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Review

Toward Biology-Driven Surveillance After Endometrial Cancer Treatment: A Molecular–Clinical Framework Integrating Recurrence Phenotype

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Simple Summary

This work should be regarded as a narrative review and expert-informed conceptual framework. The purpose of the manuscript is not to establish definitive surveillance recommendations, but to propose a biologically grounded and clinically testable model for future prospective validation. Follow-up after endometrial cancer treatment is still largely based on clinical stage and histological features, often applying similar visit schedules to biologically distinct tumors. However, molecular classification has shown that endometrial cancer subtypes differ in prognosis, recurrence pattern, and treatment options after relapse. In this paper, we propose a biology-driven follow-up framework that combines molecular subtype, clinicopathological factors, and expected recurrence phenotype. The model is based on a simple principle: surveillance should be most intensive when earlier detection of recurrence is most likely to change treatment. This approach may help reduce unnecessary follow-up in biologically low-risk disease while supporting closer monitoring in patients whose recurrence may remain treatable. The proposed framework is conceptual and requires prospective validation.

Abstract

Background: Current surveillance strategies after treatment of endometrial cancer remain largely based on clinical stage and histological grade, reflecting a pre-molecular understanding of disease behavior. However, molecular classification has revealed profound biological heterogeneity across endometrial cancer subtypes, including differences in recurrence patterns, prognosis, and treatment responsiveness. Despite this progress, surveillance strategies have not yet been systematically adapted to molecular risk stratification. **Objective:** To propose a biology-driven surveillance framework for endometrial cancer that integrates molecular subtype, clinicopathological risk factors, and recurrence phenotype. **Methods:** This narrative review and conceptual framework synthesizes evidence from cohort studies, molecular classification analyses, international guidelines, and literature addressing recurrence patterns and treatment responsiveness across molecular subtypes of endometrial cancer. **Results:** We propose a three-tier surveillance model stratifying patients into low, intermediate-, and high-risk groups. The framework integrates molecular subtype with clinicopathological modifiers and expected recurrence phenotype. Within the no specific molecular profile (NSMP) subtype, CTNNB1 mutation status is incorporated as a primary modifier, assigning CTNNB1-mutated tumors to the intermediate-risk group regardless of estrogen receptor (ER) status. In CTNNB1 wild-type NSMP tumors, ER expression functions as a secondary modifier, allowing identification of a biologically low-risk subgroup. L1CAM expression is considered a high-risk modifier within NSMP. The framework also accounts for differences in therapeutic modifiability of recurrence, including the role of immunotherapy in mismatch repair-deficient tumors. **Conclusions:** Uniform post-treatment surveillance does not reflect the biological diversity of endometrial cancer. The proposed framework provides a biologically grounded approach to surveillance that aligns follow-up intensity with recurrence phenotype and therapeutic opportunities. This model may serve

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as a conceptual basis for prospective studies evaluating personalized surveillance strategies in endometrial cancer.

Keywords: endometrial cancer; surveillance; follow-up; molecular classification; recurrence patterns; immunotherapy; CTNNB1; beta-catenin; L1CAM; precision oncology

1. Introduction

Endometrial cancer (EC) is the most common gynecologic malignancy in developed countries [1,2]. Despite the favorable prognosis observed in the majority of patients, disease recurrence remains a clinically significant problem that determines the ultimate treatment outcome and limits therapeutic options. The rising incidence observed over recent decades, driven in part by the increasing prevalence of obesity and type 2 diabetes, means that optimizing post-treatment management is becoming increasingly important from both clinical and health-economic perspectives [3].

The traditional approach to surveillance after endometrial cancer treatment originates from the pre-molecular era and relies primarily on FIGO clinical stage and histological grade. For many years, the absence of randomized clinical trial data resulted in considerable heterogeneity in follow-up schedules, both in terms of visit frequency and the scope of investigations performed. A landmark attempt to address this gap was the TOTEM trial, the largest randomized study to date evaluating follow-up intensity after endometrial cancer treatment. Conducted across 42 centers in Italy and France, it enrolled 1,847 patients [4]. After a median follow-up of 69 months, five-year overall survival was 90.6% in the intensive surveillance arm and 91.9% in the minimalist arm (HR 1.13; 95% CI 0.86–1.50), with no significant difference in any of the analyzed subgroups. The study also showed that intensive surveillance did not improve quality of life and was associated with higher costs than the minimalist approach [5]. The results of the TOTEM trial informed changes in the guidelines of numerous scientific societies.

However, the TOTEM trial was designed and conducted before the era of molecular classification of endometrial cancer. Risk stratification was based exclusively on clinical and histological criteria, without incorporating biological tumor subtype. In the past decade, however, a fundamental shift has occurred in the understanding of endometrial cancer biology, driven by the implementation of genomic classification from The Cancer Genome Atlas (TCGA) [6]. This system identifies four molecular subtypes: POLE-mutated (POLEmut), mismatch repair-deficient (MMRd), p53-aberrant (p53abn), and no specific molecular profile (NSMP). These subtypes differ profoundly not only in prognosis, but also in recurrence dynamics, relapse site, and responsiveness to systemic treatment. Patients with the POLEmut subtype have an exceptionally favorable prognosis with near-absent recurrence, while the p53abn subtype is associated with recurrence and disease-related mortality exceeding 30% [6].

