjuvant Therapies: Radiotherapy, Chemotherapy, and Hormonal Therapy

Adjuvant therapy decisions are guided by risk stratification incorporating clinicopathological and molecular parameters. Radiotherapy effectively reduces locoregional recurrence, particularly in intermediate-risk disease [32]. Combined chemoradiation improves survival in advanced or high-risk histologies. Platinum-based chemotherapy is standard for stage III–IV or serous-type cancers [33]. Hormonal therapy benefits receptor-positive, low-grade tumors and may serve as maintenance in selected cases [34]. Integration of molecular data into adjuvant algorithms continues to refine therapeutic precision [35].

Response to Therapy and Predictive Biomarkers

Therapeutic response varies considerably across molecular subtypes. POLE-mutant and MSI-high tumors demonstrate enhanced sensitivity to immune-checkpoint inhibitors and, in some cases, to radiotherapy [36]. Conversely, TP53-mutant tumors exhibit chemoresistance and poor outcomes, underscoring the need for targeted approaches [37]. Predictive biomarkers such as MMR status, HER2 overexpression, and PI3K/AKT/mTOR pathway mutations are being validated to personalize therapy [38].

Recurrence Patterns and Survival Outcomes

Recurrence remains a major determinant of survival, occurring in up to 25% of patients overall. Most recurrences develop within three years post-treatment, with distant metastases more frequent in serous and clear-cell subtypes [39]. Prognosis following recurrence is generally poor, although molecular subtype influences pattern and timing of relapse [40]. Early detection and individualized surveillance protocols may improve post-recurrence survival [41].

Emerging Molecular Classifications (TCGA and ProMisE)

The TCGA molecular taxonomy has been operationalized into the clinically feasible Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE), which utilizes immunohistochemistry and targeted sequencing [42]. ProMisE categorizes tumors into POLE-mutant, MMR-deficient, p53-abnormal, and NSMP (no specific molecular profile) groups, mirroring TCGA prognostic hierarchies [43]. Implementation of ProMisE in routine diagnostics has shown strong reproducibility and independent prognostic value across diverse populations [44].

Integrating Clinicopathological and Molecular Data for Prognostication

Recent guidelines advocate a combined model that merges molecular subgrouping with classical clinicopathological parameters. This integrated approach enhances risk prediction accuracy and informs treatment de-escalation or intensification strategies [45]. For instance, POLE-mutant tumors may safely omit adjuvant therapy despite high-grade morphology, while TP53-mutant tumors warrant aggressive multimodal treatment [46]. Such integration represents a pivotal shift toward precision oncology in uterine cancer [47].

Future Directions and Personalized Medicine

Future management of uterine cancer lies in personalized and molecularly guided therapy. Advances in next-generation sequencing, liquid biopsy, and artificial intelligence promise dynamic risk modeling and real-time treatment adaptation [48]. Immunotherapy, targeted agents against PI3K/AKT/mTOR and HER2, and combination regimens are under active clinical evaluation [49]. Comprehensive genomic profiling should become a standard component of care to optimize survival and quality of life [50].

Fertility-Sparing and Quality-of-Life Considerations

For young women with early-stage, low-grade, receptor-positive disease, conservative hormonal therapy with levonorgestrel intrauterine systems or high-dose progestins offers fertility preservation with

acceptable oncologic safety [51]. Long-term surveillance and careful patient selection remain essential to prevent undertreatment [52]. Survivorship care addressing sexual function, metabolic health, and psychosocial wellbeing is increasingly recognized as a crucial component of holistic management [53].

Health Disparities and Access to Care

Socioeconomic and racial disparities significantly affect diagnosis stage, treatment access, and outcomes. Black women, for instance, experience higher mortality despite similar stage distribution, reflecting differences in biology, comorbidity, and healthcare access [54]. Addressing inequities through community outreach, guideline implementation, and equitable clinical trial enrollment is essential to reduce survival gaps [55].

Conclusion

Clinicopathological determinants remain fundamental to prognostication in uterine cancer, yet their predictive power is greatly enhanced by integration with molecular and patient-specific factors. The transition toward a combined clinicopathologic-molecular paradigm enables precise risk assessment, optimized therapy selection, and improved survival outcomes. Ongoing research focusing on molecular biomarkers, targeted therapy, and individualized management will continue to redefine uterine cancer care and enhance the prospects for long-term disease control and survivorship [56].

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