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ASSESSING THE DIAGNOSTIC ACCURACY OF 3D TRANSVAGINAL ULTRASONOGRAPHY FOR ENDOMETRIAL CANCER STAGING: A COMPARATIVE ANALYSIS OF DIFFERENT METHODS

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ABSTRACT

Background: Endometrial carcinoma (EC) is among the most prevalent malignancies in the female population and represents the only gynecological cancer currently characterized by a rising trend in both incidence and mortality, ranking as the third most frequent carcinoma among women aged 50 to 69 in Italy. Recently, the understanding of the disease has shifted from the traditional Bokhman dualistic model to a complex molecular framework (TCGA), identifying four distinct prognostic subgroups. The main therapeutic strategy involves a tailored surgical approach, typically incorporating total extrafascial hysterectomy, bilateral salpingo-oophorectomy, and sentinel lymph node (SLN) mapping, which has largely replaced systematic lymphadenectomy for early-stage disease. Following the surgical procedure, an integrated anatomopathological and molecular staging is conducted, in accordance with the landmark 2023 FIGO staging system and the updated 2025 ESGO-ESTRO-ESP guidelines.

To ensure the most appropriate surgical management and accurately evaluate critical prognostic parameters, such as the depth of myometrial invasion, cervical involvement, and lymph node status, dedicated preoperative imaging is mandatory. While pelvic Magnetic Resonance Imaging (MRI) remains a cornerstone and the gold standard modality for local staging, its routine application can be limited by costs and patient-related contraindications.

Consequently, three-dimensional transvaginal ultrasound (3D-TVUS) has emerged as a pivotal and highly accessible diagnostic tool. By allowing multiplanar reconstruction and objective volumetric assessments, current evidence demonstrates that 3D-TVUS is a dependable imaging modality, offering a diagnostic test accuracy comparable to MRI for the preoperative staging of deep myometrial and cervical stromal invasion in patients with endometrial cancer.

Aim: To assess the suitability of three-dimensional transvaginal ultrasound (3D-TVUS) as a valid support or alternative to Magnetic Resonance Imaging (MRI) during the preoperative assessment of endometrial cancer (EC). Specifically, we aim to

evaluate and compare their diagnostic accuracy in detecting deep myometrial invasion (≥ 50%) as a primary endpoint, alongside cervical and vaginal involvement as secondary endpoints.

Materials and method: A prospective, double-blind, non-profit observational study was conducted on patients with a histopathological diagnosis of EC referred to the Gynecologic Oncology Clinic of the University of Padua. Patients underwent 3D-TVUS and pelvic MRI to assess myometrial (≥ 50%), cervical, and vaginal invasion. For each patient, clinical data (e.g., date of birth, parity, BMI, menopausal status), histological data from diagnostic biopsies and surgical specimens (histotype and grade), and radiological parameters (infiltration of the myometrium, cervix, vagina, and the presence of pathological lymph nodes) were collected. The diagnostic performances of 3D-TVUS and MRI were evaluated and compared using the final surgical histopathological examination as the reference standard.

Results: 3D-TVUS showed a higher overall agreement with final histology compared to MRI (Cohen's Kappa 0.29 vs 0.25). For deep myometrial invasion, 3D-TVUS demonstrated slightly superior sensitivity (75.7% vs 71.4%) and NPV (78.1% vs 74.4%), with comparable overall accuracy (67.4% vs 66.7%). Regarding cervical invasion, MRI was more sensitive (58.3% vs 41.7%), but 3D-TVUS maintained an excellent specificity (98.7%), making it an optimal method for excluding cervical involvement. Regarding vaginal invasion, the extremely low prevalence in our cohort (7 cases) limited the statistical evaluation, showing poor sensitivity for both MRI and 3D-TVUS.

Conclusions: 3D-TVUS is a valuable diagnostic tool, comparable to MRI for the preoperative staging of endometrial cancer. Given its rapid accessibility and lower costs, 3D-TVUS is proposed as a first-line imaging modality for immediate and personalized risk stratification, reserving MRI for doubtful cases.

RIASSUNTO

Premesse dello studio: Il carcinoma endometriale è una delle neoplasie più diffuse nella popolazione femminile e rappresenta l'unico tumore ginecologico attualmente caratterizzato da un trend in aumento sia in termini di incidenza che di mortalità, posizionandosi come la terza neoplasia più frequente tra le donne di età compresa tra i 50 e i 69 anni in Italia. Recentemente, la comprensione della patologia è passata dal tradizionale modello dualistico di Bokhman a un complesso sistema di classificazione molecolare (TCGA), che identifica quattro distinti sottogruppi prognostici. L'approccio terapeutico principale prevede una chirurgia su misura, che tipicamente include l'isterectomia totale extrafasciale, la salpingo-ooforectomia bilaterale e la mappatura del linfonodo sentinella, una tecnica che ha ampiamente sostituito la linfoadenectomia sistematica per la malattia in stadio iniziale. A seguito della procedura chirurgica, viene condotta una stadiazione anatomo-patologica e molecolare integrata, in accordo con il recente sistema di stadiazione FIGO 2023 e le linee guida aggiornate ESGO-ESTRO-ESP del 2025.

Per garantire la gestione chirurgica più appropriata e valutare con precisione i parametri prognostici critici, come la profondità dell'invasione miometriale, il coinvolgimento cervicale e lo stato linfonodale, un accurato imaging preoperatorio è di fondamentale importanza. Sebbene la risonanza magnetica (RM) pelvica rimanga un pilastro e la metodica "gold standard" per la stadiazione locale, la sua applicazione di routine può essere limitata dai costi elevati e da specifiche controindicazioni legate alle pazienti.

Di conseguenza, l'ecografia transvaginale tridimensionale (3D-TVUS) è emersa come uno strumento diagnostico fondamentale, rapido e altamente accessibile. Consentendo la ricostruzione multiplanare e valutazioni volumetriche oggettive, le evidenze attuali dimostrano che la 3D-TVUS è una metodica di imaging altamente affidabile, in grado di offrire un'accuratezza diagnostica paragonabile a quella della RM per la stadiazione preoperatoria dell'invasione miometriale profonda e del coinvolgimento dello stroma cervicale nelle pazienti affette da carcinoma endometriale.

Scopo dello studio: Lo scopo di questo studio è valutare l'idoneità dell'ecografia 3D come valido supporto o alternativa alla RM nella valutazione preoperatoria del

carcinoma endometriale. Nello specifico, lo studio mira a confrontare la loro accuratezza diagnostica nel rilevare l'invasione miometriale profonda (≥ 50%) come obiettivo primario, e il coinvolgimento cervicale e vaginale come obiettivi secondari.

Materiali e metodi: È stato condotto uno studio osservazionale prospettico in doppio cieco, senza fini di lucro, su pazienti con diagnosi istopatologica di CE indirizzati alla Clinica di Ginecologia Oncologica dell'Università di Padova. Le pazienti sono state sottoposte a 3D-TVUS e RM pelvica per valutare l'invasione miometriale (≥ 50%), cervicale e vaginale. Per ogni paziente sono stati raccolti dati clinici (es. data di nascita, parità, BMI, stato menopausale), dati istologici derivati da biopsie diagnostiche e dai pezzi operatori (istotipo e grading) e parametri radiologici (infiltrazione del miometrio, della cervice, della vagina e la presenza di linfonodi patologici). Le performance diagnostiche della 3D-TVUS e della RM sono state valutate e confrontate utilizzando l'esame istopatologico chirurgico finale come reference standard.

Risultati: La 3D-TVUS ha mostrato una concordanza globale con l'esame istologico superiore alla RM (Kappa 0,29 vs 0,25). Per l'invasione miometriale, la 3D-TVUS ha evidenziato sensibilità (75,7% vs 71,4%) e VPN lievemente superiori alla RM (78.1% vs 74.4%), a fronte di un'accuratezza globale comparabile (67.4% vs 66.7%). Per l'invasione cervicale, la RM è risultata più sensibile (58,3% vs 41,7%), ma la 3D-TVUS ha mantenuto un'eccellente specificità (98,7%), dimostrandosi ottimale per escludere l'interessamento di tale sede. Per quanto riguarda l'invasione vaginale, la bassissima prevalenza nel campione ha limitato la valutazione statistica, evidenziando una scarsa sensibilità per entrambe le metodiche.

Conclusioni: La 3D-TVUS si conferma uno strumento diagnostico valido e comparabile alla RM per la stadiazione preoperatoria del carcinoma endometriale. Garantendo tempistiche e costi ridotti, si propone come esame di imaging di primo livello per una stratificazione immediata e personalizzata del rischio, riservando la RM ai casi ecograficamente dubbi.

1 INTRODUCTION

1.1 EPIDEMIOLOGY, RISK AND PROTECTIVE FACTORS

1.1.1 Epidemiology

Endometrial carcinoma (EC) is among the most prevalent malignancies in the female population and represents the only gynecological cancer currently characterized by a rising trend in both incidence and mortality. In 2024, approximately 8.652 new cases were diagnosed in Italy, accounting for 5.5% of all female oncological diagnoses and ranking as the third most frequent neoplasm among women aged 50–69 years. Regarding mortality, 2.500 deaths were attributed to uterine cancers in 2022. Currently, there are an estimated 133.300 women in Italy surviving after a diagnosis of uterine corpus cancer (1).

Furthermore, global incidence rates exhibit significant geographical variability, with up to a tenfold difference between regions. The highest rates are documented in North America, Europe, Micronesia/Polynesia, and Australia/New Zealand, whereas the lowest incidence is observed across most of Africa and South-Central Asia. Regional disparities in mortality rates are less pronounced, although peak values are primarily recorded in Eastern Europe, Micronesia/Polynesia, the Caribbean, and North America (2).

1.1.2 Risk Factors

The disparate geographical distribution of endometrial carcinoma (EC) is primarily attributable to the heterogeneity of its associated risk factors. In accordance with the World Cancer Research Fund (WCRF) report, the association between sedentary behavior and endometrial cancer risk is supported by suggestive evidence (3).

Obesity and conditions related to metabolic syndrome, such as type 2 diabetes mellitus, represent major risk factors for the development of EC (4). Evidence indicates that this

correlation follows a dose-response relationship with the Body Mass Index (BMI), showing a threefold to fourfold increased risk in women with a BMI > 30 kg/m² (5). Hyperinsulinemia, which frequently precedes the onset of diabetes, also appears to be causally linked to EC. This association is likely mediated by both direct mitogenic effects and an increase in bioavailable estrogen levels resulting from the downregulation of sex hormone-binding globulin (SHBG) (6).

Furthermore, conditions characterized by estrogen excess, such as estrogen-secreting tumors or hormone replacement therapy without progestogen opposition, significantly elevate the risk of EC (7). Tamoxifen, which exerts anti-estrogenic effects on breast tissue but pro-estrogenic activity on the uterus, approximately doubles the risk of developing both endometrioid and non-endometrioid EC subtypes; this risk may increase up to fourfold when treatment duration exceeds five years (4,8).

In women with polycystic ovary syndrome (PCOS) and irregular menstrual cycles, the protective effect of progesterone is diminished or absent. The resulting chronic, unopposed estrogenic stimulation increases the risk of endometrial hyperplasia, irregular bleeding, and malignancy (9).

Beyond common lifestyle, metabolic factors and isolated genetic predisposition, a familial susceptibility to malignancies across multiple organ systems may occur, as characterized by Lynch Syndrome (LS) Type II, which involves the endometrium, breast, colon, and ovaries. In women with Lynch Syndrome, the lifetime risk of developing malignancies is estimated at 40–80% for colorectal carcinoma, 40–60% for endometrial carcinoma, and 10–12% for ovarian cancer. The clinical presentation of endometrial neoplasia in a young patient should be considered a sentinel event for Lynch Syndrome; this necessitates the implementation of specialized diagnostic testing, rigorous screening protocols, and targeted preventive strategies aimed at reducing LS-associated morbidity and mortality (10,11).

1.1.3 Protective Factors

Epidemiological evidence, synthesized in a large-scale meta-analysis, indicates a significant inverse association between parity and the risk of endometrial carcinoma (EC). Specifically, multiparous women exhibit a substantially lower risk of developing EC compared to nulliparous individuals, with a pooled relative risk (RR) of 0.69 (12). The protective mechanism of parity is primarily driven by the profound shift in the hormonal profile during delivery, characterized by a high-progestogen environment during pregnancy that opposes estrogen-driven proliferation, followed by a hormonal clearing at delivery. Epidemiological data suggest that among multiparous women, each birth following the second child is associated with an incremental 10% reduction in the risk of developing the disease (13).

Furthermore, advanced maternal age at the time of the last pregnancy appears to be a critical determinant; women who give birth later in their reproductive years exhibit a lower risk of EC compared to younger mothers. Specifically, childbearing after the age of 40 is linked to a risk reduction of up to 60%. This phenomenon may be explained by the 'mechanical exfoliation' hypothesis, which posits that the physical shedding of the endometrium during delivery removes epithelial cells in early or advanced stages of premalignant or malignant transformation (14).

In addition to parity, breastfeeding has been identified as a significant modifiable protective factor against the development of endometrial carcinoma. Findings from a large-scale pooled analysis involving 17 studies demonstrate that women who have ever breastfed exhibit an 11% reduction in EC risk compared to those who have never breastfed. This protective effect appears to be duration-dependent, with longer cumulative breastfeeding periods associated with a progressively lower risk of malignancy. From a biological perspective, the risk reduction is primarily attributed to the suppression of ovulation and the resulting state of lactational amenorrhea, which significantly limits the endometrium’s exposure to the mitogenic effects of endogenous estrogens. Furthermore, breastfeeding may promote the shedding of endometrial cells post-partum, potentially eliminating cells that have undergone early oncogenic transformations (15).

Consistent with the role of hormonal exposure, the duration of a woman's reproductive lifespan significantly influences the risk profile for endometrial carcinoma. Just as pregnancy and breastfeeding limit the endometrium's exposure to cyclic hormonal fluctuations, late menarche and early menopause serve as protective factors by reducing the cumulative number of ovulatory cycles. Conversely, early menarche and late menopause are associated with an increased risk of EC, further underscoring how prolonged lifetime exposure to endogenous estrogens promotes oncogenesis (16).

In addition to endogenous factors, exogenous hormonal modulation through oral contraceptives offers substantial protection against endometrial malignancy. The use of combined oral contraceptive pills, containing both estrogen and progestin, significantly reduces the risk of EC. Remarkably, this protective effect is long-lasting, persisting for up to 20 years after the discontinuation of the treatment (14).

1.2 HISTOLOGICAL CLASSIFICATION

1.2.1 The Bokhman Model: Type I and Type II

In 1983, Bokhman identified two distinct clinico-pathological variants of endometrial carcinoma (EC) based on a prospective study of 366 patients. He hypothesized that the divergent biological, clinical, and prognostic characteristics of the disease were rooted in different endocrine and metabolic alterations underlying tumor development, thus categorizing the malignancy into Type I and Type II (17).

Type I, or endometrioid carcinoma, accounts for 60–70% of cases and is associated with hypothalamic-pituitary-ovarian hyperactivity resulting in hyperestrogenism, as well as disturbances in lipid and carbohydrate metabolism. These tumors are generally well-differentiated, maintaining histological features similar to normal tissue and exhibiting hormone dependence. Typical clinical features in these patients, who are predominantly peri-menopausal, include prolonged anovulatory uterine bleeding, antecedent ovarian and endometrial hyperplasia, uterine myomas, obesity, hyperlipidemia, diabetes mellitus, and hypertension (17).

