Review Article

Adjuvant Therapy for Endometrial Cancer in the Era of Molecular Classification

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Abstract

Endometrial cancer primarily undergoes surgical intervention, with adjuvant treatments such as external beam pelvic radiotherapy, vaginal brachytherapy, chemotherapy, and combined therapy investigated in randomized trials. Treatment decisions hinge on clinicopathological risk factors. Low-risk cases usually require surgery alone, whereas high-intermediate risk often benefit from adjuvant vaginal brachytherapy for enhanced local control with minimal side effects. Recent trials advocate pelvic radiotherapy for high-risk cases, particularly in Stage I–II tumors with risk factors. Chemoradiation proves advantageous for serous cancers and Stage III disease, improving recurrence-free, and overall survival. Molecular studies, notably the Cancer Genome Atlas project, identified four distinct molecular classes, transcending stages, and histological types. These molecular subtypes exhibit a stronger prognostic impact than histopathological characteristics, heralding a shift toward molecular-integrated diagnostics and treatments. Incorporating molecular factors into adjuvant strategies, including targeted therapies, marks a new paradigm in endometrial cancer management, underpinning ongoing research, and clinical trials. This review outlines current adjuvant approaches, underscores the emergence of molecular-integrated risk profiling, and touches on developments in targeted therapy.

Keywords: *Defective mismatch repair, endometrial cancer, microsatellite instability, polymerase epsilon exonuclease domain mutation, TP53 gene mutation*

Submitted: 01-May-2024
Accepted: 24-Jun-2024
Published: 17-Oct-2024

Introduction

Endometrial cancer, predominantly diagnosed at an early stage, generally carries a favorable prognosis, yet around 15%–20% face a higher risk of distant metastases.[1] Surgery, typically comprising total abdominal or laparoscopic hysterectomy alongside bilateral salpingo-oophorectomy, serves as the primary treatment. However, there is debate regarding the necessity of lymphadenectomy. Sentinel lymph node biopsy, emerging as an alternative, offers staging information while minimizing lymph node dissection-related morbidity, notably lymphedema. The FIRES trial employing indocyanine green for sentinel node identification demonstrated high sensitivity and negative predictive value.[2]

Adjuvant treatment decisions hinge on various clinical and pathological factors, including age, grade, histological type, depth of myometrial invasion, and presence of lymphovascular space invasion (LVSI). Notably, extensive LVSI significantly predicts pelvic recurrence, distant metastasis, and reduced overall survival.[3] Stratification into low-, intermediate-, high-intermediate, and high-risk groups based on these factors facilitates tailored treatment approaches, each with distinct prognoses and adjuvant treatment considerations [Table 1].

Adjuvant Treatment in Endometrial Cancer

Several studies have evaluated the use of radiotherapy, including external beam pelvic radiotherapy and vaginal brachytherapy, as adjuvant treatment for endometrial

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How to cite this article: Gupta S, Gupta R, Motwani V, Kalwaniya DS. Adjuvant therapy for endometrial cancer in the era of molecular classification. J Mid-life Health 2024;15:142-52.

Access this article online

Quick Response Code:

Website: https://journals.lww.com/jomh

DOI: 10.4103/jmh.jmh_88_24

cancer[4-8] [Table 2]. Recent trials have primarily targeted high-intermediate and high-risk diseases, as adjuvant treatment is not typically indicated for low-risk endometrial cancer.

Low and High Intermediate-risk Endometrial Cancer

Randomized trials have demonstrated that pelvic radiotherapy decreases locoregional relapse in comparison to no additional treatment postsurgery for endometrial cancer. However, it does not improve overall survival or reduce distant metastasis in early-stage disease and carries a risk of gastrointestinal toxicity. Most locoregional relapses occur in the vagina, with salvage treatment showing effectiveness for patients not previously irradiated.[4-7]

For isolated vaginal relapse, pelvic radiotherapy combined with vaginal brachytherapy boost yields

Table 1: Different risk groups in endometrial cancer (ESMO-ESGO-ESTRO consensus)[1]