The integration of molecular classification into clinical practice has been reflected in updated guidelines. In 2023, a revised FIGO staging system was published incorporating tumor biological factors—including molecular classification—alongside traditional anatomical factors [7]. In response, ESGO, ESTRO, and ESP updated their joint guidelines on the management of endometrial cancer [8]. Despite this progress, the implications of molecular classification for post-treatment surveillance strategies remain insufficiently defined. Current follow-up recommendations still do not adequately differentiate surveillance schedules according to molecular tumor subtype.

A key argument for individualizing surveillance is the heterogeneity of recurrence phenotype across molecular subtypes. Isolated vaginal and nodal recurrences, characteristic of the MMRd and NSMP subtypes, may be amenable to treatment with curative intent—both surgical and salvage radiotherapy—and, in the case of MMRd, immunotherapy based on immune checkpoint inhibitors. In stark contrast, peritoneal and distant recurrences, typical of the p53abn subtype, are usually systemic and unresectable, limiting the impact of early detection on treatment outcome. The value of post-treatment surveillance should therefore be assessed not by the frequency of detected recurrences

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per se, but by the potential for meaningful modification of subsequent therapeutic management following their identification.

The aim of this paper is to propose a biologically grounded surveillance framework after endometrial cancer treatment that integrates molecular subtype, clinical risk factors, and the expected phenotype and therapeutic modifiability of potential recurrence. The proposed model is based on a synthesis of published cohort data, multicenter analyses, current international guidelines, and available evidence on recurrence treatment across molecular subtypes.

It is worth noting that some national healthcare systems are already evolving toward individualized surveillance. A notable example is the Danish national guideline (Danish Centre for Health Technology Assessment), which introduced risk-based surveillance stratification, selective use of imaging, and a strong emphasis on patient education and clinical examination as the cornerstone of follow-up [9]. Although this guideline does not yet incorporate molecular classification, its organizational structure provides a practical proof of concept for stratified surveillance models—a concept that the proposed framework extends with a biological dimension.

2. Scope and Methodological Approach

This manuscript is a narrative review and conceptual framework paper. It does not present original research data and was not designed as a systematic review. Instead, it provides a focused, biologically oriented synthesis of the literature to support the development of a molecular–clinical surveillance model after endometrial cancer treatment.

The proposed framework was developed through an interpretive review of published evidence addressing: (1) molecular classification of endometrial cancer, (2) recurrence patterns across molecular subtypes, (3) clinicopathological modifiers of recurrence risk, (4) therapeutic modifiability of recurrence, and (5) international recommendations on post-treatment follow-up. Priority was given to cohort studies with molecular classification, clinically relevant translational analyses, randomized trials with informative subgroup data, and contemporary international guidelines.

The underlying conceptual assumption of this work is that the clinical value of surveillance is greatest when earlier detection of recurrence may alter management, particularly by enabling potentially curative local treatment or timely use of biologically informed systemic therapy. On this basis, the proposed model links surveillance intensity not only to baseline recurrence risk, but also to expected recurrence phenotype and therapeutic opportunity.

Because this framework has not been prospectively validated, it should be considered hypothesis-generating and intended as a basis for future prospective and health-economic evaluation.

3. Biological Rationale for Personalized Surveillance

3.1. Molecular Classification and Recurrence Risk

The foundation of the proposed model is the profound biological heterogeneity of endometrial cancer revealed by TCGA genomic classification and its clinical adaptation. The four recognized molecular subtypes—POLEmut, MMRd, p53abn, and NSMP—differ not only in prognosis, but most importantly in recurrence pattern, relapse site, and susceptibility to treatment, all of which have direct implications for post-treatment surveillance strategy [10,11].

The POLEmut subtype has an exceptionally favorable clinical course. Multiple retrospective studies have demonstrated that five-year recurrence-free survival (RFS) approaches 100% in these patients, regardless of clinical stage [12]. Data from the PORTEC-3 trial, enrolling 410 patients with high clinical risk, confirmed excellent treatment outcomes in POLEmut patients—five-year RFS was 98% in both trial arms, irrespective of adjuvant chemotherapy use [13,14]. The exceptionally low recurrence risk justifies a substantial de-escalation of surveillance intensity, and routine imaging in this group has no biological justification.

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The MMRd subtype is characterized by a distinctive recurrence pattern with a predominance of locoregional relapse. The KImBer cohort analysis, encompassing 101 patients with endometrial cancer recurrence, demonstrated that locoregional recurrences accounted for 46% of all relapses in the MMRd group, compared with only 20% in the p53abn group, and isolated vaginal recurrences occurred in 36% of MMRd patients versus 10% in the p53abn group [15]. Median post-recurrence survival was most favorable for MMRd patients (43 months), compared with 39 months for NSMP and only 10 months for p53abn ($p = 0.001$) [15]. Furthermore, the MMRd subtype is characterized by high sensitivity to immune checkpoint inhibitors, which further increases the clinical value of early recurrence identification.

The p53abn subtype exhibits a markedly different and unfavorable recurrence pattern. In the KImBer cohort, patients with p53abn most frequently experienced abdominal recurrences (43%) compared with the MMRd group (18%) and NSMP group (31%), with non-locoregional relapses accounting for 80% of all recurrences [15]. Data from a Danish study focused on high-grade stage I tumors confirm this pattern: five-year overall recurrence rates were 35% for p53abn, with abdominal and distant relapses predominating over locoregional recurrences [16]. The short post-recurrence survival—median of only 10 months—and the low response rate to conventional chemotherapy (ORR 20–30%) limit the practical benefit of early detection in this group. The primary surveillance goal in the p53abn subtype should be prompt initiation of systemic therapy or enrollment in clinical trials.