In contrast, Type II, or non-endometrioid carcinoma, occurs in 30–40% of patients and is not characterized by the aforementioned endocrine-metabolic disturbances. These are more frequently poorly differentiated tumors with a higher incidence of metastatic spread to the pelvic lymph nodes. This subtype is characterized by a brief duration of symptoms, an absence of menstrual or generative anomalies, no signs of hyperestrogenism, and a lack of preceding endometrial hyperplasia. Type II tumors typically affect post-menopausal women (17,18).

Prognostic outcomes were found to be significantly more favorable in Type I compared to Type II patients, with 5-year survival rates of 85.6% and 58.8%, respectively. This suggests that the endocrine-metabolic disturbances associated with Type I might play a role in the development of better-differentiated, less aggressive tumors (17).

While the Type I vs. Type II paradigm remains informative for educational and epidemiological purposes, it lacks sufficient utility for pathological tumor stratification due to the substantial clinical, pathological, and molecular overlaps observed between

the two subtypes. For instance, it does not account for endometrioid tumors occurring in Lynch syndrome patients, who are generally non-obese and whose pathology is often independent of hyperplasia. Furthermore, epidemiological evidence indicates that obesity is also associated with Type II tumors, albeit to a lesser extent than Type I. Consequently, Type I and Type II cancers share various risk factors (e.g., history of diabetes, age at menarche) and protective factors (e.g., multiparity, oral contraceptive use, and tobacco exposure) (19).

1.2.2 WHO Classification

Over the past decade, it has become increasingly evident that endometrial carcinoma comprises a heterogeneous group of tumors with distinct biological, clinical, morphological, and genetic profiles. Traditional classifications often fail to capture this diversity and, being primarily prognostic, offer limited utility in predicting therapeutic response. According to the WHO Classification of Tumors (5th Edition, 2020; Table I), several histological subtypes are recognized, each characterized by specific molecular features, microscopic appearance, precursor lesions, and natural history.

***Table I**: Relative frequency of endometrial carcinoma histological subtypes*

Histological Subtype	**Frequencies**
Endometrioid Carcinoma	80%
Serous Carcinoma	<10%
Clear Cell Carcinoma	2%
Undifferentiated and Dedifferentiated Carcinoma	2%
Mixed Carcinoma	2%
Carcinosarcoma	<2%
Rare Types: Mesonephric adenocarcinoma, Squamous cell carcinoma, Mucinous carcinoma - intestinal type, mesonephric-like adenocarcinoma	<2%

The primary histological subtypes include:

1. **Endometrioid Carcinoma (EEC):** Representing the most prevalent histological subtype, EEC can be categorized as either pure or mixed based on the presence of a non-endometrioid component. Specifically, the diagnosis of a "mixed" carcinoma is reserved for cases where the secondary histological component (typically serous or clear cell) constitutes more than 10% of the tumor sample; otherwise, it is classified as a pure variant, which remains the most common clinical presentation. EEC is further graded into low-grade (G1 and G2) and high-grade (G3) based on the architecture of non-squamous solid growth (G1: <5%; G2: 6–50%; G3: >50%). While low-grade cases generally carry a favorable prognosis, high-grade EEC exhibits significant nuclear atypia and increased mitotic activity. The 2020 WHO classification now incorporates the mucinous variant as a subtype of low-grade EEC, emphasizing that its biological behavior and molecular profile align with endometrioid rather than gastrointestinal-type malignancies (20).
2. **Serous Carcinoma (SC)**: An aggressive, high-grade subtype accounting for 5–10% of cases. It is more common in older women, often with a history of pelvic irradiation, Tamoxifen therapy, or breast cancer. SC has a high propensity for myometrial and lymphovascular space invasion (LVSI); consequently, up to 75% of patients present at stage III or IV(21). It carries a poor prognosis, with recurrence rates near 50%. The non-invasive form (formerly "endometrial intraepithelial serous carcinoma") is now considered part of the SC spectrum and can lead to extrauterine metastasis (20).
3. **Clear Cell Carcinoma (CCC):** A rare (~1%), high-grade malignancy typically affecting older patients. It is histologically heterogeneous and shares some features with serous carcinomas. By definition, CCC displays the same architectural features as clear cell carcinomas found in other areas of the female genital tract and is associated with a poor clinical outcome (20,22).
4. **Undifferentiated and Dedifferentiated Carcinoma**: Undifferentiated carcinoma consists of solid sheets of cells lacking identifiable glandular differentiation. Dedifferentiated carcinoma is a recently identified subtype

characterized by a combination of low-grade EEC (G1 or G2) and an undifferentiated component. These tumors are highly aggressive, frequently underrecognized, and commonly associated with Lynch Syndrome or inactivating mutations in the SWI/SNF complex proteins (SMARCA4 or SMARCB1) (20,23).

5. **Mixed Carcinoma**: These tumors comprise two or more distinct histological types, at least one of which must be a high-grade component (serous or clear cell) constituting at least 10% of the neoplasm. Strict criteria are required to distinguish them from heterogeneous endometrioid carcinomas, which may show mucinous or squamous differentiation (20).
6. **Carcinosarcoma (CS):** Previously categorized as a mixed epithelial-mesenchymal tumor, CS is now classified as a high-grade subtype of endometrial carcinoma. It exhibits a biphasic pattern with a high-grade carcinomatous component and a sarcomatous component, which may be homologous (tissues native to the uterus) or heterologous (e.g., rhabdomyoblastic, chondroid, or osteoid differentiation) (20).
7. **Rare Types**: The WHO 2020 classification also recognizes rare subtypes such as squamous cell carcinoma, mesonephric and mesonephric-like adenocarcinoma, and gastrointestinal-type mucinous carcinoma (20).

1.2.2.1 Prognostic Factors and Patterns of Spread

The degree of cellular differentiation significantly influences tumor dissemination. While G1 tumors tend to remain confined to the endometrium, G3 tumors show a higher frequency of deep myometrial involvement and lymph node metastasis. Key risk factors for distant metastasis include histological subtype, histological grade, depth of myometrial invasion, lymphovascular space invasion (LVSI), cervical involvement, and extrauterine spread. The most common sites for secondary localization include the lungs, liver, bones (primarily vertebrae), and brain (20).

1.3 THE MOLECULAR REVOLUTION: THE TCGA CLASSIFICATION

The publication of the Cancer Genome Atlas Research Network (TCGA) study in Nature (2013) marked a paradigm shift in the understanding of endometrial carcinoma. By analyzing 373 samples (including 307 endometrioid, 53 serous, and 13 mixed carcinomas) through DNA sequencing, methylation profiling, and microsatellite instability (MSI) analysis, the TCGA moved beyond the traditional dualistic classification toward a complex, four-tiered molecular framework: POLE ultramutated, MSI hypermutated, Copy number low/p53-wild-type and Copy number high/p53-mutated (24).

- **POLE Ultramutated**: Characterized by exceptionally high mutation rates, these tumors harbor hotspot mutations in the exonucleasic domain of POLE58 (DNA polymerase ϵ), an enzyme critical for DNA replication and proofreading. They are predominantly found in younger women with lower BMI and exhibit an excellent prognosis, with 5-year Relapse-Free Survival (RFS) reaching 93%. Despite often being histologically high-grade, they typically present at early stages. Genomic features include frequent C→A substitutions and mutations in PTEN, PIK3R1, PIK3CA, FBXW7, and KRAS (19,25)
- **MSI Hypermutated**: Acquired mismatch repair deficiency resulting in microsatellite instability (MSI) is a diagnostic phenotype for a multitude of cancer types. MSI is of clinical relevance, especially for colorectal cancer. Either germline mutations in the key genes MLH1, MSH2, MSH6, or PMS2 as described for the Lynch syndrome or somatic mutations can result in MMRd tumors (25,26). The group of MMRd accounts for 23–36% of EC while only 2% of all EC are associated with Lynch syndrome (27). The mutation frequency is considerably high but not as high as the POLE group. Frequent gene mutations in this group are PTEN, PIK3CA, and PIK3R. Substantial LVSI is more often present in MSI tumors. Similar to the POLE group, these patients exhibit a favorable outcome, with a 5-year RFS of approximately 95% (25).

- **Copy-Number Low (NSMP/p53-wild-type):** Comprising mostly Grade 1 and 2 endometrioid carcinomas, this subgroup is characterized by microsatellite stability, low mutation rates, and frequent CTNNB1 mutations. These tumors represent a "intermediate" prognostic group, with a 5-year RFS of 52% in high-risk cohorts (25).
- **Copy-Number High (Serous-like/p53-mutant):** Defined by extensive somatic copy-number aberrations and recurrent mutations in TP53, FBXW7 and PPP2R1A, while PTEN and KRAS mutations are rare, this subgroup carries the poorest prognosis (5-year RFS of 42%). While this category includes 95% of serous carcinomas, it also encompasses a subset of high-grade endometrioid carcinomas (24,25).

Molecular analysis revealed significant pathway overlaps: more than 92% of MSI (hypermutated) and copy-number low (endometrioid) cancers and 60% of copy-number high (serous-like) endometrial cancers showed aberrations in the PI3K pathway, with mutations in PIK3CA and PIK3R1 being mutually exclusive in most cases; and the receptor tyrosine kinase/RAS/β-catenin pathway was altered in copy-number low, hypermutated, and copy-number high tumours (82%, 71%, and 50%, respectively), with mutations in CTNNB1, KRAS, and in SOX17, FBXW7, FGFR2, and HER2 being mutually exclusive (24).

1.3.1 The ProMisE Algorithm: From Genomics to Clinical Practice

Building upon the TCGA findings, Talhouk et al. (2015) developed the Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE). This decision-making tool was designed to identify molecular subgroups using immunohistochemistry (IHC) and targeted mutational analysis, offering a cost-effective and clinically accessible alternative to comprehensive genomic sequencing. Beyond mutational profiling, the development of the algorithm integrated survival data, potential clinical benefits, and considerations regarding economic feasibility and widespread accessibility. In the years following its inception, ProMisE has undergone extensive validation across multiple endometrial cancer (EC) cohorts, confirming its robustness in risk stratification and prognostic accuracy (28,29).

The diagnostic workflow of the ProMisE algorithms follows a specific sequential hierarchy (Figure 1):

1. **MMR Status**: initially, Mismatch Repair status is assessed via IHC staining for MSH6 and PMS2 proteins. The detection of a protein deficiency (MMR-d) identifies the subgroups corresponding to the TCGA “MSI hypermutated” class.
2. **POLE Status**: In cases exhibiting MMR-wild-type (wt) expression, the exonucleasic domain of Polymerase ϵ (POLE) is sequenced (exons 9–14). The presence of a pathogenic mutation classifies the neoplasm as POLE EDM (ultramutated).
3. **p53 Status**: Finally, for POLE-wt tumors, p53 IHC is performed to differentiate between normal expression (IHC score 1+, identifying the Copy Number Low/NSMP subgroup) and p53-abnormal expression. The latter is characterized by either the complete absence of protein (null pattern, score 0) or significant protein accumulation (overexpression, score 2+), identifying the p53-abnormal/Copy Number High subgroup.

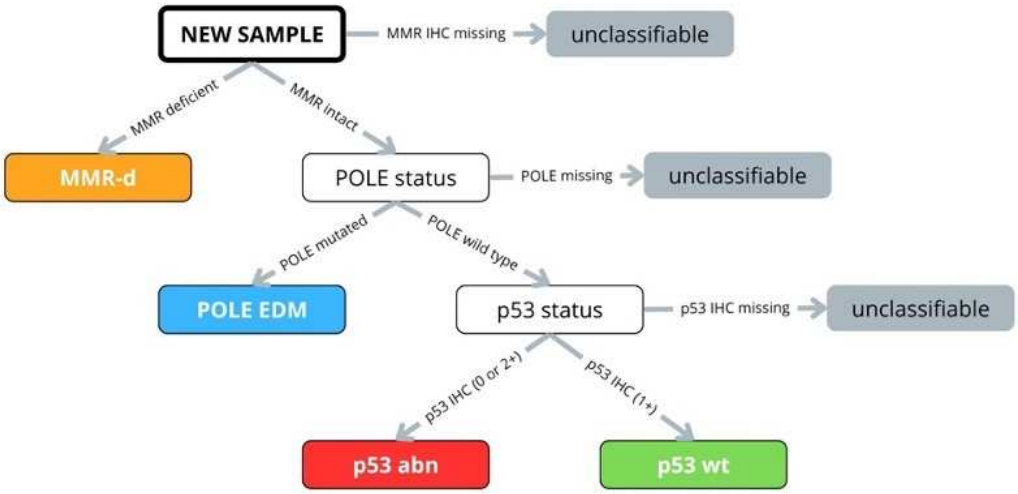


***Figure 1**, ProMisE Algorithm*

This approach utilizes a combination of immunohistochemistry (IHC for p53, MSH6, and PMS2) and targeted POLE sequencing.

The clinical utility of this surrogate model is particularly evident in high-grade endometrioid carcinomas (G3), which often fall into a "gray zone" between endometrioid and serous histotypes. Molecular stratification allows for the identification of G3 tumors with excellent outcomes (POLE-mutated) versus those with highly aggressive behavior (p53-abnormal), whereas MSI-H and NSMP G3 tumors exhibit intermediate prognosis. While its application to clear cell, undifferentiated, and carcinosarcomas is currently considered experimental, it remains a vital tool for risk refinement.

1.3.2 Current Guidelines and Therapeutic Implications

In 2020, the European Society of Gynaecological Oncology (ESGO), the European Society for Radiotherapy and Oncology (ESTRO), and the European Society of Pathology (ESP) published joint guidelines that officially incorporated TCGA molecular findings into clinical risk stratification (30). Building upon this foundation,

the 2025 guidelines update marks a profound shift toward precision medicine by formally adopting the 2023 FIGO staging system.

This updated system directly integrates molecular and histological features into anatomical stages, creating distinct molecularly defined stages annotated with an "m" (e.g., stage IAm POLEmut or IICm p53abn) (31) (Figure 2).

While previous guidelines proposed distinct prognostic algorithms based on the availability of molecular data, the 2025 update strongly recommends that molecular classification (POLEmut, MMRd, NSMP, p53abn) should be performed for all types of endometrial carcinomas (31). Furthermore, strict hierarchical rules have been introduced for tumors with concurrent molecular alterations (multiple classifiers): a pathogenic POLE mutation overrides both MMRd and p53abn (classifying the tumor as POLEmut), while MMRd overrides p53abn (31).

The clinical implications for the extremes of the prognostic spectrum remain significant: given their exceptionally favorable outcomes, treatment de-escalation is recommended for the POLEmut subtype, allowing for management via observation alone without the need for adjuvant therapy. Conversely, an intensified adjuvant protocol is strictly recommended for the high-risk p53abn subgroup (30).