Risk group	Molecular classification unknown	Molecular classification known
Low risk	Stage IA endometrioid + low-grade + LVSI negative or focal	Stage I–II POLEmut endometrial carcinoma, no residual disease
		Stage IA MMRd/NSMP endometrioid carcinoma + low-grade + LVSI negative or focal
Low-intermediate risk	Stage IB endometrioid + low-grade + LVSI negative or focal	Stage IB MMRd/NSMP endometrioid carcinoma + low-grade + LVSI negative or focal
	Stage IA endometrioid + high-grade + LVSI negative or focal	Stage IA MMRd/NSMP endometrioid carcinoma + high-grade + LVSI negative or focal
	Stage IA nonendometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) without myometrial invasion	Stage IA p53abn and/or nonendometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) without myometrial invasion
High-intermediate risk	Stage I endometrioid + substantial LVSI regardless of grade and depth of invasion	Stage I MMRd/NSMP endometrioid carcinoma + substantial LVSI regardless of grade and depth of invasion
	Stage IB endometrioid high-grade regardless of LVSI status	Stage IB MMRd/NSMP endometrioid carcinoma high-grade regardless of LVSI status
	Stage II	Stage II MMRd/NSMP endometrioid carcinoma
High	Stage III–IVA with no residual disease	Stage III–IVA MMRd/NSMP endometrioid carcinoma with no residual disease
	Stage I–IVA nonendometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) with myometrial invasion, and with no residual disease	Stage I–IVA p53abn endometrial carcinoma with myometrial invasion, with no residual disease
		Stage I–IVA NSMP/MMRd serous, undifferentiated carcinoma, carcinosarcoma with myometrial invasion, with no residual disease
Advanced/ metastatic	Stage III–IVA with residual disease	Stage III–IVA with residual disease of any molecular type
	Stage IVB	Stage IVB of any molecular type

POLE: Polymerase epsilon, LVSI: Lymphovascular space invasion, MMRd: Mismatch repair deficiency, NSMP: Nonspecific molecular profiling, ESMO: European society for medical oncology, ESGO: European society of gynaecological oncology, ESTRO: European society for radiotherapy and oncology

Table 2: Adjuvant radiotherapy in Stage I–II endometrial cancer

Trial	Year of enrollment	Number of patients	Surgery	Eligibility	Randomization	Loco-regional recurrence	Survival
GOG-99[4]	1987–1995	392	TAH-BSO + LND	Stages IB/C; Stage II (occult)	EBRT versus NAT	2 years: 3% versus 12% (P=0.007)	4 years: 86% versus 92% (P=0.0557)
PORTEC-1[5]	1990–1997	714	TAH-BSO	Stages IB G2–3; Stages IC G1–2	EBRT versus NAT	5 years: 4% versus 14% (P<0.001)	5 years: 85% versus 81% (P=0.31)
Swedish[7]	1997–2008	527	TAH-BSO	Stage I intermediate risk	VBT versus VBT + EBRT	5 years: 5% versus 1.5% (P=0.013)	5 years: 90% versus 89% (P=0.55)
ASTEC/ EN.5[6]	1996–2008	905	TAH-BSO +/− LND	Stages IA/B G3; IC; Stage II; serous/CC	EBRT versus NAT	5 years: 6% versus 3% (P=0.02)	5 years: 84% versus 84% (P=0.98)
PORTEC-2[8]	2002–2006	427	TAH-BSO	Age >60 and Stage IB G3 or Stages IC G1–2; Stage IIA	EBRT versus VBT	5 years: 5% versus 2% (P=0.17)	5 years: 85% versus 80% (P=0.57)

LND: Lymph node dissection, G: Grade, EBRT: External beam radiation therapy, GOG: Gynecologic oncology group, NAT: No adjuvant treatment, PORTEC: Postoperative radiation therapy for endometrial carcinoma, TAH-BSO: Total hysterectomy and bilateral salpingo-oophorectomy, VBT: Vaginal brachytherapy

high remission rates and survival rates. Conversely, the prognosis is poor for patients experiencing pelvic or distant relapse. Despite these findings, approximately 30% of patients in trials such as PORTEC-1 and GOG-99, characterized by older age, higher grade tumors, deeper invasion, and LVSI, benefit from adjuvant pelvic radiotherapy in terms of pelvic control. The results of PORTEC-1 and GOG-99 have led to reduced use of adjuvant radiotherapy in low-intermediate and intermediate-risk endometrial cancer, mitigating radiotherapy-related morbidity.[4,5]

The PORTEC-2 trial compared adjuvant vaginal brachytherapy to pelvic radiotherapy in high-intermediate risk endometrial cancer patients. Results revealed similarly low rates of vaginal recurrence in both arms, with no significant differences in disease-free or overall survival.[8] Patients receiving brachytherapy experienced lower treatment-related toxicity and better quality of life, comparable to the general population. These findings support adjuvant vaginal brachytherapy as the standard of care for high-intermediate risk endometrial cancer, offering effective vaginal control with minimal morbidity.