The NSMP subtype is a biologically heterogeneous group. Low-grade tumors (G1–2) without additional risk factors exhibit a recurrence pattern similar to MMRd—with predominant locoregional relapse and relatively favorable post-recurrence prognosis. In contrast, high-grade NSMP (G3) or tumors with substantial LVSI behave more aggressively, with a higher proportion of distant and abdominal relapses, making them biologically closer to the p53abn subtype. This internal heterogeneity of the NSMP group requires the incorporation of additional clinicopathological factors when assigning patients to risk groups.

3.2. Time to Recurrence and the Therapeutic Window

Regardless of molecular subtype, the majority of endometrial cancer recurrences occur within the first two years after primary treatment. The median time to first recurrence was 16 months across the entire cohort, with no statistically significant differences between subtypes [15]. Surveillance in the first two years after treatment has the greatest clinical justification and should be most intensive. At the same time, late recurrences—beyond five years—were observed almost exclusively in the MMRd and NSMP subtypes, supporting the continuation of follow-up in these groups beyond the standard five-year surveillance period.

3.3. Implications for the Surveillance Goal

The described differences in recurrence biology lead to a practical conclusion that underpins the proposed framework: not all recurrences carry equal clinical value from a surveillance perspective. Locoregional relapses are potentially curable, and their early detection has a direct therapeutic impact. Peritoneal relapses typical of p53abn rarely qualify for local treatment. Surveillance strategy should therefore be guided by the question of whether detecting a given recurrence changes subsequent clinical management. This distinction provides the conceptual basis for a surveillance model that prioritizes clinically actionable recurrence detection over uniform visit intensity.

4. Recurrence Phenotype and Therapeutic Implications

The pattern of endometrial cancer recurrence carries fundamental significance not only in terms of prognosis, but—more importantly—in terms of therapeutic management. The feasibility of treatment with curative intent following recurrence is critically dependent on its phenotype: the site,

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extent, and biology of the relapse. Not every recurrence is clinically equivalent from the standpoint of therapeutic modifiability.

Isolated vaginal recurrence represents the paradigmatic example of a potentially curable relapse. Retrospective data demonstrate that salvage radiotherapy achieves five-year overall survival of 83%, with locoregional control of 89% and regional control of 91.5% [17]. Independent predictors of favorable outcome included isolated vaginal site and a recurrence interval of more than nine months from completion of primary treatment. Data from the PORTEC-1 trial analysis indicate that in patients without adjuvant radiotherapy who developed vaginal recurrence, five-year overall survival after salvage treatment was 70%, with a complete response rate to salvage radiotherapy of 89% [18]. These results provide direct justification for intensive clinical surveillance in risk groups where isolated vaginal recurrence is the biologically expected phenotype—primarily the MMRd and NSMP subtypes.

Isolated nodal recurrences—pelvic and para-aortic—represent a second category amenable to treatment with curative intent. Multimodality treatment of nodal recurrences, incorporating cytoreductive surgery, radiotherapy, and chemotherapy, can achieve two-year progression-free survival rates of 50–60% [19,20], although data from randomized trials in this area remain limited. The key criterion is an isolated recurrence without concurrent peritoneal dissemination or distant metastases.

Oligometastatic recurrences—isolated pulmonary, hepatic, or bone metastases—represent a distinct category. Although prognosis in this group is less favorable than with locoregional recurrences, in carefully selected cases, stereotactic body/ablative radiotherapy (SBRT/SABR) or surgical resection may lead to durable remission, particularly when disease-free interval is prolonged. This applies primarily to the MMRd subtype and selected NSMP patients.

In marked contrast to the above, peritoneal, multifocal, and disseminated recurrences—characteristic of the p53abn subtype—rarely qualify for local treatment. Systemic therapy in this group is primarily palliative in intent. For patients with advanced or recurrent endometrial cancer of the p53abn subtype treated with platinum-taxane chemotherapy, median progression-free survival is below six months and median overall survival is approximately 12 months. In this group, early detection of recurrence—unless it alters therapeutic options—has limited impact on ultimate prognosis.

The detailed characterization of individual recurrence phenotypes, their association with molecular subtype, and implications for surveillance strategy are presented in Table 1.

Table 1. Recurrence phenotypes in endometrial cancer: anatomical distribution, molecular subtype associations, and implications for surveillance strategy.

Recurrence Phenotype	Typical Location	Molecular Subtype Association (incl. ER status)	Potential for Curative Treatment	Implications for Surveillance Strategy
Isolated vaginal recurrence	Vaginal vault	MMRd; NSMP (particularly ER+ low-grade)	**High** (radiotherapy ± surgery)	Early detection has high clinical value; 5-year OS after salvage RT **70–83%** [17,18]
Isolated pelvic recurrence	Pelvis	MMRd; NSMP (preferentially ER+)	**Moderate** (RT or surgery in selected cases)	Clinical examination has high value; pelvic MRI recommended when recurrence is suspected
Isolated nodal recurrence	Pelvic / para-aortic lymph nodes	MMRd; NSMP (more frequently ER+); occasionally p53abn	**Moderate–high** (resection ± RT)	Secondary treatment with curative intent is feasible