For the intermediate-risk groups (MMRd and NSMP), therapeutic decisions are further refined by integrating molecular status with traditional clinicopathological parameters, such as lymphovascular space invasion (LVSI) and histological grade, alongside newly mandated biomarkers (31). Specifically, Estrogen Receptor (ER) status evaluation via immunohistochemistry is now recommended for all endometrial carcinomas to correctly stratify the NSMP category into low-grade/ER-positive versus high-grade/ER-negative risk groups. Additionally, HER2 testing is now recommended for advanced and recurrent p53abn tumors, serous carcinomas, and carcinosarcomas to identify candidates for targeted therapies (31).

Another major paradigm shift introduced in 2025 is the incorporation of immunotherapy (immune checkpoint inhibitors). This is now considered a first-line standard of care in combination with chemotherapy for advanced or recurrent MMRd carcinomas, as well as in the adjuvant setting for stage IIIm-IVAm MMRd disease (31).

Consequently, the systematic incorporation of the molecular classification, the new FIGO 2023 staging, and comprehensive complementary biomarker profiling into clinical practice is imperative to optimize patient risk stratification and advance personalized therapeutic strategies (31).

	Molecular classification*				
	POLE^{mut}	MMRd	NSMP low-grade and oestrogen receptor-positive	NSMP high-grade or oestrogen receptor-negative (or both)†	p53abn
Confined to the uterine corpus					
No myoinvasion, confined to polyp or endometrium	IAm *POLE*^{mut}	IA1 or IC‡	IA1	IA1 or IC‡	IA1 or IC‡
Myoinvasion <50%, no or focal lymphovascular space invasion	IAm *POLE*^{mut}	IA2 / IIC‡	IA1	IA2 or IIC‡	IICm p53abn
Myoinvasion ≥50%, no or focal lymphovascular space invasion	IAm *POLE*^{mut}	IB or IIC‡	IB	IB or IIC‡	IICm p53abn
Confined to the uterus (uterine corpus with or without cervical invasion)					
Cervical stromal invasion, no or focal lymphovascular space invasion	IAm *POLE*^{mut}	IIA or IIC‡	IIA	IIA or IIC‡	IICm p53abn
Uterine corpus with or without cervical invasion, substantial lymphovascular space invasion§	IAm *POLE*^{mut}	IIB or IIC‡	IIB	IIB or IIC‡	IICm p53abn
Local spread, regional spread, or both					
Spread to ovary or fallopian tube¶	IIIA1	IIIA1	IIIA1	IIIA1	IIIA1
Involvement of uterine subserosa or spread through the uterine serosa	IIIA2	IIIA2	IIIA2	IIIA2	IIIA2
Metastasis or direct spread to the vagina, parametrium, or both	IIIB	IIIB	IIIB	IIIB	IIIB
Metastasis to the pelvic peritoneum	IIIB2	IIIB2	IIIB2	IIIB2	IIIB2
Metastasis to the pelvic lymph nodes	IIIC1	IIIC1	IIIC1	IIIC1	IIIC1
Metastasis to the para-aortic lymph nodes	IIIC2	IIIC2	IIIC2	IIIC2	IIIC2
Locally advanced					
Invasion of bladder mucosa, intestinal mucosa, or both	IVA	IVA	IVA	IVA	IVA
Low-grade endometrioid carcinoma of both the endometrium and ovary					
Myoinvasive <50%, no lymphovascular space invasion, ovarian tumour pT1a	IA3	IA3	IA3	IA3**	IA3
Metastatic or residual disease after surgery					
Local spread, regional spread, or both with residual disease	III with residual disease				
Invasion of bladder mucosa, intestinal mucosa, or both with residual disease	IVA with residual disease				
Peritoneal metastasis beyond pelvis	IVB				
Distant metastasis	IVC				

***Figure 2**, Definition of risk groups based on anatomic tumour extent, lymphovascular space invasion status, and molecular classification, showing corresponding FIGO 2023 stages (31).*

1.4 CLINICAL AND RADIOLOGICAL DIAGNOSIS

1.4.1 Clinical Presentation

The clinical onset of EC is most frequently characterized by abnormal uterine bleeding (AUB). In post-menopausal patients, this manifests as vaginal bleeding (post-menopausal bleeding, PMB), while in pre-menopausal women, it presents as irregular or heavy menstrual cycles. Although a subset of cases may remain asymptomatic and be discovered incidentally during routine examinations, the rising incidence of EC in younger demographics underscores the necessity of a rigorous diagnostic workup for any fertile patient presenting with abnormal bleeding pattern (20,32).

In advanced stages, the disease may present with pelvic pain and leukoxanthorrhea (a purulent or blood-stained vaginal discharge), often resulting from tissue necrosis and liquefaction. Furthermore, significant lymphatic involvement can lead to obstructive symptoms, such as lymphedema of the lower extremities, the pubic region, or the vagina. Late-stage symptoms indicative of metastatic spread include chronic abdominal, pelvic, or lumbosacral pain, bowel obstruction, bone pain, and dyspnea (20).

1.4.2 Radiological Diagnosis

Transvaginal ultrasound (TVUS) represents the first-line imaging modality for the investigation of suspected EC, owing to its high sensitivity, cost-effectiveness, and widespread availability. This technique allows for a detailed assessment of the uterine cavity and the endometrial lining in the majority of patients. A critical parameter in TVUS is the measurement of endometrial thickness (ET).

While a definitive universal consensus on the optimal ET threshold has not been reached, clinical data indicate that an endometrial thickness of 5 mm or less in post-menopausal women is associated with a 96% sensitivity for detecting EC, reducing the post-test probability of malignancy to approximately 2.5% (33). Based on these findings, the American College of Obstetricians and Gynecologists (ACOG) suggests

that an ET of 4 mm or less should be considered normal in post-menopausal patients. Conversely, an ET exceeding 5 mm, especially when accompanied by persistent bleeding, necessitates further histopathological evaluation (33).

In clinical scenarios where TVUS is suboptimal, such as in the presence of bulky leiomyomas or a significantly enlarged uterus, a trans-abdominal approach may be required to provide a broader diagnostic window. Furthermore, trans-rectal sonography serves as a viable alternative when the transvaginal route is contraindicated or inappropriate (e.g., in virgin patients, or cases of vaginismus and secondary vaginal stenosis) and trans-abdominal imaging remains inconclusive.

The integration of Color and Power Doppler provides essential data regarding the vascular architecture of both healthy and neoplastic tissues. Evidence suggests a strong correlation between specific sonographic patterns and the clinicopathological characteristics of endometrial carcinoma (EC). High-risk malignancies, characterized by Stage IB or higher, Grade 3 histology, or a tumor-to-uterine ratio ≥ 50%, frequently present with hypoechoic or heterogeneous echotextures and hypervascularization. Conversely, low-risk tumors (Stage IA, Grade 1 or 2, or a ratio < 50%) are typically hyperechoic and exhibit minimal to absent vascular flow (34).These distinct sonographic signatures are instrumental in differentiating low-risk from high-risk disease and may correlate with the likelihood of lymph node metastasis (34).

To further characterize suspicious findings, diagnostic hysteroscopy with targeted biopsy is the gold standard for histopathological confirmation, unless precluded by anatomical constraints (33).

1.4.2.1 Cross-sectional Imaging: CT vs. MRI

The requirement for advanced radiological investigation, such as Computed Tomography (CT) or Magnetic Resonance Imaging (MRI), is determined by the patient's clinical and pathological risk profile.

Regarding CT, its utility in the primary assessment of EC is limited by low soft-tissue contrast. Specifically, CT exhibits reduced sensitivity in evaluating myometrial invasion, particularly in small-volume or low-risk (Stage IA) carcinomas (35). Comparative analyses by Kim SH et al. demonstrated that CT achieves a diagnostic

accuracy of only 58–61% for myometrial infiltration, significantly lower than the 68–69% reported for ultrasound and the 88–89% achieved by MRI (36).

Consequently, pelvic MRI is the preferred modality for the preoperative staging of EC, offering superior anatomical resolution for assessing pelvic tumor extent. Dynamic contrast-enhanced MRI (DCE-MRI) has proven more effective than both unenhanced MRI and TVUS in determining the depth of myometrial invasion. On T2-weighted imaging (T2WI), the loss of integrity of the low-signal-intensity junctional zone is a hallmark of myometrial involvement. Deep myometrial invasion is diagnosed when the tumor, typically displaying intermediate signal intensity, infiltrates 50% of the total myometrial thickness (37).

Research indicates that expert-performed TVUS can achieve a diagnostic accuracy comparable to MRI in evaluating both myometrial and cervical stromal invasion. However, the performance of TVUS is frequently hindered by specific patient-related and anatomical factors, including high Body Mass Index (BMI), the presence of leiomyomas or adenomyosis, large tumor volumes, and atypical uterine orientations (such as a retroflexed or vertical uterus). Given these constraints, a selective diagnostic approach has been proposed, reserving MRI primarily for cases where TVUS yields suboptimal image quality (38).

1.4.2.2 The Emergence of Three-Dimensional Ultrasound (3D-TVUS)

A significant advancement in gynecological diagnostics is the introduction of three-dimensional transvaginal ultrasound (3D-TVUS). While originally developed for obstetric applications, its utility in evaluating suspected endometrial malignancies has become increasingly evident (39). By allowing for multiplanar reconstruction, 3D-TVUS overcomes the inherent limitations of conventional 2D imaging, enabling the interrogation of any anatomical plane within the organ.

Furthermore, the ability to acquire and store volumetric data facilitates retrospective analysis through virtual navigation and multiplanar visualization. A key feature of this technology is the Virtual Organ Computer-aided AnaLysis(VOCAL™) software, which allows for precise volumetric calculations of even irregularly shaped structures.

This automated method has proven superior to traditional 2D estimations in terms of accuracy and reproducibility (40).

The integration of 3D Power-Doppler (3D-PD) with the VOCAL™ system enables a comprehensive, three-dimensional reconstruction of the tumor's vascular architecture. This technique provides a quantitative assessment of tissue perfusion through three specific indices (41):

- Vascularization Index (VI): Reflects the presence of vessels within the tissue.
- Flow Index (FI): Represents the intensity of blood flow.
- Vascularization-Flow Index (VFI): Combines information on both vessel presence and flow intensity.

In summary, 3D-TVUS offers a more nuanced and detailed visualization of the endometrium and neoplastic masses. Compared to 2D techniques, it facilitates higher diagnostic precision and potentially earlier detection of EC. By providing critical data for effective and personalized therapeutic planning, 3D-TVUS represents a pivotal tool in the clinical management and optimization of patient outcomes in endometrial carcinoma (39).

A primary constraint of conventional 2D-TVUS is the requirement for the clinician to mentally synthesize a 3D anatomical view from disparate two-dimensional planes. This cognitive process is inherently labor-intensive, often inefficient, and highly subjective, which may introduce diagnostic discrepancies and affect therapeutic planning. Furthermore, physiological organ movement during the examination complicates the maintenance of consistent imaging planes. These factors collectively limit the reproducibility of 2D-TVUS, particularly during longitudinal follow-up.

Consequently, while 2D-TVUS remains the standard for baseline screening, advanced modalities such as 3D-TVUS or Power Doppler are preferred for precise surgical planning and monitoring. Adopting these modern techniques is essential to ensure diagnostic accuracy and optimize patient-specific therapeutic guidance (42).

In several clinical aspects, 3D-TVUS offers distinct advantages over MRI. While MRI is a high-resolution modality, it is often limited by higher costs, logistical complexity,

and patient-related contraindications such as claustrophobia or high adiposity. In contrast, 3D-TVUS is a more rapid, cost-effective, and patient-centered alternative (43)

According to Christensen et al., 3D-TVUS achieves diagnostic parity with MRI when image quality is optimized (44). Research indicates that while both modalities exhibit similar sensitivity, MRI maintains slightly higher specificity. Thus, MRI may serve as a valuable adjunctive tool specifically for patients where superficial myometrial invasion (< 50%) is suspected, although definitive conclusions are often limited by the variability in ultrasound image quality (44).

1.4.2.3 The evolving role of 18F-FDG PET/TC

The clinical utility of 18F-FDG Positron Emission Tomography/Computed Tomography (PET/CT) in endometrial carcinoma is currently undergoing re-evaluation. A recent meta-analysis reported a sensitivity of 72.0%, a specificity of 94.0%, and an overall accuracy of 88.0% for the detection of lymph node metastasis (45).

However, the routine application of PET/CT for the preoperative staging of early-stage disease is not generally recommended. This is primarily because many ECs present as Grade 1 (G1) tumors, which exhibit lower glucose metabolic rates and, consequently, reduced FDG uptake. Nevertheless, PET/CT remains an important diagnostic asset for investigating suspected distant metastatic disease (46).

1.4.2.4 Saline Infusion Sonography

Saline Infusion Sonography (SIS), or hysterosonography, remains a specialized adjunctive procedure utilized when endometrial biopsy or standard TVUS results are inconclusive. By infusing sterile saline into the uterine cavity during sonographic visualization, SIS provides superior contrast to delineate the endometrial architecture. This technique is particularly effective for identifying focal intracavitary pathology, such as endometrial polyps, submucosal leiomyomas, or localized hyperplasia (33).

1.5 STAGING

Historically, clinical staging alone has been associated with a significant rate of understaging, estimated between 13% and 22%, where the extent of the disease is underestimated compared to the final surgical findings. To resolve this diagnostic discrepancy, two standardized surgical-pathological staging systems have been established: the FIGO (International Federation of Gynecology and Obstetrics) and the AJCC (American Joint Committee on Cancer) classifications (47). Importantly, with the 2023 update, the FIGO staging has evolved beyond a purely surgical-pathological system into a comprehensive framework that formally integrates tumor biology and molecular classifications (48).

Consistent with the updated 2025 joint guidelines from ESGO, ESTRO, and ESP, accurate staging requires a comprehensive surgical-pathological evaluation. The standard surgical protocol includes total hysterectomy and bilateral salpingo-oophorectomy (TH-BSO).

Regarding nodal assessment, the paradigm has shifted significantly: sentinel lymph node biopsy (SLNB) combined with pathological ultrastaging is now the preferred staging method for all patients with presumed uterus-confined disease (31). Systematic pelvic and para-aortic lymphadenectomy is no longer considered the upfront gold standard for high-risk early-stage malignancies; rather, side-specific systematic lymphadenectomy is reserved for cases where SLN mapping fails in high-intermediate and high-risk patients (31). Additionally, in clinically overt advanced stages (III/IV), systematic lymphadenectomy is not recommended, and only the resection of macroscopic suspicious lymph nodes is indicated.

Furthermore, major international institutions, including the ACR (American College of Radiology), NCCN (National Comprehensive Cancer Network), and ESUR (European society of Urogenital Radiology), increasingly advocate for dedicated preoperative imaging to refine surgical planning and improve staging accuracy (47). Modalities such as expert transvaginal ultrasound (TVUS) or pelvic magnetic resonance imaging (MRI) are mandatory for assessing local extension, while additional

imaging (e.g., PET/CT or CT scans) is recommended to evaluate nodal and distant metastases based on clinical and pathological risk (30).

1.5.1 The 2023 FIGO Staging System

The FIGO staging system remains the most widely utilized classification in gynecological oncology. Its latest revision, published in 2023, represents a landmark evolution in the field, necessitated by the imperative to integrate the molecular landscape into anatomical parameters (30). Although the 2023 framework is currently in the process of full clinical implementation, it introduces several critical refinements compared to the 2009 version (Table II).