High-risk Endometrial Cancer

Around 15%–20% of women with endometrial cancer fall into the high-risk category, characterized by the increased likelihood of distant metastases and disease-related mortality. This group includes various histological types and stages, such as high-grade endometrioid cancers with deep myometrial invasion, as well as nonendometrioid types such as serous or clear cell, which carry a poorer prognosis due to higher metastatic potential.[9]

Pelvic radiotherapy historically served as the standard adjuvant treatment for reducing pelvic recurrence in high-risk endometrial cancer. However, there has been an exploration into chemotherapy's role in improving survival by addressing the metastatic disease. Trials initially compared adjuvant pelvic radiotherapy alone with chemotherapy alone, with mixed results regarding overall survival and toxicity rates.[10-12]

Further studies investigated the combination of radiotherapy with chemotherapy (chemoradiation) to target both pelvic and distant recurrence, with ongoing research to optimize treatment strategies for this heterogeneous patient population.

The NSGO-9501/EORTC-5591 trial demonstrated the efficacy of chemoradiation in improving outcomes for women predominantly diagnosed with Stage I endometrial cancer exhibiting Grade 3 and/or deep invasion.[13] This trial, along with the ongoing ManGO Iliade-III trial, pooled their data, revealing a significant enhancement in recurrence-free survival and a suggestive trend toward improved overall survival when chemotherapy was added to radiotherapy. Conversely, the GOG-249 trial, involving 601 women with Stage I–II endometrial cancer and high-intermediate or high-risk factors, found no disparity in recurrence-free or overall survival between pelvic radiotherapy combined with carboplatin–paclitaxel chemotherapy and brachytherapy combined with carboplatin–paclitaxel chemotherapy.[14] Notably, the latter approach was associated with a notable increase in pelvic and para-aortic recurrences.

In the international PORTEC-3 trial, comprising 660 evaluable patients with high-risk endometrial cancer, various treatment modalities were compared. These included pelvic radiotherapy alone versus pelvic radiotherapy combined with two concurrent cycles of cisplatin followed by four cycles of adjuvant carboplatin and paclitaxel at 3-week intervals, based on prior findings from a Phase II Radiation Therapy Oncology Group (RTOG) trial.[15,16] The study revealed a notable 5% increase in overall survival with adjuvant chemotherapy. Notably, significant improvements were observed in women with Stage III disease and those with serous cancers after combined chemoradiation. For Stage III, overall survival improved by 10% and failure-free survival by 13%. In serous cancers, overall survival increased by 18% and failure-free survival by 13%.

Contrastingly, the GOG-258 trial, involving 736 evaluable women with more advanced disease (Stage III–IVa with or without residual disease up to 2 cm), investigated pelvic radiotherapy with concurrent and adjuvant chemotherapy versus chemotherapy alone (six cycles of carboplatin and paclitaxel).[17] While no significant differences were detected in recurrence-free and overall survival, there were significantly higher rates of pelvic and para-aortic nodal recurrence (11% vs. 20%, hazard ratio [HR] = 0.43; 95% confidence interval [CI], 0.28–0.66) observed in the chemotherapy-only arm [Table 3].

The incorporation of adjuvant chemotherapy into treatment regimens presents a notable increase in severe treatment-related morbidity. Within the PORTEC-3 trial, a significant disparity in Grade ≥3 toxicities emerged during and posttreatment in the chemoradiation group compared to the radiotherapy-alone group (60% vs. 12%), primarily manifesting as hematological, gastrointestinal, bone, joint, and muscle-related adverse events.[18] Although patients exhibited satisfactory recovery within the initial year following treatment