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Oligometastatic recurrence	Lung, liver, bone (isolated lesions)	NSMP (more frequently ER+); rarely p53abn	**Limited**, but feasible (SBRT/SABR, surgery)	Early detection may enable targeted local treatment
Peritoneal / multifocal recurrence	Peritoneum, abdominal cavity	Typical for p53abn; NSMP ER− or high-grade	**Low** (systemic treatment as standard)	Early imaging has limited impact on prognosis
Systemic recurrence	Multiorgan	Most commonly p53abn; NSMP ER−	**Very low**	Priority: prompt initiation of systemic therapy

Background colors: green—recurrences with high or moderate potential for radical treatment; gray—recurrences with limited therapeutic modifiability. ER—estrogen receptor; OS—overall survival; RT—radiotherapy; SBRT/SABR—stereotactic body radiotherapy / stereotactic ablative radiotherapy. Survival data for salvage radiotherapy are based on Arden et al. [17] and Creutzberg et al. [18].

5. Proposed Surveillance Stratification Model

5.1. Rationale for the Three-Tier Model

Based on the relationships described above between molecular subtype, recurrence pattern, and therapeutic potential, we propose a three-tier surveillance model that would assign patients to one of three groups: low, intermediate, and high risk. This model is not intended as a prognostic classification system—its purpose is to suggest a biologically informed approach to stratifying surveillance intensity in a clinically useful manner.

It should be noted that the updated ESGO–ESTRO–ESP 2025 guidelines distinguish four prognostic groups: low, intermediate, high-intermediate, and high risk. In the proposed surveillance model, the intermediate and high-intermediate groups according to ESGO 2025 could reasonably be merged into a single intermediate surveillance category—on the grounds of broadly similar recurrence phenotype (locoregional predominance, therapeutic potential) and comparable rationale for clinical surveillance intensity. This pragmatic simplification is distinct from adjuvant treatment stratification, for which the distinction between these subgroups remains clinically important.

The key conceptual feature distinguishing the proposed model from existing surveillance schemes is that surveillance intensity would be determined not solely by the baseline risk of recurrence, but by the expected recurrence phenotype and the anticipated possibility of its therapeutic modification. This means that some patients with high biological recurrence risk (e.g., p53abn at advanced stage) may require intensive clinical surveillance aimed primarily at facilitating rapid initiation of systemic therapy, rather than intensive routine imaging. Conversely, patients in biologically intermediate groups (MMRd, NSMP) may justify heightened clinical vigilance precisely because their recurrences could remain amenable to curative-intent treatment.

5.2. Proposed Risk Group Assignment Criteria

Within the low-risk group, two broad patient categories could be considered. The first would include all patients with the POLEmut subtype, irrespective of clinical stage and histological grade, reflecting the consistently observed, exceptionally low recurrence risk in this subgroup. The second category could encompass patients with the NSMP subtype who simultaneously fulfill low-risk clinicopathological criteria—stage I, G1–2, myometrial invasion <50%, absent/focal LVSI, pN0—and who demonstrate absence of CTNNB1 mutation, positive ER expression, and absence of L1CAM overexpression. The inclusion of CTNNB1, ER, and L1CAM as modifiers is proposed exclusively within the NSMP group and reflects its biological heterogeneity. This profile may correspond to the most biologically indolent form of NSMP and could justify de-escalation of surveillance intensity [21].

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Within the intermediate-risk group, surveillance may carry the greatest clinical value, as the expected recurrence phenotype is more frequently locoregional or nodal—and therefore potentially amenable to local treatment—and, in the MMRd subtype, also to immunotherapy. This group could include: (i) patients with the MMRd subtype who do not meet proposed high-risk criteria; (ii) patients with NSMP and intermediate clinicopathological risk factors; (iii) patients with NSMP and CTNNB1 mutation, irrespective of ER status, who anatomically fulfill low-risk criteria; and (iv) patients with ER-negative NSMP in the absence of CTNNB1 mutation or without CTNNB1 assessment. In the proposed model, CTNNB1 mutation would serve as the primary modifier within NSMP, while ER would carry a secondary role, applied primarily when CTNNB1 results are unavailable.

Within the high-risk group, recurrence—if it occurs—may more frequently carry a systemic character, and post-recurrence prognosis tends to be significantly worse. Assignment to this group could be considered in the presence of: (i) the p53abn subtype, irrespective of stage; (ii) stage III–IV disease, irrespective of molecular subtype; or (iii) adverse clinicopathological features such as sentinel lymph node macro/micrometastases, substantial LVSI, or L1CAM overexpression, particularly within NSMP. In the NSMP subtype, a more aggressive biological phenotype—especially high-grade, ER-negative, or L1CAM-positive tumors—in combination with advanced anatomical stage could support high-risk assignment. In this group, the proposed surveillance goal would be primarily rapid initiation of systemic therapy or enrollment in clinical trials, rather than routine detection of asymptomatic recurrence.

In cases where CTNNB1 testing is unavailable, classification within NSMP may reasonably be based on ER status, with the understanding that this approach is inherently surrogate and could result in underestimation of risk in tumors that otherwise appear to fulfill the criteria of biologically favorable NSMP.

5.3. Proposed Classification Algorithm

The proposed classification algorithm for surveillance risk group assignment is illustrated in Figure 1. It suggests a four-step sequential decision-making approach based on molecular subtype assessment followed by evaluation of clinicopathological factors that may modify recurrence risk. The algorithm assumes the availability of basic molecular classification, including assessment of POLE mutation status, MMR status, and p53 immunohistochemical phenotype.