The 2023 revision effectively transitions from a purely anatomical classification to an integrated surgical-pathological-molecular model that considers (Table III):

- **Histological Differentiation and Aggressiveness**: It formally adopts the WHO binary grading system for endometrioid carcinomas and distinguishes between non-aggressive histotypes (i.e., low-grade endometrioid, G1-G2) and aggressive variants (i.e., high-grade endometrioid [G3], serous, clear cell, mixed, undifferentiated, carcinosarcoma, mesonephric-like, and gastrointestinal-type mucinous carcinomas) (48).
- **Lymphovascular Space Invasion (LVSI):** Refined into a quantitative assessment, where LVSI is defined as "negative" (absent), "focal" (involving < 5 vessels), or "substantial" (involving ≥ 5vessels) (48).
- **Molecular Profiling**: Explicitly incorporating the four molecular subgroups (POLEmut, MMRd, NSMP, and p53abn) directly into the staging criteria to better reflect biological behavior and patient prognosis. When the molecular subtype is known, it is recorded in the FIGO stage with the addition of the letter "m" (e.g., Stage IAm POLEmut or Stage IICm p53abn). Crucially, in early-stage disease, the detection of pathogenic POLE mutations or p53 abnormalities automatically results in the downstaging or upstaging of the tumor, respectively (30).

***Table II**, 2009 FIGO staging system for endometrial adenocarcinoma*

Stage	Defining Criteria
Stage I	Confined to the uterine corpus
IA	Tumor confined to uterus, <50% myometrial invasion
IB	Tumor confined to uterus, ≥50% myometrial invasion
Stage II	Cervical stromal invasion
Stage III	Local and/or regional spread of the tumor
IIIA	Tumor invasion into serosa or adnexa
IIIB	Vaginal or Parametrial involvement
IIIC1	Pelvic Node involvement
IIIC2	Paraaortic Node involvement
Stage IV	Spread to the bladder and/or bowel mucosa, and/or distant metastases
IVA	Tumor invasion into Bladder or Bowel Mucosa
IVB	Distant metastases (including abdominal metastases) or inguinal lymph node involvement

***Table III**, 2023 FIGO staging system for endometrial adenocarcinoma*

Stage	Defining Criteria
Stage I	Confined to the uterine corpus and ovary
IA	Disease limited to the endometrium OR non- aggressive histological type with invasion of less than half of myometrium with no or focal LVSI OR good prognosis disease **IA1**: Non-aggressive histological type limited to an endometrial polyp OR confined to the endometrium **IA2**: Non-aggressive histological types involving less than half of the myometrium with no or focal LVSI **IA3**: Low-grade endometrioid carcinomas limited to the uterus and ovary
IB	Non-aggressive histological types with invasion of half or more of the myometrium, and with no or focal LVSI
IC	Aggressive histological types limited to a polyp or confined to the endometrium
IAmPOLEmut	POLEmut endometrial carcinoma, confined to the uterine corpus or with cervical extension, regardless of the degree of LVSI or histological type

Stage II	Invasion of cervical stroma without extrauterine extension OR with substantial LVSI OR aggressive histological types with myometrial invasion
IIA	Invasion of the cervical stroma of non-aggressive histological types
IIB	Substantial LVSI of non-aggressive histological types
IIC	Aggressive histological types with any myometrial involvement
IICmp53abn	p53abn endometrial carcinoma confined to the uterine corpus with any myometrial invasion, with or without cervical invasion, and regardless of the degree of LVSI or histological type
Stage III	Local and/or regional spread of the tumor of any histological subtype
IIIA	Invasion of uterine serosa, adnexa, or both by direct extension or metastasis **IIIA1**: Spread to ovary or fallopian tube **IIIA2**: Involvement of uterine subserosa or spread through the uterine serosa
IIIB	Metastasis or direct spread to the vagina and/or to the parametria or pelvic peritoneum **IIIB1**: Metastasis or direct spread to the vagina and/or the parametria **IIIB2**: Metastasis to the pelvic peritoneum
IIIC	Metastasis to the pelvic or para-aortic lymph nodes or both **IIIC1**: Metastasis to the pelvic lymph nodes **IIIC1i**: Micrometastasis **IIIC1ii**: Macrometastasis **IIIC2**: Metastasis to para-aortic lymph nodes up to the renal vessels, with or without metastasis to the pelvic lymph nodes **IIIC2i**: Micrometastasis **IIIC2ii**: Macrometastasis
Stage IV	Spread to the bladder mucosa and/or intestinal mucosa and/or distant metastasis
IVA	Invasion of the bladder mucosa and/or the intestinal/bowel mucosa
IVB	Abdominal peritoneal metastasis beyond the pelvis
IVC	Distant metastasis, including metastasis to any extra- or intra-abdominal lymph nodes above the renal vessels, lungs, liver, brain, or bone

1.5.2 AJCC Staging System

Another method used for staging, although less common in gynecological oncology than the FIGO system, is the AJCC (American Joint Committee on Cancer) TNM system. This classification categorizes the tumor based on three key parameters: the extent of the primary tumor (T), the involvement of regional lymph nodes (N), and the presence of distant metastases (M) (Table IV) (49).

***Table IV**, TNM Staging System*

	Primary Tumor (T)
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ (preinvasive carcinoma)
T1	Tumor confined to corpus uteri
T1a	Tumor limited to endometrium or invades less than one half of the myometrium
T1b	Tumor invades one half or more of the myometrium
T2	Tumor invades stromal connective tissue of the cervix but does not extend beyond uterus
T3	Local and/or regional spread of the tumor
T3a	Tumor involves serosa and/or adnexa (direct extension or metastasis)
T3b	Vaginal involvement (direct extension or metastasis) or parametrial involvement
T4	Tumor invades bladder mucosa and/or bowel mucosa (bullous edema is not sufficient to classify a tumor as T4)
	Regional Lymph nodes (N)
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis to pelvic lymph nodes
N1mi	Regional lymph node metastasis > 0.2 mm but ≤ 2.0 mm in diameter to pelvic lymph nodes
N1a	Regional lymph node metastasis > 2.0 mm in diameter to pelvic lymph nodes
N2	Regional lymph node metastasis to para-aortic lymph nodes, with or without positive pelvic lymph nodes

N2mi	Regional lymph node metastasis > 0.2 mm but ≤ 2.0 mm in diameter to para-aortic lymph nodes, with or without positive pelvic lymph nodes
N2a	Regional lymph node metastasis > 2.0 mm in diameter to para-aortic lymph nodes, with or without positive pelvic lymph nodes

	Distant Metastasis (M)
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis (includes metastasis to inguinal lymph nodes, intraperitoneal disease, or lung, liver, or bone metastases; it excludes metastasis to para-aortic lymph nodes, vagina, pelvic serosa, or adnexa)

Once a patient's T, N, and M categories have been determined, this information is combined in a process called stage grouping to assign an overall stage (50).

Historically, the AJCC TNM and FIGO staging systems have been strictly harmonized (30). However, it is crucial to note that the current AJCC 8th Edition relies primarily on anatomical and traditional pathological parameters. Consequently, it does not yet formally incorporate the molecular subtypes (POLEmut, MMRd, NSMP, p53abn) or the quantitative assessment of lymphovascular space invasion (LVSI) recently introduced by the landmark FIGO 2023 revision (48). Despite this temporary discrepancy in stage grouping, the TNM system remains a fundamental tool in pathological reporting (pTNM), particularly for its rigorous stratification of nodal involvement. The AJCC system specifically categorizes the exact size of lymphatic spread, distinguishing between isolated tumor cells (ITCs, ≤ 0.2 mm, classified as pN0(i+)), micrometastases (> 0.2 mm to ≤ 2 mm, classified as pN1mi/pN2mi), and macrometastases (> 2 mm, classified as pN1a/pN2a) (48).

The staging system uses the pathologic stage (pTNM) as the gold standard, determined by the comprehensive examination of tissue removed during surgical staging. Sometimes, if immediate surgical intervention is contraindicated or not feasible, the cancer will be assigned a clinical stage (cTNM) instead. The clinical stage is based on the results of physical examinations, endometrial biopsies, and advanced preoperative imaging tests (such as expert pelvic MRI or PET/CT) done before surgery (50) (Table V).

***Table V**: TNM staging*

Stage	Stage Grouping	Stage Description
I	T1 N0 M0	The tumor is growing inside the uterus and/or is limited to the uterus and ovary for non-aggressive types. The cancer has not spread to nearby lymph nodes (N0) or to distant parts of the body (M0)
II	T2 N0 M0	The cancer has spread from the body of the uterus and is growing into the cervical stroma OR there is substantial LVSI OR the cancer is an aggressive histologic type with any invasion into the myometrium. The cancer has not spread to nearby lymph nodes (N0) or distant parts of the body (M0)
IIIA	T3a N0 M0	The tumor has spread to the ovary or fallopian tube (IIIA1) OR to the uterus' serosa (IIIA2). The cancer has not spread to nearby lymph nodes (N0) or to distant parts of the body (M0)
IIIB	T3b N0 M0	The cancer has spread to the vagina or to the parametrium (IIIB1) OR to the pelvic peritoneum (IIIB2). It has not spread to nearby lymph nodes (N0) or to distant parts of the body (M0)
IIIC1	T1-T3 N1, N1mi or N1a M0	The cancer has spread to pelvic lymph nodes (N1, N1mi, or N1a), but not to lymph nodes around the aorta or distant parts of the body (M0).
IIIC2	T1-T3 N2, N2mi or N2a M0	The cancer has spread to para-aortic lymph nodes (N2, N2mi, or N2a), but not to distant parts (M0)
IVA	T4 Any N M0	The cancer has spread to the mucosa of the rectum or urinary bladder (T4). It may or may not have spread to nearby lymph nodes (Any N), but has not spread to distant parts of the body (M0)
IVB	Any T Any N M1	The cancer has spread to the abdominal peritoneum; it can be any size (Any T) and it might or might not have spread to other lymph nodes (Any N).

1.5.3 Instrumental Staging

To plan the correct surgical management, it's mandatory to evaluate several specific characteristics of the neoplasm. These include tumor grade, molecular subtype, LVSI, non-endometrioid histology, deep myometrial invasion, cervical involvement, nodal status, and distant metastases. While grade and molecular class are determined through pathology, the remaining features must be assessed preoperatively using cross-sectional and ultrasound imaging techniques (51).

1.5.3.1 The role of MRI

According to the updated 2025 ESGO-ESTRO-ESP guidelines, mandatory preoperative work-up includes either an expert transvaginal ultrasound (TVUS) or pelvic MRI (31). While contrast-enhanced MRI has historically been considered the most accurate imaging modality for local staging (with a reported diagnostic accuracy ranging from 83% to 92%) (52), current evidence demonstrates that TVUS, when performed by an expert sonographer or utilizing 3D techniques (3D-TVUS, achieves a diagnostic performance entirely comparable to MRI for detecting deep myometrial and cervical invasion (51). Nevertheless, MRI remains a cornerstone in disease staging, providing exceptionally detailed anatomical information due to its excellent soft-tissue resolution, lack of radiation exposure, and the availability of multiple sequences that allow for both qualitative and quantitative tumor assessment (53).

T2-weighted images are essential for evaluating the anatomy of the uterus, cervix, and vagina, as well as for identifying the primary tumor (52). This sequence provides a strong contrast between the endometrial tumor, the myometrium, and the cervical stroma. Conversely, on unenhanced T1-weighted images, the endometrium, junctional zone, and myometrium display similar signal intensities, making them difficult to distinguish from one another (52).

On T2-weighted scans, the three layers of the uterine body can be clearly identified (52):

- The endometrium, which shows a high signal intensity and varies in thickness from 1 to 7 mm during the menstrual cycle.

- The junctional zone, which displays a low signal intensity and represents the inner myometrium.
- The peripheral myometrium, which shows an intermediate signal intensity. The combined thickness of the junctional zone and outer myometrium typically ranges from 14 to 21 mm.

The different signal intensities between the inner and outer myometrium depends on the significantly lower water content of the inner myometrium caused by closely packed compact smooth muscle cells with little extracellular matrix, which consequently changes the signal (54).

Evaluating the junctional zone is crucial for detecting myometrial infiltration by the tumor. An intact junctional zone reliably rules out myometrial invasion, whereas its disruption indicates tumor infiltration. In post-menopausal women, both the endometrium and myometrium undergo atrophy, and the myometrial signal on T2-weighted images appears weaker than in pre-menopausal patients (52). This anatomical change can make interpretation more challenging, which is clinically significant since endometrial carcinoma occurs most frequently after menopause (52).

To overcome this limitation, Dynamic Contrast-Enhanced MRI (DCE-MRI) using gadolinium is highly recommended (54). During the equilibrium and portal venous phases of a DCE-MRI, the endometrial carcinoma typically enhances more slowly and to a lesser degree than the surrounding healthy myometrium (53). This asynchronous enhancement maximizes the contrast-to-noise ratio, allowing the radiologist to precisely visualize the tumor boundaries and estimate the depth of invasion even when the physiological zonal anatomy is obscured by age-related atrophy (53,54).

1.5.3.2 MRI findings across FIGO Stages

When the tumor is confined to the uterus, if the malignancy is limited to the endometrium or an endometrial polyp (Stage IA1 for non-aggressive types, Stage IC for aggressive histologies), MRI typically shows a thickened endometrium with an intact junctional zone (the dark inner band of the myometrium on T2-weighted images) and a sharply defined border between the tumor and the muscle (52). If a non-aggressive tumor superficially invades the muscle (less than 50%, Stage IA2), MRI

will reveal an incomplete disruption of this junctional zone (52,53). If the tumor extends into 50% or more of the myometrial thickness (Stage IB for non-aggressive types), MRI demonstrates a complete loss or disruption of the junctional zone; the tumor signal penetrates deeply into the myometrium, leaving only the outermost layer of the normal uterine muscle intact (52,54).

In Stage II disease, the tumor extends beyond the uterine body into the cervix or exhibits high-risk features. True cervical involvement (Stage IIA for non-aggressive histologies) requires the invasion of the cervical stroma. On MRI, this is characterized by the clear disruption of the low-signal-intensity fibrocervical stroma by the higher-signal endometrial carcinoma on T2-weighted images (52). It is important to note that endocervical canal widening can be caused by non-invasive conditions, such as a polypoid extension of the tumor, debris, or a benign cervical polyp; therefore, contrast-enhanced dynamic images are essential to differentiate these benign findings from true stromal invasion.

Stage III disease indicates that the tumor has spread outside the uterus but remains within the true pelvis. In Stage IIIA, the tumor invades the uterine serosa or the adnexa, and peritoneal cytology is often positive. MRI reveals a complete interruption of the uterine serosa, which appears as a loss of the normal hypointense serosal border on T2-weighted images (54). In Stage IIIB, the parametrial invasion is best visualized on T1-weighted images as an abnormal change in the signal intensity of the surrounding parametrial fat (53). Vaginal involvement appears on T2-weighted images as a hyperintense, thickened vaginal wall, representing a segmental loss of the vagina's normally dark structural appearance (54).