Table 3: Trials of adjuvant radiotherapy and chemotherapy

Trial	Year of enrollment	Number of patients	Eligibility	Randomization	5-year overall survival	5-year *P*rogression-free survival
Italian[11]	1990–1997	345	Stage I–II with grade 3 tumor; Stage III	Pelvic RT versus 5x CAP	69% versus 66% (NS)	63% versus 63% (NS)
GOG-122[10]	1992–2000	396	Stage III and IV, up to 2 cm residual disease postsurgery allowed	Whole abdomen irradiation versus 8x AP	42% versus 55% (P<0.01)	38% versus 50% (P<0.01)
Japanese[12]	1994–2000	385	Stage I–II with >50% myometrial invasion	Pelvic RT versus 3x CAP	85% versus 87% (NS)	84% versus 82% (NS)
NSGO/EORTC pooled with Iliade-III[13]	1996–2007	534, NSGO/EORTC 378 and Iliade 156	NSGO/EORTC Stage I–III; Iliade Stage II–III	Pelvic RT versus pelvic RT and 4x AP or TAP or TC or TEP	75% versus 82% (P=0.07)	69% versus 78% (P=0.02)
PORTEC-3[16]	2006–2013	686	Stage I–II with high-risk factors, Stage III	Pelvic RT versus pelvic RT with 2x CP followed by 4x TC	76% versus 81% (P=0.034) Stage III 69% versus 79% Serous EC 53% versus 71%	69% versus 77% (P=0.016) Stage III 58% versus 71% Serous EC 47% versus 60%
GOG-249[14]	2009–2013	601	Stage I–II with high-intermediate or high-risk factors	Pelvic RT versus VBT and 3x TC	87% versus 85% (NS)	76% versus 76% (NS)
GOG-258[17]	2009–2014	736	Stage III and IVa without residual disease up to 2 cm	Pelvic RT with 2x CP followed by 4x TC versus 6x TC	70% versus 73% (NS)	59% versus 58% (NS)

AP: Doxorubicin plus cisplatin, CAP: Cyclophosphamide, doxorubicin, and cisplatin, CP: Cisplatin, EC: Endometrial cancer, GOG: Gynecologic oncology group, NS: Not significant, PORTEC: Postoperative radiation therapy for endometrial carcinoma, TAP: Doxorubicin, cisplatin, and paclitaxel, TC: Paclitaxel plus carboplatin, TEP: Paclitaxel, epirubicin, and cisplatin, VBT: Vaginal brachytherapy, NSGO/EORTC: Nordic Society of Gynecologic Oncology/European Organization for Research and Treatment of Cancer, RT: Radiotherapy

completion, a persistently higher incidence of Grade 2 toxicity, particularly sensory neuropathy, persisted within the chemoradiation arm at the 3 years. Approximately 25% of women in the chemoradiation arm reported notable tingling or numbness.[19] These findings align with toxicity and quality of life reports from the GOG-249 trial.

Recent trials suggest that current evidence advocates for employing chemoradiation to optimize recurrence-free and overall survival, alongside pelvic and para-aortic nodal control in women with Stage III disease and/or serous histology. Nevertheless, ongoing debate among clinicians centers on whether the combined chemoradiation regimen should be prioritized over chemotherapy alone, given similar relapse-free survival rates in the GOG-258 trial and concerns regarding potential heightened toxicity. Notably, the chemotherapy-alone arm demonstrated significantly more vaginal, pelvic, and para-aortic nodal recurrences, although it remains undisclosed how many patients in this arm underwent radiotherapy at relapse. Severe toxicities in both the GOG-258 and PORTEC-3 trials were predominantly chemotherapy-related notably hematological, joint- and muscle-related symptoms, and sensory neuropathy.[19]

While salvage rates for isolated vaginal recurrence are favorable, patients experiencing pelvic and/or para-aortic nodal recurrence, particularly those with high-grade/advanced disease, face a poor prognosis attributed to lower control rates and an elevated risk of subsequent distant metastases.[20] Recent small case series investigating intensity-modulated radiation therapy (IMRT) with or without chemotherapy for nodal relapse in radiotherapy-naive patients demonstrated 2-year overall survival rates hovering around 70% with tolerable toxicity levels. An ongoing GOG trial (Clinical-Trials.gov Identifier NCT00492778) is assessing the potential benefits of concurrent cisplatin with radiation therapy for women experiencing pelvic and/or vaginal recurrences.[21-23]

Over the past two decades, conventional pelvic radiation techniques utilizing three-dimensional (3D) conformal four-field approaches have increasingly given way to IMRT and volumetric arc techniques. Both IMRT and volumetric arc techniques offer the advantage of delivering reduced doses to organs at risk, thereby mitigating radiation-related toxicities. The landmark RTOG 1203 trial marked the first randomized comparison between IMRT and 3D conformal techniques concerning acute patient-reported toxicity.[24,25] The

trial demonstrated significantly less gastrointestinal and urinary morbidity reported by patients receiving IMRT.