In the first step, identification of POLEmut tumors would lead to low-risk assignment irrespective of stage and other clinicopathological features. In the second step, identification of p53abn would support high-risk assignment irrespective of stage. The third step would involve assessment of high-risk clinicopathological factors—stage III–IV, sentinel lymph node macro/micrometastases, substantial LVSI, and, within NSMP, L1CAM overexpression—the presence of which could support high-risk group assignment.

Within the NSMP subtype, assessment of CTNNB1 mutation status is proposed as the primary modifier. The presence of a CTNNB1 mutation would support intermediate-risk assignment, even when anatomical low-risk criteria are otherwise fulfilled. When CTNNB1 mutation is absent or test results are unavailable, further classification could be based on ER status. In this context, patients with ER-positive NSMP presenting with low anatomical stage, absence of CTNNB1 mutation, and absence of L1CAM overexpression could be considered for low-risk surveillance. Conversely, ER-negative NSMP in an analogous setting could reasonably be treated as intermediate risk.

The proposed algorithm is pragmatic in character and is not intended to replace prognostic systems used for adjuvant treatment selection. Rather, it is designed to suggest how follow-up intensity might be aligned with the biologically anticipated recurrence phenotype. In the absence of complete molecular classification, surveillance strategy would appropriately fall back on classical clinicopathological factors in accordance with current guidelines.

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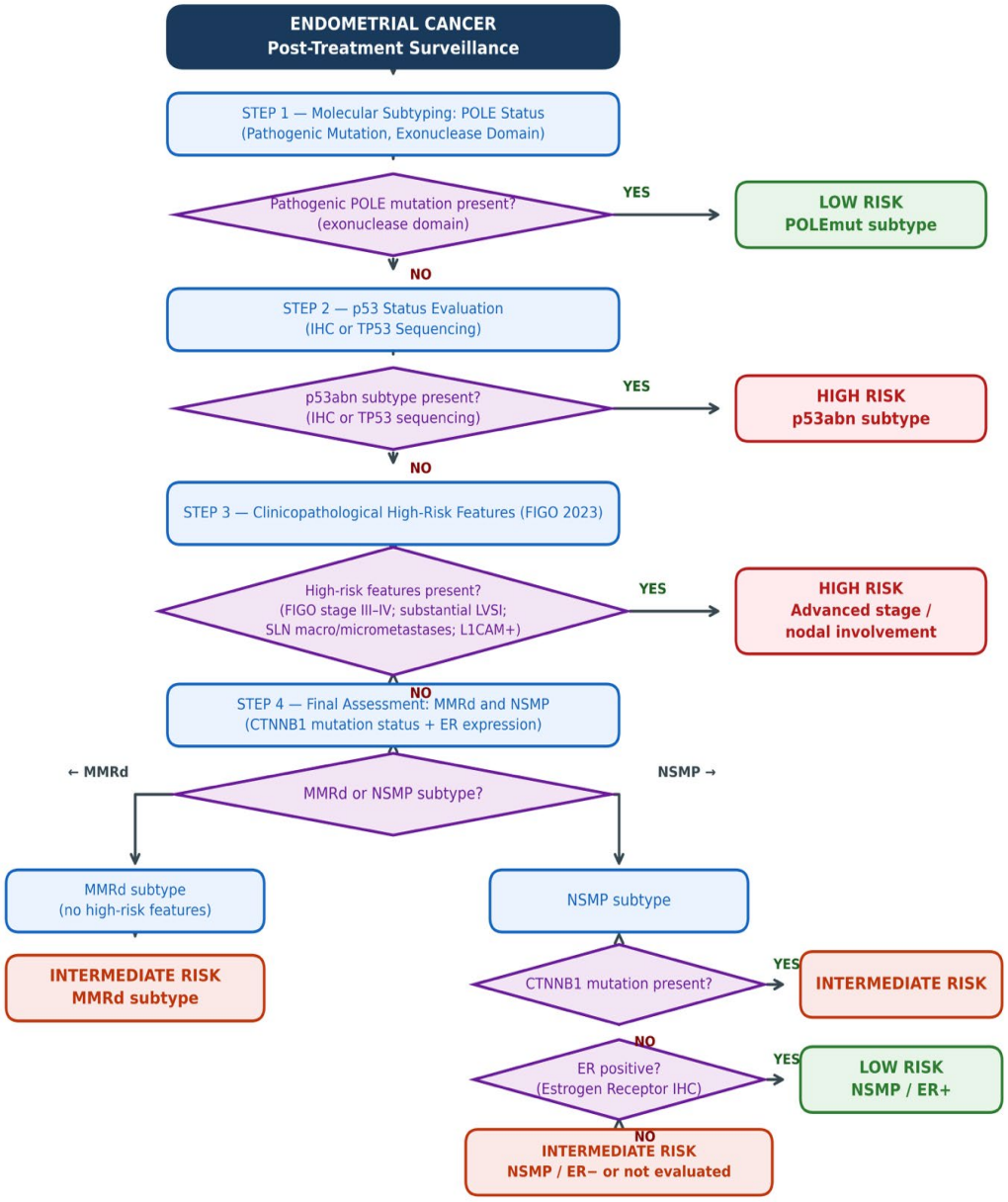