Stage IIIC involves pelvic or para-aortic lymph nodes, where nodes larger than 1 cm are generally considered pathological. The role of standard MRI in detecting lymph node metastases has been a subject of debate. For example, Manfredi et al. reported a baseline sensitivity of 50% (which can be improved with specific contrast agents) and a specificity of 90% (54). However, Lin et al. demonstrated that the addition of Diffusion-Weighted Imaging (DWI) significantly improves diagnostic performance, increasing sensitivity to 83% (compared to 25% with conventional MRI) while maintaining a high specificity of 99% (53).

Stage IV tumors extend beyond the pelvis, invading the bladder or the rectum. In Stage IVA, MRI shows a disruption of the normal fat planes that separate the uterus from the bladder or rectum. Crucially, there is a focal loss of the normal low-signal-intensity wall of the bladder or intestine on T2-weighted images, confirming that the tumor has breached the organ wall (52,54). Stage IVB indicates distant metastases, which often manifest as ascites or peritoneal implants that are best visualized on T1-weighted, fat-suppressed gadolinium images (55).

1.5.3.3 The Role of CT

MRI remains the preferred modality for local staging since CT has a lower diagnostic accuracy within the uterus due to its suboptimal soft-tissue contrast. Statistically, CT has shown a sensitivity of 83% and a specificity of 42% for detecting deep myometrial invasion, and a sensitivity of 25% with a specificity of 70% for identifying cervical invasion (55). However, CT is highly effective for evaluating extrauterine disease, making it a valuable tool for assessing para-aortic and pelvic lymph nodes metastasis with a specificity and sensitivity of 92% and 52%, respectively (56). It is important to note, however, that due to this low sensitivity, systematic reviews consider CT less accurate than both MRI and PET/CT for nodal assessment, as it can only reliably detect macroscopically enlarged metastatic nodes (53).

The primary strength of CT lies in its rapid acquisition and its role in distant disease staging (53). Depending on the clinical and pathological risk, an abdominal and pelvic CT scan is highly recommended to evaluate ovarian spread, extra-pelvic peritoneal implants (FIGO Stage IVB), and distant organ metastases such as in the liver (FIGO Stage IVC) (30). Furthermore, while chest CTs are not routinely ordered for early-stage disease due to the low frequency of pulmonary metastases, they are strictly indicated for patients with higher FIGO stages or aggressive histological subtypes (e.g., serous or carcinosarcoma) who are at a higher risk for distant thoracic dissemination (53).

1.5.3.4 The Role of 3D-TVUS

The clinical role of three-dimensional transvaginal ultrasound (3D-TVUS) in the local staging of EC focuses primarily on assessing the depth of myometrial invasion and cervical stromal involvement. According to the updated 2025 ESGO-ESTRO-ESP

guidelines and recent comprehensive meta-analyses, 3D-TVUS demonstrates a diagnostic test accuracy (DTA) that is highly comparable to Magnetic Resonance Imaging (MRI) for identifying both DMI and cervical invasion (30).

The integration of 3D techniques introduces unique anatomical advantages over conventional 2D-TVUS. While standard 2D-TVUS is commonly used to evaluate the sagittal and transverse planes, it exhibits technical limitations when visualizing the coronal plane of the uterus. Conversely, 3D-TVUS allows for the effective reconstruction of the coronal view, which adds extremely valuable information for assessing myometrial infiltration specifically in tumors located in the uterine cornua (51). Furthermore, 3D rendering techniques significantly increase the contrast between tissues, resulting in an enhanced demarcation of the tumor boundaries (51).

In the pursuit of standardizing preoperative staging, researchers have explored various objective measurement techniques using 3D volumes. A study by Lindauer et al. demonstrated that the tumor-free distance to the uterine serosa (TFD), defined as the distance from the serosa to the deepest point of myometrial invasion, is an accurate and reliable predictor of disease recurrence and surgical-pathological risk factors (43). Based on these findings, Alcazar et al. hypothesized that TFD could be reliably measured using 3D-TVUS by performing a virtual navigation through the entire uterine volume (39).

Whether utilizing subjective evaluation or objective metrics like TFD, the primary clinical goal of 3D-TVUS under the 2023 FIGO staging system remains the accurate binary categorization of myometrial invasion ($< 50\%$ vs. $\geq 50\%$) to distinguish between stage IA and IB, and the reliable exclusion of cervical stromal invasion (48).

Additionally, the transvaginal acquisition and storage of 3D datasets require only a few seconds, are relatively straightforward, and allow for offline analysis by expert readers later. This significantly reduces diagnostic discrepancies caused by inter-observer subjectivity during real-time endometrial evaluation, further solidifying 3D-TVUS as a highly valid, cost-effective, and widely accessible alternative to MRI for preoperative staging (44).

1.6 TREATMENT

1.6.1 Surgical Management

The surgical management of endometrial carcinoma (EC) has evolved significantly in recent years. Driven by the latest clinical frameworks, including the updated ESGO-ESTRO-ESP and AIOM guidelines, modern gynecological oncology has shifted toward a tailored, less invasive approach. Surgical radicality is now carefully stratified based on tumor biology, molecular profiling, and the anatomical extent of the disease.

1.6.1.1 Early-Stage Disease (Stage I and II)

For clinically presumed Stage I and II EC, the standard surgical procedure is a Class A hysterectomy with bilateral salpingo-oophorectomy (TH-BSO) with or without lymph node assessment (47). A Class A hysterectomy is an extrafascial procedure that ensures the complete removal of the uterus and cervix. Unlike more radical surgeries, it does not require unroofing the ureters; the uterosacral and vesicouterine ligaments are divided close to the uterus, and vaginal resection is minimal (typically less than 10 mm), leaving the vaginal paracervix intact (57).

Infracolic (total or partial) omentectomy should be done for clinical Stage I and II serous endometrial carcinoma, carcinosarcoma and undifferentiated carcinoma while it is not necessary in other histological types (31). For patients with Stage II disease and cervical involvement, more extensive procedures should be done if required to achieve free surgical margins (31).

Ovarian preservation with bilateral salpingectomy can be considered in premenopausal patients younger than 45 years with FIGO 2023 IA1 or IA2 who have a low risk of recurrence by molecular classification. However, this conservative approach must be avoided in patients at hereditary risk of ovarian cancer, such as carriers of germline BRCA mutations or MLH1, MSH2, MSH6, or PMS2 mutations (Lynch syndrome), or with a family history of ovarian or breast cancer (31).

1.6.1.1.1 Minimally Invasive Surgery vs Laparotomy

Based on randomized clinical trials (58–60), a Minimally Invasive Surgery (MIS: laparoscopy or robotic-assisted surgery) is the preferred modality over open laparotomy for the surgical staging of apparent early-stage endometrial cancer, even for patients harboring high-risk disease. While the ability to cure the cancer remains identical, MIS offers profound advantages regarding patient safety, recovery, and quality of life.

The multinational LACE trial (61) confirmed that total laparoscopic hysterectomy (TLH) is statistically equivalent to total abdominal hysterectomy (TAH) regarding disease-free survival (81.6% vs. 81.3% at 4.5 years) and overall survival (92.0% vs. 92.4%) (61). Similarly, the LAP2 trial, published by Walker et al. in 2012 (62), demonstrated that the 5-year overall survival is almost identical in both approaches (89.8%), with only a clinically negligible difference in the 3-year recurrence rate (11.4% for laparoscopy vs. 10.2% for laparotomy) (62).

While intraoperative complication rates (such as vascular or bowel injuries) are statistically similar between the two surgical approaches (63), laparoscopy is associated with a significantly decreased risk of major postoperative adverse events.

The LACE trial reported that severe postoperative adverse events (grade 3 or higher) occurred in only 11.6% of TLH patients, compared to a staggering 23.2% of TAH patients (60). The LAP2 trial echoed these findings, reporting moderate-to-severe postoperative adverse events in 14% of laparoscopy patients versus 21% of laparotomy patients (59).

MIS also results in significantly less intraoperative blood loss, less requirement for postoperative pain medication and a notably shorter hospital stay (58). For instance, prolonged hospitalization (>2 days) was required in 94% of laparotomy patients but only 52% of laparoscopy patients (59).

Furthermore, in the first 1 to 6 months post-surgery, patients undergoing TLH report significantly greater improvements in physical well-being, functional well-being and body image compared to those undergoing laparotomy (60). Remarkably, this benefit persists over time. A long-term follow-up study (with a median of 9 years after surgery)

demonstrated that physical and functional well-being remained significantly better among women who were treated with TLH compared to those who received a TAH (64).

1.6.1.1.2 Lymph Node Staging

The surgical management of lymph nodes in clinical stage I and II endometrial cancer has undergone a paradigm shift, transitioning from systematic lymphadenectomy to Sentinel Lymph Node (SLN) mapping.

Historically, systematic pelvic and para-aortic lymphadenectomy was routinely performed to detect extrauterine spread (65). However, two large randomized clinical trials (the ASTEC trial (66) and the Italian trial by Benedetti Panici et al. (65)) definitively demonstrated that systematic pelvic lymphadenectomy does not improve overall or disease-free survival in early-stage endometrial cancer (65,66). Furthermore, systematic lymphadenectomy is associated with significantly higher rates of early and late postoperative morbidities, including lymphedema, lymphocysts, and longer operative times (65).

To minimize morbidity while accurately staging the disease, Sentinel Lymph Node (SLN) biopsy has become the preferred and highly accurate alternative to systematic lymphadenectomy for all patients with presumed uterus-confined disease (31).

The FIRES trial (67), a large multicenter prospective study, demonstrated that SLN mapping using indocyanine green (ICG) has a 97.2% sensitivity for detecting node-positive disease and a 99.6% negative predictive value (67). SLN biopsy safely replaces complete lymphadenectomy, as it can correctly identify metastatic disease in nearly all patients while exposing them to fewer surgical risks (67). Additionally, the SENTI-ENDO study (68) confirmed that SLN mapping often detects occult micrometastases and isolated tumor cells that would be missed by standard histological evaluation, thanks to the mandatory pathological ultrastaging (serial sectioning and immunohistochemistry) performed on the sentinel nodes (68).

For high-risk endometrial cancers (e.g., G3 endometrioid, serous, clear cell, and carcinosarcoma), SLN mapping is also highly effective and increasingly recommended. While previous retrospective data, such as the SEPAL study (69),

suggested a survival benefit to extending lymphadenectomy to the para-aortic region for intermediate and high-risk patients (69), this required an extensive and morbid surgical dissection. More recently, a prospective validation trial by Soliman et al. (70) specifically investigated SLN mapping in high-risk endometrial cancer patients. The study found an 89% SLN detection rate and a 95% sensitivity for identifying nodal metastases in these aggressive histologies (70). Similarly, research focusing specifically on uterine carcinosarcomas has shown that patients undergoing surgical staging via a SLN mapping algorithm have equivalent progression-free survival outcomes compared to those who undergo routine comprehensive lymphadenectomy (71).

However, the oncological safety of the SLN technique for both low- and high-risk early-stage disease is strictly contingent upon adherence to a standardized surgical algorithm (31). The core rules are:

- If a sentinel lymph node is successfully detected, it is excised and sent for pathological ultrastaging (31).
- If the mapping fails to identify a sentinel node in one or both hemipelvises, side-specific systematic lymphadenectomy on the unmapped side should be done for patients at high-intermediate or high risk, and can be considered in patients at presumed intermediate risk (72).

When this strict algorithm is applied the false-negative rate drops to an exceptionally low 4.3% even in high-risk cohorts (70). Conversely, restricting completion lymphadenectomy strictly to cases where mapping fails drastically reduces the overtreatment and morbidity associated with universal lymphadenectomy (72).

1.6.1.1.3 Fertility preserving treatment

Fertility sparing surgery is a viable alternative for a highly selected group of women under the age of 40 (relative indication) who still wish to have children. To be eligible for this approach, patients must present with an histological diagnosis of G1 endometrioid adenocarcinoma (Type 1) that is progesterone receptor (PR) positive. The tumor must be small (< 2.0 cm), completely confined to the endometrium (Stage IA

without myometrial invasion), and negative for lymphovascular space invasion (LVSI) (73).

An accurate pre-treatment workup, done by an hysteroscopic directed biopsy, expert pelvic MRI and/or 3D-TVUS, is mandatory to confidently exclude any subclinical myometrial infiltration or synchronous ovarian malignancies (73,74). Genetic counseling for Lynch syndrome (MMR deficiency) should also be considered, as 5-10% of young EC patients may harbor a germline mutation (74).

The traditional cornerstone of conservative management relies on high-dose continuous oral progestins, such as Megestrol acetate 160 mg/day or Medroxyprogesterone acetate, or the placement of a Levonorgestrel-releasing intrauterine device (LNG-IUD) for a minimum of 6 months (74). For obese and insulin-resistant patients, conditions intimately linked to EC, adjunctive treatments like Metformin or aromatase inhibitors (e.g., anastrozole) combined with progestins are emerging to actively counteract peripheral estrogen conversion in adipose tissue (73).

However, recent evidence demonstrates that a combined surgical-medical approach yields superior outcomes. This involves a standardized three-step hysteroscopic resection: excising the tumor lesion, the adjacent endometrium, and the underlying myometrium, followed by adjuvant progestin therapy (LNG-IUD or oral) for at least 6 months (74). Studies report that this combined modality significantly improves the efficacy of progestins alone, achieving complete regression rates between 93% and 96.3%, with a median time to complete regression of 3 months and a lower recurrence rate (approximately 7.7%) compared to exclusive hormonal therapy (74).

Given the underlying risk factors for infertility in these patients (such as PCOS or obesity), early referral to a reproductive endocrinologist for Assisted Reproductive Technology (ART) is highly recommended (73).

However, it is important to specify that conservative management is strictly temporary and serves the specific goal of allowing the patient to conceive. Pregnancy should be actively encouraged as soon as a complete tumor response is achieved. If the disease progresses, or if a complete response is not reached within 12 months, standard surgical treatment is strongly recommended (47).

Following the combined hysteroscopic-hormonal approach, pregnancy rates can reach up to 70-93%, with live birth rates of 86.6% among women attempting to conceive (73,74).

1.6.1.2 Advanced Disease (Stage III and IV)

In clinically advanced stages (Stage III and IV, including carcinosarcomas), the surgical paradigm fundamentally shifts from comprehensive staging to surgical cytoreduction. According to the updated 2025 ESGO-ESTRO-ESP guidelines, primary surgical cytoreduction should be considered only when a complete macroscopic resection of the tumor is deemed feasible with acceptable surgical morbidity and preservation of the patient's quality of life (31).

The clinical rationale for this aggressive approach is heavily supported by literature demonstrating that the volume of residual disease is one of the most critical determinants of overall survival. Historical analyses of patients with Stage IVB endometrial carcinoma have shown that maximal cytoreduction provides a statistically significant survival advantage, with the amount of residual disease, patient age, and performance status acting as independent prognostic predictors (75).

Unlike in Stages I and II, where sentinel lymph node mapping is the standard approach, systematic pelvic and para-aortic lymphadenectomy is not recommended for advanced disease. Instead, surgeons should limit nodal resection exclusively to macroscopically enlarged or suspicious lymph nodes as part of the overall cytoreductive effort (31).