The optimal sequencing of chemotherapy and radiotherapy remains a contentious subject. While many centers favor sequential treatment with chemotherapy preceding radiotherapy, driven by logistical considerations and the belief that early initiation of chemotherapy addresses occult distant metastases, the pooled MaNGO/Iliade trials revealed no discernible difference in outcomes between patients receiving chemotherapy before or after radiotherapy, with the majority receiving chemotherapy first. Some centers advocate for a "sandwich therapy" approach, involving chemotherapy followed by radiation and then chemotherapy again, which showed promising 3-year outcomes in a multicenter retrospective analysis.[26] However, recent large prospective randomized trials have demonstrated the safety and efficacy of a combined chemotherapy and radiotherapy schedule, aligned with the regimen from the RTOG Phase II trial. This schedule offers the advantage of commencing both adjuvant treatments promptly after surgery and entails a shorter overall treatment duration compared to sequential therapy.

The optimal adjuvant treatment for Stage IA serous and clear cell endometrial cancers without myometrial invasion remains uncertain, with conflicting findings from recent studies. While a Mayo Clinic study suggests vaginal brachytherapy as the preferred option, a retrospective analysis from the National Cancer Database indicates variable outcomes with adjuvant therapy, leading to the conclusion that there is insufficient data to uniformly recommend chemotherapy for noninvasive serous endometrial cancer at this time. Further prospective research is needed to guide treatment decisions for this specific patient population.[27,28]

Pathology Evaluation

Pathological assessment of female reproductive tract malignancies, particularly endometrial cancer, is prone to significant interobserver variability, impacting adjuvant treatment decisions. Studies highlight discrepancies in grading, histological type determination, and evaluation of endocervical involvement and LVSI.[29-31]

To enhance agreement and prognostic accuracy, a binary grading system (low-grade vs. high-grade) and immunohistochemistry for histological typing are recommended. A three-tiered system for LVSI assessment (no, focal, or substantial) minimizes discordance, with substantial invasion indicating diffuse or multifocal involvement.[32,33]

Molecular Subgroups Of Endometrial Cancer

The Cancer Genome Atlas (TCGA) project has provided comprehensive insights into the molecular landscape of endometrial cancers, focusing primarily on endometrioid, and serous histologies through analysis of 373 cases. TCGA delineated four distinct molecular subtypes based on somatic mutational burden and copy number alterations: (i) ultramutated endometrial cancer characterized by mutations in the exonuclease domain of DNA polymerase epsilon (POLE), (ii) hypermutated endometrial cancer with microsatellite instability, (iii) copy-number-high endometrial cancer with frequent TP53 mutations, and (iv) copy-number-low endometrial cancer. Discriminating between these subgroups holds prognostic significance.[34]

Ultramutated endometrial cancers exhibit pathogenic variants in the exonuclease domain of POLE, resulting in impaired proofreading during DNA replication and leading to an exceptionally high mutational burden. A subset of pathogenic POLE variants within this domain induces the ultramutated phenotype in endometrial cancer, accounting for approximately 8%–10% of cases. In molecular classification, these cases are denoted as POLEmut tumors.[35,36]

Typically occurring in relatively young women, POLEmut endometrial cancers manifest as early-stage, high-grade tumors with prominent lymphocytic infiltration. Despite their high grade, POLEmut tumors are associated with remarkably favorable prognoses, with rare relapses observed irrespective of adjuvant treatment. It is theorized that ultramutated tumors may provoke a robust immune response due to the presence of tumor neuropeptides resulting from extensive mutation. In addition, the ultramutated status may impair the functionality of POLEmut cancer cells, potentially reducing their metastatic potential.[37]

The microsatellite instable subgroup, often synonymous with mismatch repair deficiency, constitutes approximately 25%–30% of endometrial cancers. Characterized by the loss of nuclear expression of mismatch repair proteins, typically due to somatic events such as MLH1 promoter hypermethylation, this subgroup accumulates mismatches, insertions, and deletions. While predominantly sporadic, a fraction of cases stem from germline mutations in mismatch repair genes, defining Lynch syndrome. Mismatch repair deficiency cancers prompt a strong immune response and display an intermediate prognosis.[38,39]