Figure 1. Proposed surveillance risk stratification algorithm for endometrial cancer patients following primary treatment. The algorithm follows a sequential molecular-to-clinicopathological logic: (1) identification of the ultra-favorable POLE^{mut} group; (2) exclusion of the high-risk p53abn subtype; (3) assessment of clinicopathological high-risk features (FIGO 2023 stage III–IV, substantial LVSI, macro/micro-metastases in lymph nodes, L1CAM expression); and (4) final refinement of MMRd and NSMP cohorts using CTNNB1 mutation status and Estrogen Receptor (ER) expression. Risk groups are colour-coded: green = low risk, orange = intermediate risk, red = high risk. **Abbreviations:** POLE = DNA polymerase epsilon (exonuclease domain); p53abn = abnormal p53 expression (IHC); IHC = immunohistochemistry; LVSI = lymphovascular space invasion; L1CAM = L1 cell adhesion molecule; MMRd = mismatch repair deficient; NSMP = no specific molecular profile; CTNNB1 = beta-catenin gene; ER = estrogen receptor; FIGO = International Federation of Gynecology and Obstetrics 2023.

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6. Proposed Surveillance Schedule

Table 2. Proposed post-treatment surveillance schedule for endometrial cancer patients according to risk group.

Parameter	Low Risk	Intermediate Risk	High Risk	Notes
Molecular-clinical profile	POLE^mut or NSMP: ER+, CTNNB1 wt, L1CAM−; stage I, G1–2, MI <50%, LVSI absent/focal	MMRd without high-risk features; NSMP CTNNB1^mut; NSMP ER− at low stage	p53abn; stage III–IV; macro- or micro-metastases; substantial LVSI; L1CAM+	CTNNB1—primary modifier within NSMP
Years 1–2	Every 6 months	Every 4 months	Every 3 months	Highest recurrence risk within the first 24 months
Years 3–5	Every 12 months	Every 6 months	Every 4–6 months	Late recurrences possible in MMRd and NSMP
After 5 years	Discharge or primary care follow-up	Individualized follow-up (approx. 12 months)	Individualized follow-up (6–12 months)	Further surveillance based on ongoing risk assessment
Clinical examination	History + gynaecologic examination	History + gynaecologic examination	History + gynaecologic examination	Cornerstone of surveillance
Imaging	Not routinely	Pelvic MRI or CT if symptomatic	Individualized chest/abdominal/pelvic CT; low threshold for suspected recurrence	Aim: rapid eligibility assessment for salvage treatment
CA125	Not routinely	Consider if elevated at baseline or recurrence suspected	Low threshold for testing	Adjunct marker
Vaginal cytology	Not recommended	Not recommended	Not recommended	Per ESGO–ESTRO–ESP 2025 guidelines

* Routine vaginal vault cytology is not recommended per ESGO–ESTRO–ESP 2025 guidelines. Abbreviations: MI—myometrial invasion; LVSI—lymphovascular space invasion; ER—estrogen receptor; CA125—cancer antigen 125; CT—computed tomography; MRI—magnetic resonance imaging; ESGO—European Society of Gynaecological Oncology; ESTRO—European Society for Radiotherapy and Oncology; ESP—European Society of Pathology.

These observations may suggest that patterns of recurrence, and therefore optimal surveillance strategies, could be influenced by previous adjuvant treatment. However, this hypothesis requires prospective validation.

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Below, we discuss the rationale for the individual components of the surveillance schedule and the key differences in follow-up strategy that arise from the distinct expected recurrence phenotype across risk groups.

Clinical examination forms the cornerstone of surveillance in all three risk groups—a targeted history focused on symptoms of recurrence and a gynecological physical examination including speculum examination and bimanual pelvic assessment. The value of clinical examination in detecting symptomatic recurrence is well established, and data from the TOTEM trial confirm that extending the surveillance schedule to include routine laboratory tests and imaging does not improve overall survival [4,5]. Additional investigations should therefore be used selectively, based on individual clinical assessment and tumor biology.

The intensity and focus of the clinical examination differ across risk groups, however. In the intermediate-risk group (MMRd, NSMP with risk factors), where the expected recurrence phenotype is frequently locoregional, particular emphasis should be placed on a thorough pelvic examination—both speculum assessment for early vaginal vault changes and careful bimanual evaluation of the parametria, pelvic sidewalls, and accessible lymph nodes. The history should focus on locoregional symptoms: vaginal bleeding or discharge, pelvic pain, and lower limb edema. In the high-risk group (p53abn, stage III–IV), where systemic recurrences predominate, the history should encompass a broader spectrum of symptoms: abdominal pain, bloating, increase in abdominal girth, dyspnea, cough, and unexplained weight loss. Physical examination should include abdominal palpation (ascites, masses) and assessment of performance status.

CA125 measurement is primarily justified in the intermediate- and high-risk groups, but in distinct clinical contexts. In the intermediate-risk group, CA125 may be measured regularly (every three to six months) in patients in whom it was elevated at baseline, as an adjunct marker for early detection of locoregional recurrence. In the high-risk group, a low threshold for regular CA125 testing (every three to four months in the first two years) reflects the need to monitor for systemic progression and facilitate prompt treatment initiation. The value of CA125 remains limited, however—sensitivity for detecting early recurrences is low, and false-positive results can generate unnecessary diagnostic workup and patient anxiety.

Imaging—pelvic MRI, abdominal and thoracic CT, PET-CT—is not recommended routinely in the low-risk group. The key difference between the intermediate- and high-risk groups concerns the type and purpose of imaging, reflecting the distinct expected recurrence phenotype.