When surgical intervention is completely ruled out, either due to the massive extent of the disease or severe medical contraindications, a scenario affecting about 3.4-9% of patients, alternative paths are necessary (76). Depending on the patient's molecular profile and clinical status, clinicians may opt for definitive radiotherapy (often incorporating external beam radiotherapy and image-guided brachytherapy) or primary systemic therapy (31,76). For systemic treatment, standard chemotherapy regimens utilizing carboplatin and paclitaxel are employed, which are now recommended in combination with immune checkpoint inhibitors for patients with mismatch repair deficient (MMRd) tumors (31).

1.6.2 Adjuvant Treatment

Traditional clinicopathological factors, such as patient age, tumor histology, grade, depth of myometrial invasion, and lymphovascular space invasion (LVSI), remain fundamental for prognostic assessment (31). Notably, recent evidence highlights that the presence of substantial LVSI significantly increases the risk of both disease recurrence and overall mortality (77).

While the four original TCGA molecular subgroups carry distinct prognostic implications, performing comprehensive genomic sequencing for every patient is not always feasible. To bridge this gap, subsequent research demonstrated that equivalent molecular profiles can be reliably identified using surrogate markers on standard formalin-fixed paraffin-embedded (FFPE) tissues. This highly accessible alternative relies on a select panel of well-established immunohistochemical stains combined with targeted DNA sequencing.

By merging these molecular profiles with traditional clinicopathological data, the oncological community has developed an updated recurrence risk stratification system. This modern framework applies specifically to women with Stage I to IVA endometrial carcinoma who have no macroscopic residual disease following primary surgery (31) (Table VI).

***Table VI**, Risk class according to 2023 FIGO stages*

RISK CLASS	FIGO 2023 Stage
Low	• I-IIm POLEmut • IAm MMRd, NSMP G1/2 and ERpos • ICm MMRd
Intermediate	• IBm MMRd, NSMP G1/2 and ERpos • IIAm NSMP G1/2 and ERpos • IICm MMRd no or focal LVSI
High-intermediate	• IIAm MMRd • IIBm MMRd, NSMP G1/2 and ERpos • IICm MMRd, with cervical stromal invasion and/or substantial LVSI
High	• IA2-IBm NSMP G3 or ERneg, p53abn • IIm NSMP G3 or ERneg, p53abn • III-IVAm MMRd, NSMP G1/2 and ERpos, NSMP G3 or ERneg, p53abn

1.6.2.1 Low Risk Group

For low-risk endometrial carcinoma, adjuvant therapy is not clinically indicated since the overall risk of recurrence in this group is exceptionally low (less than 5%). When relapses do occur, they are isolated to the vaginal vault in roughly 70% of cases, with five-year disease control and survival rates ranging from 50% to 70% (78,79).

Furthermore, landmark data from the PORTEC-1 and PORTEC-2 trials have definitively established that POLE gene mutations serve as a powerful biological indicator of a highly favorable prognosis, completely independent of traditional clinicopathological variables. Consequently, patients presenting with Stage I or II POLE-mutated (POLEmut) tumors are automatically classified into the low-risk category (25,80). For these women, postoperative adjuvant treatment can be safely omitted, avoiding unnecessary toxicity without compromising oncological outcomes.

1.6.2.2 Intermediate Risk Group

For patients classified as intermediate-risk, adjuvant vaginal brachytherapy (VBT) is standard practice, though active observation following surgery is also a valid clinical option (47).

Important clinical trials, such as PORTEC-1 (25) and GOG-99 (81) established that pelvic external beam radiotherapy (EBRT) significantly reduces locoregional recurrences in this specific risk cohort. However, since the vast majority of these relapses naturally occur at the vaginal vault, the subsequent PORTEC-2 trial (80) shifted the focus to compare the efficacy and toxicity profiles of VBT against traditional EBRT. The 10-year follow-up data were definitive: both study arms achieved excellent vaginal control rates exceeding 96% (82). Similarly, there were no significant differences regarding isolated pelvic recurrences, distant metastases, or overall survival (OS) (82).

The alternative approach, omitting adjuvant radiation entirely, has also been extensively evaluated. A Danish population-based study (83) confirmed that withholding VBT does increase the locoregional recurrence rate to approximately 14% (83). Interestingly, this increase does not negatively impact overall survival. This is largely due to the high success rate of curative salvage therapies administered when a vaginal relapse actually occurs (83). Given these outcomes, omitting postoperative adjuvant treatment is a safe and feasible strategy, provided the decision is highly individualized based on patient characteristics and shared decision-making.

1.6.2.3 High-Intermediate Risk Group

Adjuvant management for the high-intermediate risk category is notably heterogeneous. Due to an inherently higher risk of relapse compared to lower-tier cohorts, pelvic external beam radiotherapy (EBRT) is widely recommended as the standard of care to achieve optimal locoregional control (47).

However, treatment de-escalation is a valid consideration in highly specific clinical scenarios. For instance, in patients who have undergone comprehensive surgical nodal staging that definitively confirms negative lymph nodes, isolated vaginal

brachytherapy (VBT) or even the complete omission of adjuvant therapy may serve as viable alternatives (47).

The ultimate therapeutic choice relies heavily on specific histopathological features. Long-term data from the PORTEC-2 trial confirmed that the presence of substantial lymphovascular space invasion (LVSI) is strongly associated with an elevated risk of disease recurrence (77). For patients harboring this unfavorable prognostic factor, EBRT demonstrated strictly superior disease control compared to VBT alone (77).

To explore whether adding systemic therapy could improve outcomes, the Phase III GOG-249 (84) trial compared standard pelvic EBRT against a combination regimen of vaginal cuff brachytherapy (VCB) followed by three cycles of paclitaxel and carboplatin. The trial results showed no significant difference in recurrence-free survival (RFS) between the two treatment arms (84). Conversely, the chemotherapy group experienced a significantly higher incidence of severe acute and neurological toxicities (84).

While the evaluation of late-onset side effects requires extended follow-up, these findings clearly demonstrated that substituting comprehensive pelvic radiotherapy with short-course chemotherapy offers no survival benefit. Consequently, pelvic EBRT remains the undisputed standard of care for this patient population.

1.6.2.4 High Risk Group

For aggressive histologies, advanced stages, or p53-abnormal tumors, the therapeutic paradigm is primarily oriented toward maximizing locoregional control and preventing distant metastases, the leading cause of cancer-related mortality (31). The standard approach for this high-risk category is multimodal: external beam radiotherapy (EBRT) combined with concurrent and adjuvant chemotherapy, or alternatively, sequential chemotherapy and radiotherapy. Chemotherapy alone, with or without vaginal brachytherapy, represents another valid alternative option (31).

The crucial role of chemoradiotherapy was definitively validated by the international randomized PORTEC-3 trial (85). The study demonstrated that the addition of chemotherapy (two concurrent cycles of cisplatin followed by four adjuvant cycles of carboplatin and paclitaxel) to EBRT significantly improved both the 5-year overall

survival (81.4% vs. 76.1%) and the 5-year failure-free survival (76.5% vs. 69.1%) compared to radiotherapy alone (85). Furthermore, a pooled analysis of the NSGO-EC-9501/EORTC-55991 and MaNGO ILIADE-III trials reinforced these data, highlighting that the sequential use of chemotherapy and radiotherapy significantly reduced the risk of relapse or death by 37% (HR 0.63) and significantly improved cancer-specific survival (86).

To further emphasize the importance of locoregional control, the GOG-258 trial randomized 813 women with stage III-IVA endometrial cancer to receive either pelvic EBRT with concurrent chemotherapy or chemotherapy alone (six cycles of carboplatin and paclitaxel) (87). Although there were no significant differences in relapse-free and overall survival between the two treatment arms, patients treated with chemotherapy alone experienced a higher incidence of vaginal, pelvic, and/or para-aortic recurrences (87). This finding was strongly corroborated by a retrospective multicenter study by Angeles Alvarez Secord et al. on 265 patients with stage IIIC disease (88). The study highlighted that patients receiving only chemotherapy had a significantly higher risk of developing vaginal recurrences (35%) compared to those treated with radiotherapy (18%) or chemoradiotherapy (5%), as well as double the risk of isolated pelvic recurrences (18% vs. 9% vs. 7%, respectively) (88). These data confirm the critical role of integrating radiotherapy with chemotherapy to ensure better control of locoregional recurrences and improve overall survival.

Treatment intensification inevitably impacts clinical morbidity (89). During the combined therapy in the PORTEC-3 trial, approximately 60-61% of patients in the chemoradiotherapy arm experienced grade 3 or worse adverse events (primarily hematological and gastrointestinal toxicity), compared to only 12-13% in the radiotherapy-alone arm (85,89). However, Health-Related Quality of Life (HRQoL) data indicate a rapid recovery between 6 and 12 months post-treatment (89). The primary late toxicity that tends to become chronic at 24 months is sensory peripheral neuropathy, which persists at grade 2 or higher in roughly 10% of patients treated with chemotherapy (versus <1% with RT alone), underscoring the critical need for adequate patient counseling (85,89). To mitigate these adverse effects, it has been observed that the use of Intensity-Modulated Radiation Therapy (IMRT) can significantly reduce

acute gastrointestinal and genitourinary toxicity compared to standard radiotherapy, allowing patients to experience a better quality of life during the treatment itself (90).

The main limitation of the traditional clinical approach was the risk of overtreating or undertreating certain patients (91). The retrospective molecular analysis of the PORTEC-3 trial revolutionized high-risk management, demonstrating that the efficacy of adjuvant chemotherapy varies drastically depending on the molecular subgroup (91):

- **p53abn tumors**: Despite having the worst overall prognosis (5-year RFS of 48%), this group derives the greatest absolute benefit from the addition of chemotherapy (91). The 5-year RFS significantly increased from 36% with radiotherapy alone to 59% with combined chemoradiotherapy (91). For these patients, combined chemoradiotherapy is strongly indicated regardless of the histologic type.
- **POLEmut tumors**: Despite being classified as "high-risk" by traditional anatomical criteria, these patients exhibit an excellent prognosis with a 5-year RFS of 98-100% (91). The addition of chemotherapy provided no survival advantage over radiotherapy alone, establishing that therapeutic de-escalation is a highly safe option to consider (91).
- **MMRd tumors**: In this molecular cohort, the addition of standard cytotoxic chemotherapy did not significantly improve clinical outcomes compared to radiotherapy alone (5-year RFS 68% with chemoradiotherapy vs. 76% with RT alone) (91). However, for patients with locally advanced disease (Stage IIIm-IVAm) harboring MMRd tumors, the integration of an immune checkpoint inhibitor alongside adjuvant chemotherapy (with or without EBRT) should be strongly considered (31,91).
- **NSMP tumors**: Within this heterogeneous intermediate group, a trend favoring chemoradiotherapy was observed (5-year RFS 80% vs. 68%), although it did not reach statistical significance, thus requiring individualized multidisciplinary team discussions (91).

Ultimately, adjuvant treatment for high-risk endometrial cancer is no longer dictated solely by FIGO stage and histology; it requires rigorous integration with the tumor's molecular profile to balance oncological efficacy and mitigate unnecessary toxicity.

1.6.3 Treatment of recurrent and metastatic disease

Patients presenting with recurrent endometrial carcinoma represent a highly heterogeneous clinical population, ranging from individuals with an isolated vaginal relapse curable with targeted radiotherapy to those with widely metastatic disease treated primarily with palliative intent. According to data from the PORTEC-1 trial, in cases of isolated vaginal recurrence in patients without prior pelvic irradiation, external beam radiotherapy (EBRT) with or without brachytherapy can achieve a complete remission in 89% of cases and a 5-year overall survival rate of 65% (92). Conversely, patients with isolated oligometastatic disease (defined as one to five metastases, such as an isolated para-aortic lymph node recurrence) benefit from targeted local treatments, including surgical resection or radical and stereotactic radiotherapy, which can yield a prolonged progression-free interval (31).

However, the majority of patients present with multifocal or distant metastases, making systemic chemotherapy or hormone therapy the only viable therapeutic options. Endocrine therapy (e.g., progestins) is the preferred initial approach for patients with low-grade, estrogen receptor-positive, asymptomatic, or indolent slow-growing tumors (31). For rapidly progressive or symptomatic disease in chemotherapy-naive patients, the standard cytotoxic backbone remains the combination regimen of carboplatin and paclitaxel (31).

The true paradigm shift in the management of advanced disease, as established by the updated 2025 ESGO-ESTRO-ESP guidelines, lies in the integration of immunotherapy guided strictly by the tumor's molecular profile. Specifically, if the disease is mismatch repair deficient (MMRd), the addition of an immune checkpoint inhibitor (such as dostarlimab, durvalumab, or pembrolizumab) to first-line chemotherapy, followed by immunotherapy maintenance, is now the standard recommendation (31). For patients with mismatch repair-proficient (non-MMRd) tumors, the phase III DUO-E clinical trial has demonstrated that treatment with durvalumab in combination with carboplatin

and paclitaxel, followed by combined maintenance with durvalumab and the PARP inhibitor olaparib, leads to a significant and clinically meaningful reduction in the risk of disease progression or death, thus introducing a highly valid, novel therapeutic option for this specific subgroup (93).

2 AIM

Our aim is to evaluate whether transvaginal ultrasound with volumetric integration and three-dimensional assessment can be appropriately used for the preoperative staging of EC, comparing the performance of this technique with MRI, which is currently recommended by the 2025 ESGO-ESTRO-ESP guidelines.

Primary endpoint

To determine the agreement between the myometrial, cervical and vaginal infiltration obtained with 3D-TVUS and MRI and the actual histological infiltration, and calculate the diagnostic accuracy expressed as sensitivity (SE), specificity (SP), positive predictive value (PPV) and negative predictive value (NPV) of 3D-TVUS in assessing the degree of myometrial and cervical infiltration in patients with EC.

Secondary endpoint

To evaluate the diagnostic efficacy of 3D-TVUS in determining the degree of myometrial and cervical invasion by EC, comparing its accuracy with that of MRI.

Another endpoint is to provide data supporting the potential contribution of 3D-TVUS in the preoperative assessment process of patients with EC, so that it can establish as a first-line diagnostic technique

3 MATERIALS AND METHODS

Study Design and Setting:

This research was designed as a prospective observational cohort study. All clinical data were collected at the Gynecologic Oncology and Second-Level Gynecological Ultrasound outpatient clinics within the Department of Women's and Children's Health at the University Hospital of Padua (Azienda Ospedale-Università di Padova). The study cohort comprises patients who were surgically treated between December 2021 and February 2026.

Study Population:

The study population included women with a suspected instrumental diagnosis of endometrial carcinoma (EC). For all participants, the diagnosis was histologically confirmed via operative hysteroscopy and targeted biopsy prior to surgical intervention, which was performed in accordance with the latest international guidelines.

Clinical data were systematically extracted from electronic medical records. Informed consent was obtained from all patients regarding the processing and utilization of their personal data for scientific research purposes.

Inclusion criteria for the study were strictly defined as follows:

- Availability of a definitive histopathological diagnosis of EC.
- Preoperative imaging evaluation utilizing both 3D-TVUS (with volumetric reconstruction) and pelvic Magnetic Resonance Imaging (MRI).
- Primary surgical treatment performed at our center.
- Postoperative clinical follow-up conducted either at our Gynecologic Oncology outpatient clinic or at external medical facilities (provided explicit authorization to access follow-up data was granted).