The third molecular subgroup is characterized by a high number of somatic copy number alterations and

a relatively low somatic mutation rate, with TP53 mutations present in 90% of cases. Predominantly comprising high-grade cancers, this group exhibits aggressive growth and early metastasis, leading to poor prognosis. It is primarily composed of nonendometrioid histologies such as serous cancer and carcinosarcoma, alongside approximately 50% of clear cell cancers. In addition, high-grade endometrioid endometrial cancers with TP53 mutations, which account for about 61% of Grade 3 endometrial cancers, are included and display similarly unfavorable prognoses.[40,41] Recent research indicates frequent homologous recombination deficiency in p53 abnormal staining (p53abn) endometrial cancer within this subgroup.[42]

The fourth and largest subgroup of endometrial cancer, termed copy-number-low, lacks a specific molecular profile, characterized by low mutational burden and few somatic copy-number alterations. Prognosis varies with disease stage but generally falls within the intermediate risk category. This subgroup predominantly comprises endometrioid-type cancers exhibiting positive staining for estrogen and progesterone receptors. Molecular heterogeneity within this subgroup suggests potential for further refinement into distinct subsets, with mutations in exon 3 of β-catenin (CTNNB1) emerging as a candidate for prognostic stratification. Endometrial cancers in this subgroup with CTNNB1 mutations tend to have relatively poorer prognoses compared to those lacking these mutations.[43]

While most endometrial cancers can be classified into one of the four molecular subgroups [Figure 1], a small percentage (about 3%–6%) exhibit more than one classifying alteration, termed multiple-classifier endometrial cancers.[44] Notably, TP53 mutations can occur as secondary events in mutators such as mismatch repair deficiency and POLEmut endometrial cancers without impacting prognosis. Evidence supports classifying endometrial cancers with pathogenic POLE variants as POLEmut, irrespective of co-occurring molecular alterations[45] [Table 4].

Molecular Integrated Risk Profile

Both the PORTEC group and the Proactive Molecular Risk Classifier for Endometrial Cancer (PRoMisE) study group have categorized molecular subgroups using surrogate markers in paraffin-embedded tissues. Besides TCGA molecular groups, additional clinicopathological and molecular risk factors have shown prognostic value, including substantial LVSI, L1-cell adhesion molecule overexpression, CTNNB1 mutation, and 1q32.1 amplification, particularly discriminative within the "no specific molecular profile" subgroup.

L1-cell adhesion molecule, associated with TP53 mutations and aggressive tumor characteristics, serves as an independent risk factor for both loco-regional and distant spread. CTNNB1 mutations stimulate endometrial tissue growth, increasing the risk of recurrence and reducing recurrence-free survival. Amplification of 1q32.1 correlates with a significantly worse prognosis within the "no specific molecular profile" subgroup.[39-41]

A multivariate analysis, utilizing >800 Stage I endometrial cancers from PORTEC-1 and PORTEC-2 biobanks, comprehensively analyzed the prognostic significance of these risk factors alongside TCGA subgroups. Resulting in molecular-integrated risk profiles identified favorable, intermediate, and unfavorable profiles within the high-intermediate risk category, demonstrating distinct recurrence-free survival outcomes with high diagnostic reproducibility. ProMisE validation studies also emphasized the combined

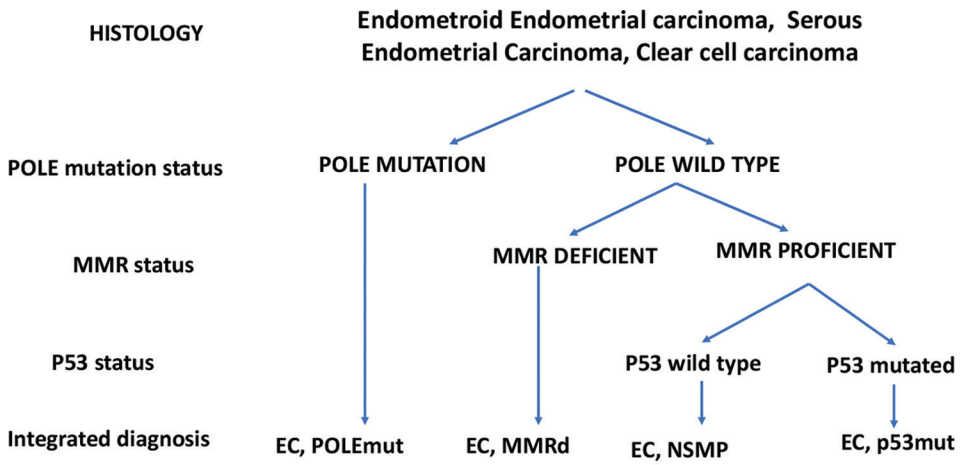

Figure 1: Diagnostic algorithm of subclassification of four molecular subtypes. EC: Endometrial cancer, MMR: Mismatch repair, MMRd: Mismatch repair deficiency, NSMP: Nonspecific molecular profiling