In the intermediate-risk group (MMRd, NSMP with risk factors), the priority is detection of locoregional recurrence—vaginal, pelvic, or nodal—that may qualify for radical treatment (salvage radiotherapy, surgical resection) or, in the case of MMRd, for immunotherapy. In this context, selective use of pelvic MRI when clinical suspicion arises (abnormality on gynecological examination, pelvic pain, lower limb edema, rising CA125) has greater diagnostic value than routine whole-body CT. MRI offers superior soft tissue resolution and more precise assessment of the vaginal vault, parametria, and regional lymph nodes. Imaging in this group is targeted in nature—employed on specific clinical suspicion rather than as routine screening. A lower threshold for imaging should be considered in patients with ER-negative NSMP or NSMP with CTNNB1 mutation, given the more unpredictable clinical course in these subgroups.

In the high-risk group (p53abn, stage III–IV, ER-negative NSMP at stage I), the expected recurrence phenotype is systemic dissemination—pulmonary, hepatic, peritoneal, and distant nodal metastases. The surveillance goal in this group is not routine detection of asymptomatic recurrence, but rather prompt eligibility assessment for systemic therapy or clinical trials at the earliest sign of progression. Chest, abdominal, and pelvic CT may be considered on an individualized basis in the first two years after treatment (e.g., every six to twelve months), particularly in p53abn patients at stage I–II, where early detection of asymptomatic recurrence could potentially influence eligibility for systemic treatment. It should be emphasized, however, that the impact of routine imaging on overall survival in this group remains unproven, and the potential benefits must be weighed against costs, radiation exposure, and the risk of false-positive results generating unnecessary diagnostic

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workup. In advanced stages (III–IV) or in patients following adjuvant treatment, routine imaging is not recommended—imaging should be performed based on clinical symptoms or rising CA125.

Routine vaginal vault cytology is not recommended in any risk group. Multiple lines of evidence indicate that its sensitivity for detecting locoregional recurrence is lower than that of clinical examination, and the current ESGO 2025 guidelines do not recommend it as a component of standard follow-up [8].

An independent but important complementary element of the surveillance visit structure is patient education. Patients in all risk groups should be informed about symptoms requiring prompt medical contact, with the educational content tailored to the expected recurrence phenotype. In the intermediate-risk group, particular emphasis should be placed on locoregional symptoms: vaginal bleeding or discharge, pelvic pain, and lower limb edema. In the high-risk group, education should cover a broader spectrum of systemic symptoms: abdominal pain, bloating and increase in abdominal girth, new changes in bowel habits, dyspnea, cough, and unexplained weight loss. This approach—referred to as *symptom-triggered follow-up* or *patient-led surveillance*—complements scheduled clinical visits and may shorten the interval between symptom onset and diagnosis, particularly in the low-risk group where visit frequency is deliberately limited. These standards are consistent with practices employed in national oncology models—including the Danish endometrial cancer follow-up guidelines—which explicitly incorporate patient education as an integral component of surveillance [9].

7. Discussion

7.1. Post-Treatment Surveillance and the Question of Clinical Value

The proposed framework stems from a fundamental reframing of the surveillance question. Rather than asking *how often and how intensively* patients should be monitored, we suggest the more clinically productive question is *which recurrences are worth detecting earlier, because doing so changes management*. Within this framework, the value of surveillance is defined by the therapeutic modifiability of recurrence, rather than by detection frequency per se. This distinction has direct practical consequences: it argues for de-escalation in groups where detected recurrences are unlikely to alter treatment, and for targeted intensification where early identification enables curative-intent intervention or biologically informed systemic therapy.

The TOTEM trial, despite demonstrating no survival benefit from intensive surveillance and no improvement in health-related quality of life [4,5], was designed before molecular subtype was recognized as a determinant of recurrence biology. Its results therefore do not preclude benefit from molecularly stratified follow-up, and should not be extrapolated to patient groups defined by molecular criteria.

7.2. Molecular Subtype as a Determinant of Surveillance Value

The clinical heterogeneity of endometrial cancer recurrence—documented most comprehensively in the KImBer cohort [15] and corroborated by molecular analyses of the PORTEC-3 trial [12]—directly informs the proposed stratification logic. The critical surveillance implication is not simply that recurrence rates differ by subtype, but that the phenotype of recurrence differs in a therapeutically meaningful way. Locoregional relapses in MMRd and NSMP may be intercepted at a stage where curative-intent treatment remains feasible; systemic relapses in p53abn typically are not. Surveillance intensity should therefore reflect this asymmetry rather than baseline recurrence probability alone.

Post-recurrence survival differences across subtypes—ranging from 43 months in MMRd to 10 months in p53abn [15]—further support this argument. In groups where post-recurrence prognosis is more favorable, earlier detection may be more likely to create an opportunity for clinically meaningful intervention. Importantly, long-term follow-up data from PORTEC-3 confirm that molecular subtype differences in recurrence risk and treatment benefit persist beyond ten years of

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observation [14], reinforcing the rationale for sustained, biology-informed surveillance rather than uniform time-limited follow-up.

7.3. The Particular Role of Immunotherapy in MMRd Surveillance

The emergence of effective immunotherapy for MMRd endometrial cancer substantially strengthens the case for attentive surveillance in this subgroup. Immune checkpoint inhibitors—used as monotherapy or in combination with kinase inhibitors—have demonstrated durable responses in the recurrent MMRd setting [22,23], meaning that early identification of relapse may now translate not only into eligibility for local salvage treatment but also into timely access to highly active systemic therapy. This dual benefit—local and systemic—is specific to the MMRd subtype and represents a qualitative shift in the surveillance calculus compared with the pre-immunotherapy era.