Conversely, patients were excluded based on the following exclusion criteria:

- Interruption of the diagnostic workup at our institution.
- Lack of either a preoperative 3D-TVUS or an MRI scan.
- Patient refusal to undergo the proposed surgical treatment.
- Transfer of clinical management or follow-up to external facilities resulting in unavailable clinical data.

Data Collection:

To ensure comprehensive analysis, the following preoperative variables were extracted from the medical record for each patient:

- Clinical Data: Date of birth, weight, height, Body Mass Index (BMI), parity, history of cancer, menopausal status and patient age at the time of surgery
- Diagnostic Histological Data: Tumor histotype and clinical grading. These parameters were obtained from the preoperative hysteroscopic biopsy, which was evaluated by the Pathology Unit (U.O.C. Anatomia e Istologia Patologica) at the University Hospital of Padua.
- Preoperative Imaging Data: Radiological staging, depth of myometrial invasion, cervical stromal involvement, vaginal infiltration, and the presence of suspicious lymph nodes. This information was derived from both 3D-TVUS and contrast-enhanced pelvic MRI scans, performed by the Radiology Unit (U.O.C. Radiologia) at the University Hospital of Padua.

Following surgical treatment, postoperative data were recorded to evaluate diagnostic accuracy and ultimate clinical outcomes:

- Surgical Data: Date and type of the surgical procedure.
- Definitive Histopathological Data: Tumor histotype and final grading, surgical-pathological staging, and the confirmed presence or absence of myometrial, cervical, vaginal, and lymph node infiltration, all based on the comprehensive analysis of the surgical specimen.

Clinical Management and Multidisciplinary Approach

Within our institution, all enrolled patients underwent comprehensive preoperative staging utilizing 3D-TVUS (in conjunction with standard 2D-TVUS) and pelvic MRI. To rigorously prevent interpretative bias, these two diagnostic imaging modalities were performed in a blinded manner; the sonographers did not have access to the MRI reports, and vice versa.Once acquired, the imaging and histological reports were brought before a Multidisciplinary Team (MDT) meeting. This board, comprising medical oncologists, radiologists, pathologists, and gynecologic oncologists, convenes weekly to review all gynecological malignancies. This collaborative framework ensures a highly thorough and holistic evaluation of every clinical case. Therapeutic decisions were strictly aligned with the international ESGO-ESTRO-ESP guidelines. By integrating these recommendations with precise FIGO staging, the MDT ensures that every patient receives optimal, high-quality, and personalized oncological care.

Statistical Analysis

Upon finalizing data collection, a primary statistical analysis was conducted to determine the accuracy of 3D-TVUS in assessing myometrial, cervical stromal and vaginal infiltration. This was achieved by cross-referencing the preoperative radiological findings with the definitive postoperative histopathological results, which served as the gold standard. Subsequently, a comparative analysis was performed to evaluate the diagnostic performance of 3D-TVUS directly against contrast-enhanced pelvic MRI. Statistical computations were carried out using MedCalc® software, version 23.5.5 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2026).

Descriptive statistics for categorical variables were expressed as absolute frequencies and percentages. Continuous numerical variables were reported as medians alongside their respective interquartile ranges (IQR). Diagnostic accuracy was quantified reporting Sensitivity (SE), Specificity (SP), Positive Predictive Value (PPV), and Negative Predictive Value (NPV), all presented with their 95% Confidence Intervals (CI).

4 RESULTS

This study enrolled a total of 89 patients, all of whom received a histologically confirmed diagnosis of endometrial carcinoma (EC) via targeted hysteroscopic biopsy. All participants subsequently underwent primary surgical treatment between December 2021 and February 2026.

Regarding baseline anthropometric characteristics, the median Body Mass Index (BMI) of the cohort was 27.10 (IQR 24.20–31.6). The patients had a median weight of 70.90 kg (IQR 62.12–82.99) and a median height of 162 cm (IQR 158–166). At the time of surgery, the median patient age was 63 years (IQR 56.00–72.00).

Obstetric history revealed that 74.16% of the women (66 out of 89) were parous, having had at least one child, whereas 25.84% (23 out of 89) were nulliparous. Furthermore, at the time of diagnosis, 8.99% of the patients (8 out of 89) were premenopausal, while the remaining 91.01% (81 out of 49) were already postmenopausal.

Surgical management was predominantly minimally invasive, successfully performed in 95.50% of the cohort (85 out of 89 patients). Within this specific group, 20.00% of the procedures (17 out of 85) were completed utilizing a robotic-assisted approach.

Regarding radicality, 97.75% of the overall study population (87 out of 89 patients) underwent a total hysterectomy with bilateral salpingo-oophorectomy. Nodal staging within this cohort of 87 patients reflected varying clinical scenarios:

- Optimal mapping: 44 patients achieved successful bilateral sentinel lymph node (SLN) mapping and excision.
- Side-specific pelvic lymphadenectomy: In 8 cases, the tracer failed to map unilaterally, prompting the surgeons to perform a side-specific pelvic lymphadenectomy to ensure complete staging.
- Systematic lymphadenectomy: 21 patients underwent a comprehensive systematic pelvic lymphadenectomy, with or without para-aortic nodal dissection

- Incomplete mapping: Finally, 3 patients underwent exclusively a unilateral SLN biopsy, without any further side-specific nodal dissection on the unmapped side.

A detailed summary of the continuous patient variables, alongside the categorical histological data derived from the diagnostic operative hysteroscopy, is provided in Tables VIIa and VIIb.

Table VIIa: *Patient characteristics*

Variable	**Median (IQR)**
Age (years)	63 (56 - 72)
Height (cm)	162 (158 - 166)
Weight (kg)	70.9 (62.1 - 82.9)
BMI (kg/m^2)	27.1 (24.2 - 31.6)

Table VIIb*: Histological findings obtained from the diagnostic hysteroscopic biopsy*

Variable	**n (%)**
Histotype	
Endometrioid	79 (88.8)
Non-endometrioid	10 (11.2)
Grade	
Low Grade (G1-G2)	69 (77.5)
High Grade (G3)	20 (22.5)

Preoperative radiological data and definitive histological findings derived from the surgical specimen are detailed in Table VIII.

Of note, pelvic MRI data were unavailable for 8 patients; therefore, the MRI analysis is based on a subset of 81 patients.

***Table VIII**: Radiological and histological findings regarding myometrial, cervical stromal and vaginal invasion*

Modality	Myometrial Invasion n (%)	Cervical stromal Invasion n (%)	Vaginal Invasion n (%)
MRI			
Absent	39 (48.1)	73 (90.1)	80 (98.8)
Present	42 (51.9)	8 (9.9)	1 (1.2)
3D-TVUS			
Absent	41 (46.1)	83 (93.3)	89 (100)
Present	48 (53.9)	6 (6.7)	0 (0)
Histology			
Absent	52 (58.4)	77 (86.5)	82 (92.1)
Present	37 (41.6)	12 (13.5)	7 (7.9)

Subsequently, relative frequencies were calculated for the various tumor stages. This comparison evaluated the preoperative instrumental staging (assessed via MRI and 3D-TVUS) against the definitive surgical-pathological staging, in accordance with the FIGO 2009 (Table IX) classification.

***Table IX:** FIGO 2009 classification according to instrumental and pathological staging*

FIGO 2009	MRI	3D-TVUS	Surgical Staging
IA	38 (46.9)	40 (44.9)	47 (52.8)
IB	29 (35.8)	43 (48.3)	21 (23.9)
II	3 (3.8)	6 (6.8)	6 (6.6)
IIIA	0 (0)	0 (0)	0 (0)
IIIB	0 (0)	0 (0)	6 (6.6)
IIIC1	7 (8.5)	0 (0)	8 (9)
IIIC2	3 (3.8)	0 (0)	0 (0)
IVA	1 (1.2)	0 (0)	1 (1.1)
Total	**81**	**89**	**89**

Afterward, the agreement between preoperative radiological staging (assessed via MRI and 3D-TVUS) and definitive surgical staging, according to the FIGO 2009 classification, was evaluated (Table Xa and Xb). To accurately assess the diagnostic reliability of the imaging modalities (3D-TVUS and MRI) in evaluating loco-regional disease extension (myometrial, cervical stromal, and vaginal invasion), the agreement analysis using Cohen's Kappa was performed on a subset of patients with a definitive histological stage ≤ IIIB (FIGO 2009). Cases presenting with isolated lymph node involvement or distant metastases (Stages IIIC and IV) were excluded from this specific analysis, as the evaluation of these sites exceeds the spatial resolution limits and primary anatomical targets of transvaginal ultrasound.

***Table Xa**: Agreement between preoperative MRI staging and definitive histological staging*

	MRI Staging, n (%)					
Surgical staging	IA	IB	II	IIIA	IIIB	**Total**
IA	27 (42.2)	12 (18.8)	1 (1.6)	0 (0.0)	0 (0.0)	40 (62.6)
IB	7 (10.9)	10 (15.6)	0 (0.0)	0 (0.0)	0 (0.0)	17 (26.5)
II	1 (1.6)	2 (3.1)	1 (1.6)	0 (0.0)	0 (0.0)	4 (6.3)
IIIA	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
IIIB	1 (1.6)	1 (1.6)	1 (1.6)	0 (0.0)	0 (0.0)	3 (4.6)
Total	36 (56.2)	25 (39.2)	3 (4.6)	0 (0.0)	0 (0.0)	64 (100)

***Table Xb**: Agreement between preoperative 3D-TVUS staging and definitive histological staging*

	3D-TVUS Staging, n (%)					
Surgical staging	IA	IB	II	IIIA	IIIB	**Total**
IA	31 (38.8)	16 (20)	0 (0.0)	0 (0.0)	0 (0.0)	47 (58.8)
IB	6 (7.5)	14 (17.5)	1 (1.2)	0 (0.0)	0 (0.0)	21 (26.2)
II	0 (0.0)	5 (6.2)	1 (1.2)	0 (0.0)	0 (0.0)	6 (7.5)
IIIA	0 (0.0)	0 (0.0)	0 (0)	0 (0.0)	0 (0.0)	0 (0.0)
IIIB	0 (0.0)	3 (3.8)	3 (3.8)	0 (0.0)	0 (0.0)	6 (7.5)
Total	37 (46.3)	38 (47.5)	5 (6.2)	0 (0.0)	0 (0.0)	80 (100)

The agreement analysis using the Cohen's Kappa demonstrated a fair concordance between MRI staging and definitive histology, yielding a κ of 0.25 (95% CI: 0.03–0.47, p = 0.027). Contrariwise, preoperative 3D-TVUS staging demonstrated a slightly higher concordance with histological findings, yielding a κ of 0.29 (95% CI: 0.11–0.47, p = 0.002). Both coefficients fall within the range of fair agreement ($0.21 \leq \kappa \leq 0.40$); however, it is evident that the concordance achieved with 3D-TVUS is superior to that observed with MRI.

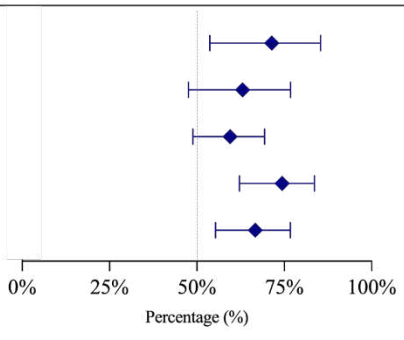
Subsequently, for both imaging modalities (MRI and 3D-TVUS), the agreement between the preoperative assessment of myometrial, cervical and vaginal invasion and the definitive histological findings derived from surgical specimens was evaluated (Tables XIa, XIb, XIIa, XIIb, XIIIa and XIIIb).

***Table XIa-1**: Agreement between MRI-assessed myometrial invasion and definitive histological findings*

	MRI Myometrial Invasion, n (%)		
Histological Myometrial Invasion	Absent (<50%)	Present (≥50%)	Total
Absent (<50%)	29 (35.8)	17 (21.0)	46 (56.8)
Present (≥50%)	10 (12.3)	25 (30.9)	35 (43.2)
Total	39 (48.1)	42 (51.9)	81 (100.0)

***Table XIa-2**: Statistical data between MRI-assessed myometrial invasion and definitive histological findings*

Statistic	Value	95% CI
Sensitivity	71.43%	58.70% - 85.36%
Specificity	63.04%	47.55% - 76.79%
Positive Predictive Value (PPV)	59.52%	48.85% - 69.37%
Negative Predictive Value (NPV)	74.36%	62.15% - 83.66%
Accuracy	66.67%	55.32% - 76.76%
Positive Likelihood Ratio (LR+)	1.93	1.26 - 2.98
Negative Likelihood Ratio (LR-)	0.45	0.26 - 0.80



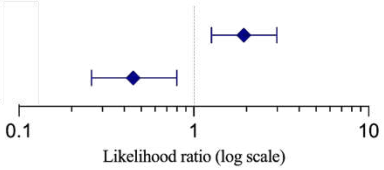
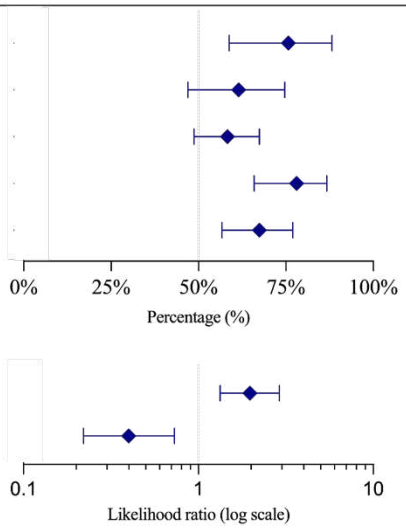


***Table XIb-1**: Agreement between 3D-TVUS assessed myometrial invasion and definitive histological findings*

	3D-TVUS Myometrial Invasion, n(%)		
Histological Myometrial Invasion	Absent (<50%)	Present (≥50%)	**Total**
Absent (<50%)	32 (35.9)	20 (22.5)	52 (58.4)
Present (≥50%)	9 (10.1)	28 (31.5)	37 (41.6)
Total	41 (46.0)	48 (54.0)	89 (100.0)

***Table XIb-2**: Statistical data between 3D-TVUS assessed myometrial invasion and definitive histological findings*

Statistic	Value	95% CI
Sensitivity	75.68%	58.80% - 88.23%
Specificity	61.54%	47.02% - 74.70%
Positive Predictive Value (PPV)	58.33%	48.68% - 67.39%
Negative Predictive Value (NPV)	78.05%	65.95% - 86.72%
Accuracy	67.42%	56.66% - 76.98%
Positive Likelihood Ratio (LR+)	1.97	1.33 - 2.90
Negative Likelihood Ratio (LR-)	0.40	0.22 - 0.73



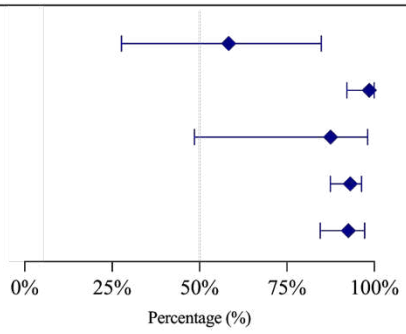
When comparing the diagnostic performance of the two imaging modalities for the detection of myometrial invasion, 3D-TVUS and MRI demonstrated comparable overall accuracy (67.4% and 66.7%, respectively). The agreement analysis yielded a fair concordance for both techniques, with an unweighted Cohen's Kappa of 0.34 (95% CI: 0.13–0.54, p = 0.001) for MRI and 0.36 (95% CI: 0.17–0.55, p <0.001) for 3D-TVUS. Notably, 3D-TVUS exhibited a slightly higher sensitivity (75.7% vs. 71.4%) and negative predictive value (78.0% vs. 74.4%) compared to MRI, whereas MRI showed a marginally superior specificity (63.0% vs. 61.5%). These findings suggest that both modalities offer similar reliability in assessing the presence of myometrial invasion, with 3D-TVUS representing a highly valuable and comparable diagnostic tool in the preoperative setting.