Table 4: Molecular and clinicopathological features of molecular subtypes

	POLEmut EC	MMRd EC	NSMP EC	P53abn EC
Frequency	5%–15%	20%–30%	30%–60%	10%–25%
Surrogate marker	NGS Sanger	MMR protein IHC: PMS, MSH6 (MLH1, MSH2) MSI assay		P53-IHC NGS
Molecular features	Ultramutated (>100 mut/Mb) Somatic copy number alteration - low 20% with MMRd or MSI 20% with p53 mutant expression	Hypermutated (>10 mut/Mb) Somatic copy number alteration - low MSI 10% with p53 mutant expression	Low tumor mutation burden Somatic copy number alteration - low MSS TP53 - wild type PTEN mutation PI3CA mutation CTNNB1 mutation	Low tumor mutation burden Somatic copy number alteration - high MSS TP53-mutated Frequent homologous recombinant deficiency 20%–25% Her2 amplification
Associated histological features	Mostly high-grade endometrioid Tumor giant cells High tumor infiltrate CD8 + lymphocytes	Mostly high-grade endometrioid Substantial LVSI MELF-like invasion High tumor infiltrate CD8 + lymphocytes	Mostly low-grade endometrioid Squamous metaplasia ER/PR positive	Mostly high-grade endometrioid Substantial LVSI High-grade atypia
Associated clinical features	Low BMI Early stage Younger patient	High BMI 10% Lynch syndrome carrier Local recurrence	High BMI	Low BMI Advance stage Older patient Distant recurrences
Prognosis	Excellent	Intermediate	Intermediate to poor depends on stage and histological grade	Poor
Potential biomarkers		MLH 1 promoter methylation, Germline mutation	CD8 intra-epithelial lymphocytes LCAM CTNNB1 mutation ER/PR expression	CD8 intra-epithelial lymphocytes

EC: Endometrial cancer, MMR: Mismatch repair, MMRd: MMR deficiency, NSMP: Nonspecific molecular profiling, NGS: Next generation sequencing, MSI: Microsatellite instability, BMI: Body mass index, CTNNB1: β-catenin 1, ER/PR: Estrogen and progesterone, IHC: Immunohistochemistry, MSS: Microsatellite stability, LVSI: Lymphovascular space invasion, POLE: Polymerase epsilon, EC: Endometrial cancer

prognostic significance of molecular subgroups and clinicopathological risk factors.[46,47]

The ongoing PORTEC-4a trial (NCT03469674) represents the first prospective investigation into utilizing an integrated clinicopathological and molecular risk profile for adjuvant therapy selection in endometrial cancer. This trial combines the four molecular subgroups with additional prognostic factors to categorize patients into favorable, intermediate, or unfavorable profiles. Women with high-intermediate risk endometrial cancer are randomized (2:1) to receive adjuvant treatment based on their molecular-integrated risk profile or standard vaginal brachytherapy. Patients with a favorable profile forego adjuvant treatment, while those with an intermediate-risk profile receive standard brachytherapy. Only those with an unfavorable profile undergo pelvic radiotherapy. The PORTEC-4a trial aims to provide crucial data on optimizing treatment selection based on risk profile, thereby reducing both over-treatment and under-treatment in patients with high-intermediate risk endometrial cancer.[48]

Prognostic Relevance of Molecular Subgroup in High-Risk Endometrial Cancer

Results of translational research from PORTEC-3, presented at international meetings and recently published, revealed that molecular subgroups were present across all histological subtypes, stages, and grades of endometrial cancer. Clear differences in prognosis were observed between molecular subgroups, consistent with findings from an international analysis of grade 3 endometrial cancers.[49]

In the PORTEC-3 study, patients with p53abn endometrial cancer exhibited the worst outcomes, with significant benefit from adjuvant chemotherapy. Mismatch repair deficiency cancers had intermediate prognoses, with similar recurrence-free survival rates for radiotherapy alone and chemoradiation. Patients with POLE mut cancers experienced excellent outcomes, with minimal relapses and high recurrence-free survival rates, whether treated with radiotherapy alone or with chemoradiation. The no specific molecular profile group showed intermediate outcomes, with some benefit from additional chemotherapy, mirroring the overall PORTEC-3 trial results.[40]