One important caveat is that treatment decisions based on primary tumor biology assume molecular concordance between the primary and recurrent tumor. Available evidence suggests this concordance is generally maintained for MMR status [24], though prospective data remain limited.

7.4. The Proposed Model in Relation to Existing Guidelines

The proposed framework differs from the current ESGO–ESTRO–ESP 2025 recommendations [8] and NCCN guidelines principally in that molecular subtype serves as the primary criterion for surveillance stratification, rather than as a supplementary prognostic modifier. Current guidelines do not differentiate follow-up schedules according to molecular subtype; the proposed model argues that this differentiation is biologically justified and may be practically feasible in centers with access to standard molecular profiling.

The economic dimension also merits consideration. The TOTEM trial demonstrated that intensive surveillance is more costly than the minimalist approach without a corresponding survival or quality-of-life benefit [4,5]. De-escalation of imaging surveillance in the proposed low-risk group—which may comprise 30–40% of patients—could generate meaningful resource savings, potentially allowing reallocation toward more intensive follow-up in MMRd and p53abn groups. Formal health-economic evaluation of this reallocation would, however, be required before any system-level recommendation could be made.

Regarding biomarker integration within NSMP: ER expression and CTNNB1 mutation status are both incorporated in the proposed model as modifiers, consistent with the evolving evidence base [25] and with the direction of current guideline development [8]. L1CAM overexpression, already recognized as a high-risk modifier in ESGO 2025 [8], is similarly included [21]. The observation that molecular subtype differences in clinical outcomes persist over ten years of follow-up [14] further supports the incorporation of molecular criteria into long-term surveillance planning. None of these modifiers has been prospectively validated in a surveillance-specific context, and their inclusion should be understood as biologically motivated rather than evidence-proven.

The proposed model also introduces a more explicitly defined surveillance goal—particularly in the high-risk group, where the emphasis shifts from routine detection of asymptomatic recurrence toward prompt eligibility assessment for systemic therapy or clinical trial enrollment.

7.5. Limitations of the Proposed Model

The most important limitation of the proposed framework is the absence of prospective validation. No randomized trial evaluating molecularly informed surveillance strategies has been conducted to date, and the model should therefore be regarded as a hypothesis-generating proposal rather than a practice-changing recommendation.

A second limitation is the variable availability of molecular diagnostics. Despite expanding access to molecular profiling, complete TCGA-based classification remains inaccessible in many healthcare systems. Data from Poland illustrate the extent of inter-institutional variability in this regard [26].

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Third, the NSMP subtype remains internally heterogeneous, and the roles of ER, CTNNB1, and L1CAM as surveillance modifiers require further validation [21,25]. Fourth, prior adjuvant treatment may itself modify recurrence pattern—data from the KImBer cohort suggest that adjuvant radiotherapy shifts the recurrence distribution toward distant sites [15]—implying that surveillance strategy may need to account for treatment history in addition to molecular subtype.

Finally, the role of hormone replacement therapy after endometrial cancer treatment lies beyond the primary scope of this model. Available data suggest no substantial increase in recurrence risk in selected early-stage patients, but molecularly stratified data remain limited [27–30].

7.6. Future Directions and Prospective Validation

The proposed surveillance framework should be considered a hypothesis-generating model that requires prospective validation. Future studies should evaluate whether molecularly informed surveillance improves clinically meaningful outcomes compared with conventional follow-up strategies. Prospective cohort studies or registry-based analyses could assess recurrence patterns within molecular subtypes in the context of contemporary adjuvant therapies, including immunotherapy and combined systemic approaches. In addition to overall survival, relevant endpoints should include time to recurrence detection, proportion of salvageable recurrences, time to initiation of systemic therapy, patient-reported quality of life, and health-economic outcomes. Ultimately, a randomized comparison between biology-driven surveillance and standard follow-up strategies may be required to determine whether molecularly stratified surveillance provides measurable clinical benefit.

8. Conclusions

A uniform post-treatment surveillance schedule for endometrial cancer, based exclusively on clinical stage and histological grade, does not reflect the biological heterogeneity of this disease as revealed by TCGA-based molecular classification. The proposed framework integrates molecular subtype, clinicopathological factors, and the expected recurrence phenotype into a three-tier surveillance stratification model.

The key conceptual shift is a redefinition of the surveillance goal: instead of asking how often patients should be followed up, the more relevant question is which recurrences are worth detecting early because doing so may change clinical management. Locoregional recurrences, which are more frequent in the MMRd and NSMP subtypes, may remain amenable to curative-intent treatment and therefore justify heightened clinical vigilance. By contrast, systemic recurrences, which are more typical of p53abn disease, more often require prompt initiation of systemic therapy or consideration for clinical trial enrollment.

Prospective cohort studies are needed to evaluate recurrence patterns across molecular subtypes in the era of contemporary adjuvant treatment, particularly following the introduction of immunotherapy into the first-line setting. Ultimately, a randomized trial comparing molecularly stratified surveillance with conventional clinicopathological follow-up would be required, with endpoints including quality of life, healthcare costs, and survival.

Until such data become available, the proposed model should be regarded as a biologically grounded decision-making framework and a starting point for further validation.

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