***Table XIIa-1**: Agreement between MRI-assessed cervical invasion and definitive histological findings*

	MRI Cervical Invasion, n(%)		
Histological Cervical Invasion	Absent	Present	Total
Absent	68 (84)	1 (1.2)	69 (85.2)
Present	5 (6.2)	7 (8.6)	12 (14.8)
Total	73 (90.1)	8 (9.8)	81 (100.0)

***Table XIIa-2**: Statistical data between MRI-assessed cervical invasion and definitive histological findings*

Statistic	Value	95% CI
Sensitivity	58.33%	27.67% - 84.83%
Specificity	98.55%	92.19% - 99.96%
Positive Predictive Value (PPV)	87.50%	48.56% - 98.11%
Negative Predictive Value (NPV)	93.15%	87.44% - 96.37%
Accuracy	92.59%	84.57% - 97.23%
Positive Likelihood Ratio (LR+)	40.25	5.43 - 298.50
Negative Likelihood Ratio (LR-)	0.42	0.22 - 0.83



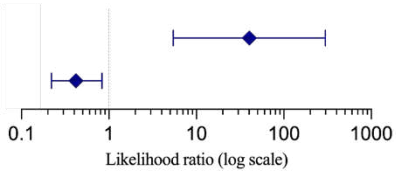
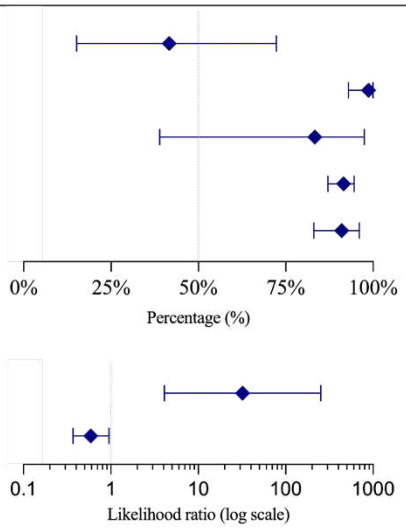


***Table XIIb-1**: Agreement between 3D-TVUS-assessed cervical invasion and definitive histological findings*

	3D-TVUS Cervical Invasion, n(%)		
Histological Cervical Invasion	Absent	Present	Total
Absent	76 (85.4)	1 (1.1)	77 (86.5)
Present	7 (7.9)	5 (5.6)	12 (13.5)
Total	83 (93.3)	6 (6.7)	89 (100.0)

***Table XIIb-2**: Statistical data between 3D-TVUS-assessed cervical invasion and definitive histological findings*

Statistic	Value	95% CI
Sensitivity	41.67%	15.17% - 72.33%
Specificity	98.70%	92.98% - 99.97%
Positive Predictive Value (PPV)	83.33%	38.94% - 97.51%
Negative Predictive Value (NPV)	91.57%	87.06% - 94.60%
Accuracy	91.01%	83.05% - 96.04%
Positive Likelihood Ratio (LR+)	32.08	4.09 - 251.50
Negative Likelihood Ratio (LR-)	0.59	0.37 - 0.95



When evaluating cervical invasion, the agreement analysis revealed a shift in the diagnostic performance of the two imaging modalities compared to the myometrial assessment. Preoperative MRI demonstrated a substantial concordance with definitive histology, yielding an unweighted Cohen's Kappa of 0.66 (95% CI: 0.40–0.92, $p < 0.001$). Furthermore, MRI exhibited a high overall accuracy of 92.6%, with a sensitivity of 58.3% and a specificity of 98.6%. Conversely, 3D-TVUS staging showed a moderate agreement with histological findings, yielding a κ of 0.51 (95% CI: 0.19 – 0.83, $p = 0.002$). The overall diagnostic accuracy for 3D-TVUS remained high at 91.0%, characterized by a specificity of 98.7% but a lower sensitivity of 41.7%. These findings suggest that while both techniques maintain excellent specificity and high negative predictive values (93.2% for MRI and 91.6% for 3D-TVUS) in effectively excluding cervical involvement, MRI represents the superior modality for the accurate

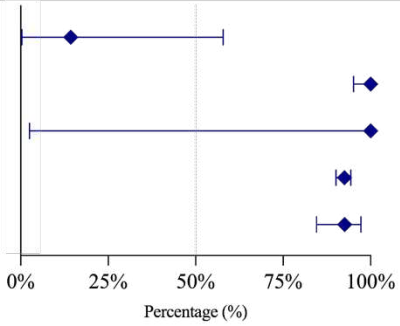
detection of cervical invasion, owing to its higher sensitivity and stronger overall inter-rater agreement.

Table XIIIa-1*: Agreement between MRI-assessed vaginal invasion and definitive histological findings*

	MRI Vaginal Invasion, n(%)		
Histological Vaginal Invasion	Absent	Present	Total
Absent	74 (91.4)	0 (0.0)	74 (91.4)
Present	6 (7.4)	1 (1.2)	7 (8.6)
Total	80 (98.8)	1 (1.2)	81 (100.0)

Table XIIIa-2*: Statistical data between MRI-assessed vaginal invasion and definitive histological findings*

Statistic	Value	95% CI
Sensitivity	14.29%	0.36% - 57.87%
Specificity	100.00%	95.14% - 100.00%
Positive Predictive Value (PPV)	100.00%	2.50% - 100.00%
Negative Predictive Value (NPV)	92.50%	90.11% - 94.35%
Accuracy	92.59%	84.57% - 97.23%



Negative Likelihood Ratio (LR-)	0.86	0.63 - 1.16

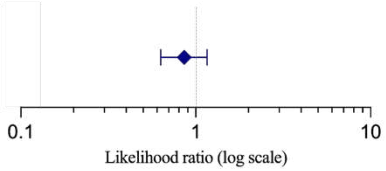
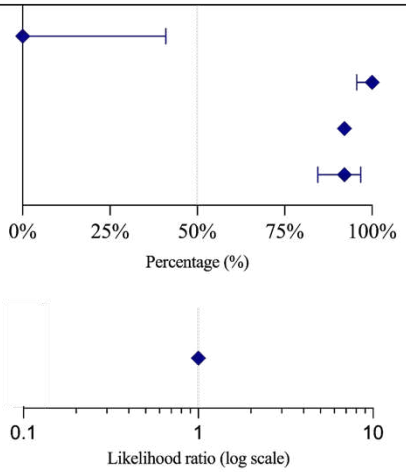


***Table XIIIb-1**: Agreement between 3D-TVUS-assessed vaginal invasion and definitive histological findings*

	3D-TVUS Vaginal Invasion, n (%)		
Histological Vaginal Invasion	Absent	Present	Total
Absent	82 (92.1)	0 (0.0)	82 (92.1)
Present	7 (7.9)	0 (0.0)	7 (7.9)
Total	89 (100.0)	0 (0.0)	89 (100.0)

***Table XIIIb-2**: Statistical data between 3D-TVUS-assessed vaginal invasion and definitive histological findings*

Statistic	Value	95% CI
Sensitivity	0.00%	0.00% - 40.96%
Specificity	100.00%	95.60% - 100.00%
Negative Predictive Value (NPV)	92.13%	92.13% - 92.13%
Accuracy	92.13%	84.46% - 96.78%
Negative Likelihood Ratio (LR-)	1.00	1.00 - 1.00



The assessment of vaginal invasion highlighted significant diagnostic limitations for both imaging modalities, a phenomenon primarily driven by the low prevalence of this specific condition within the study cohort.

Preoperative MRI correctly identified only 1 out of 7 histologically confirmed cases. This resulted in a slight and non-statistically significant agreement with definitive histology, yielding a Cohen's Kappa of 0.23 (95% CI: -0.36 - 0.82, $p > 0.05$). Although MRI demonstrated a seemingly high overall accuracy of 92.6% and a perfect specificity of 100%, its clinical sensitivity was remarkably low at 14.3%.

Conversely, 3D-TVUS staging failed to detect any cases of vaginal invasion (0 true positives out of 7 actual cases). Consequently, Cohen's Kappa for 3D-TVUS resulted in a null agreement ($\kappa = 0.00$). Despite an apparent overall diagnostic accuracy of

92.1%, this metric was derived entirely from the high number of true negatives, reflecting a clinical sensitivity of 0.0%.

These findings emphasize that while both techniques exhibit perfect specificity (100%) and are therefore highly reliable in confirming the absence of vaginal extension, their severe lack of sensitivity limits their diagnostic utility in preoperatively identifying true microscopic vaginal involvement.

5 DISCUSSION

Rationale

Currently, the main imaging techniques recommended by guidelines for the preoperative evaluation of myometrial and cervical invasion in endometrial cancer (EC) are transvaginal ultrasound (TVUS) and Magnetic Resonance Imaging (MRI). Accurate local staging is crucial to stratify patient risk and guide surgical management, particularly in deciding whether to perform or omit lymphadenectomy (94). In this context, 3D-TVUS is an emerging technique of great interest, which could offer significant advantages in terms of accessibility and costs while providing comparable diagnostic accuracy to traditional MRI.

Synthesis of results and comparison with the literature

The primary objective of this study was to compare the diagnostic accuracy of 3D-TVUS and MRI in evaluating the loco-regional extension of the disease, using definitive histology as the gold standard.

Our study included 89 patients with a histologically confirmed diagnosis of EC, who underwent both 3D-TVUS and preoperative MRI. When assessing the global agreement between instrumental staging and surgical-pathological staging (limited to stages ≤ IIIB according to the FIGO 2009 classification), 3D-TVUS demonstrated a higher concordance than MRI (Cohen's Kappa of 0.29 for 3D-TVUS versus 0.25 for MRI). Although both coefficients fall within a fair agreement range, this finding supports the value of 3D-TVUS as a reliable method.

Focusing on myometrial invasion, our results demonstrate a similarity and nearly overlapping comparability between the two modalities. 3D-TVUS and MRI showed comparable overall diagnostic accuracy (67.4% vs 66.7%, respectively) and a fair agreement with histology (Kappa 0.36 for 3D-TVUS and 0.34 for MRI). It is particularly noteworthy that 3D-TVUS exhibited a slightly higher sensitivity (75.7% vs 71.4%) and negative predictive value (78.0% vs 74.4%) compared to MRI, paired with a marginally lower specificity (61.5% vs 63.0%). These data are largely consistent

with recent literature. A meta-analysis by Alcázar et al. highlighted no statistically significant differences between TVS and MRI in diagnosing deep myometrial invasion (pooled sensitivity of 75% for TVS and 83% for MRI) (95). Our data go further, slightly reversing this trend in favor of 3D-TVUS in terms of sensitivity, approaching the excellent results reported in the meta-analysis by Costas et al., which attributes a pooled sensitivity of 84% and specificity of 82% to 3D-TVUS (96).

Regarding cervical stromal invasion, the diagnostic performances shift. In our cohort, MRI was superior as a detection method, showing higher sensitivity (58.3% vs 41.7% for 3D-TVUS) and substantial agreement (Kappa = 0.66 vs 0.51). However, a fundamental clinical finding is that both techniques showed excellent specificity (98.7% for 3D-TVUS and 98.6% for MRI) and very high negative predictive values (>91%). This means that 3D-TVUS is an optimal tool to exclude cervical involvement, aligning with previous studies. The lower ultrasound sensitivity in this anatomical area can be explained by the literature, such as the study by Eriksson et al., which demonstrated that the diagnosis of cervical invasion via TVUS is strictly operator-dependent: expert sonographers achieve significantly higher sensitivities, agreement with histopathology, and interobserver reproducibility compared to general gynecologists (94).

Finally, the assessment of vaginal invasion revealed severe diagnostic limitations for both techniques (sensitivity 14.3% for MRI and 0% for 3D-TVUS), despite a perfect specificity (100%). However, this result was strongly affected by the very low prevalence of this condition in our sample (only 7 cases).

Clinical implications

Considering our results, 3D-TVUS unequivocally emerges as a valid diagnostic tool that is comparable to MRI for the preoperative assessment of myometrial invasion. From a practical and clinical standpoint, this means that 3D-TVUS can be proposed as a first-line imaging examination (95). Due to the rapid and immediate availability of information, 3D-TVUS allows defining the local extension of the disease during the very first gynecological visit. This translates into instantaneous risk stratification, rapid

customization of the therapeutic plan for each patient, and a significant reduction in waiting times and costs associated with MRI, offering a crucial advantage in oncological management. MRI can therefore be reserved for cases where there is an ultrasound suspicion of cervical involvement or when guidelines require further investigation.

Strengths and limitations of our study

The main strengths of our study lie in having directly compared two high-level imaging modalities (MRI and 3D-TVUS) on the exact same cohort of patients (head-to-head comparison), using the undisputed gold standard, which is the definitive histology derived from the hysterectomy surgical specimens. This methodological approach eliminates biases related to comparing different populations, providing an accurate estimate of the true performance of the tests.

Among the limitations of our study, it must be noted that pelvic MRI data were unavailable for a subgroup of patients (8 out of 89), slightly reducing the sample size for the comparative analysis. Furthermore, for specific anatomical sites like the vagina, the very low prevalence of tumor infiltration severely limited the ability to calculate a statistically robust clinical sensitivity for both modalities. Finally, as widely reported in the literature, the strict dependence of 3D-TVUS accuracy, particularly for the cervix, on the individual operator's experience cannot be overlooked. Further multicenter analyses on larger samples will allow consolidating the exclusive use of this promising method in the pre-surgical planning of endometrial cancer.

6 CONCLUSION

3D-TVUS represents an invaluable tool in the pre-surgical evaluation of Endometrial Cancer (EC). In our study, it demonstrated a diagnostic accuracy comparable to, and in some parameters (sensitivity and negative predictive value) slightly superior to MRI for the preoperative assessment of deep myometrial infiltration. Regarding cervical stromal invasion, although MRI confirmed its superiority in terms of sensitivity and overall agreement, 3D-TVUS showed excellent specificity (98.7%), making it an optimal method for excluding cervical involvement.

The use of 3D-TVUS thus emerges as a fundamental turning point in the evolution toward rapid and personalized clinical management, tailored to the specific characteristics of each patient. Given its high accessibility, lower cost, and non-invasiveness, the role of 3D-TVUS as a first-line examination in defining the ideal diagnostic and therapeutic pathway is expected to grow significantly over the years, reducing waiting times and reserving MRI for doubtful or strictly necessary cases.

However, considering the limitations of our study, such as the sample size and the strong dependence of ultrasound results on the operator's experience, we believe it is necessary to conduct further multicenter clinical trials. These future studies will help to definitively outline the effectiveness of this imaging modality and consolidate its prominent role in the pre-surgical management of patients with EC within international guidelines.

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