Targeted Therapy

Patients with recurrent or metastatic endometrial cancer face poor overall survival despite a generally favorable prognosis for the disease. Standard treatments include hormonal therapy for certain tumor types and chemotherapy, typically carboplatin and paclitaxel, for others. Recent advancements in understanding the molecular characteristics of endometrial cancer have led to the identification of targetable molecular alterations across different subgroups.[1] This has spurred the development of individualized treatments utilizing targeted therapies aimed at these alterations. These targeted therapies encompass checkpoint inhibitors, DNA repair mechanisms, and cellular pathways, offering promising options either alone or in combination treatments.

Immune Checkpoint Inhibitors

Hypermutated tumors like POLE mut and mismatch repair deficient endometrial cancers exhibit high immunogenicity due to their mutational burden, resulting in elevated levels of neoantigens and infiltration by CD8+ T cells.[50,51] However, the interaction between programmed cell death ligand 1 (PD-L1) and programmed cell death protein 1 (PD-1) suppresses the immune response and inhibits apoptosis. Checkpoint inhibitors such as PD-1 inhibitors (e.g. nivolumab, pembrolizumab) and PD-L1 inhibitors (e.g. atezolizumab, avelumab, and durvalumab) have shown efficacy in various solid cancers, particularly those with mismatch repair deficiency. Pembrolizumab demonstrated an overall response rate of 57% in a study of endometrial cancer patients with unresectable or metastatic mismatch repair deficiency tumors, with a median progression-free survival of 26 months. Avelumab and durvalumab also showed promising response rates (26.7% and 43%, respectively) as monotherapy in advanced mismatch repair deficiency endometrial cancer.[52-54]

DNA Damage Response Inhibitor

PARP inhibitors, such as olaparib, niraparib, rucaparib, talazoparib, and veliparib, disrupt DNA repair mechanisms, leading to the accumulation of double-strand DNA breaks in tumor cells. This results in genomic instability and can trigger cell cycle arrest or cell death. In tumors deficient in homologous recombination repair, PARP inhibitors may induce synthetic lethality, making cancer cells more sensitive to DNA-damaging agents.[55] Homologous recombination deficiency is frequently observed in the copy-number-high subclass of endometrial cancer. While data on the efficacy of PARP inhibition in endometrial cancer patients are lacking, combination treatments targeting homologous recombination deficiency, such as platinum-based chemotherapy with PARP inhibition or a combination of PARP and checkpoint inhibitors, show promise, similar to approaches in high-grade ovarian cancer.[56]

Cellular Pathway Inhibitors

The phosphatidylinositol 3-kinase-AKT-mammalian target of rapamycin (PI3K/AKT/mTOR) pathway is frequently altered in endometrial cancer, regulating key aspects of cancer biology such as cell growth and survival. Dysregulation often involves the inactivation of PTEN or mutations in PI3K3CA and KRAS.[57] Targeted therapies for this pathway include mTOR inhibitors, PI3K inhibitors, dual mTOR/PI3K inhibitors, and AKT inhibitors. Clinical studies have primarily focused on mTOR inhibitors, either alone or in combination, showing modest results.[58] Combination therapy with everolimus and letrozole demonstrated a 32% response rate in chemo-naïve patients with recurrent disease. However, adding metformin did not enhance outcomes. Human epidermal growth factor receptor 2 (HER2), critical for cancer cell growth, is overexpressed in a subset of endometrial cancers, mainly serous or TP53-mutated. Trastuzumab trials showed limited efficacy, possibly due to patient selection and PI3K pathway mutations inducing resistance. Combining trastuzumab with chemotherapy prolonged progression-free survival in HER2-positive serous endometrial cancers.[59-61]

Conclusion

Molecular classification of endometrial cancer guides risk-based adjuvant treatments. Immune checkpoint inhibitors show promise for mismatch repair deficiency cancers. PORTEC-3 analysis reveals prognostic differences among molecular subgroups, influencing treatment benefits. RAINBO trials will further tailor adjuvant treatments based on molecular profiles.

Incorporating molecular classification in pathology improves treatment precision and may reduce unnecessary interventions. Ongoing studies on targeted agents will shape future treatment guidelines.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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