

ADVANCING PERSONALIZED MANAGEMENT OF ENDOMETRIAL CANCER

Ph.D. Thesis

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“The important thing is not to stop questioning. Curiosity has its own reason for existence.”

Albert Einstein

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1. LIST OF ABBREVIATIONS

EC	endometrial cancer
DMI	deep myometrial invasion
TVS	transvaginal ultrasound
MRI	magnetic resonance imaging
ESGO	European Society of Gynaecological Oncology
ESTRO	European Society for Radiotherapy and Oncology
ESP	European Society of Pathology
ESHRE	European Society of Human Reproduction and Embryology
ESGE	European Society for Gynaecological Endoscopy
ICI	immune checkpoint inhibitors
ChT	chemotherapy
PFS	progression-free survival
OS	overall survival
TRAE	treatment-related adverse event
RCT	randomized controlled trial
MMRd	mismatch repair-deficient
MMRp	mismatch repair-proficient
IPD	individual patient data
PI3K/AKT/mTOR	phosphatidylinositol-3 kinase/serine-threonine kinase/mammalian target of rapamycin
LVSI	lymphovascular-space invasion

2. STUDENT PROFILE

2.1. Vision and mission statement, specific goals

My vision is that the quality and duration of life of every patient with endometrial cancer can be improved using novel diagnostic and therapeutic approaches. My academic and research interests are therefore focused on advancing the management of this disease through more accurate preoperative assessment and more individualized treatment.



My mission is to contribute to better patient care by critically evaluating current scientific evidence and supporting its integration into clinical decision-making. Within my doctoral work, I examine two complementary areas of endometrial cancer management: the role of transvaginal ultrasound and magnetic resonance imaging in preoperative stratification, and the effectiveness and safety of systemic treatment strategies beyond conventional chemotherapy in recurrent or advanced disease. Through systematic reviews and meta-analyses, my specific goals are to compare the diagnostic performance of these imaging modalities, assess their clinical value in surgical planning and risk stratification, evaluate emerging systemic treatments such as immunotherapy, targeted therapy, and hormonal therapy, and identify the main limitations and gaps in the available evidence. Ultimately, my work aims to support more precise, personalized, and evidence-based diagnostic and therapeutic pathways for patients with endometrial cancer.

2.2. Scientometrics

Number of all publications:	16
Cumulative IF:	24.7
Av IF/publication:	1.54
Ranking (SCImago):	D1:2, Q1:2, Q2:1, Q3:0, Q4:1.
Number of publications related to the subject of the thesis:	2
Cumulative IF:	9.2
Av IF/publication:	4.6

Ranking (Sci Mago):	D1:0, Q1:2
Number of citations on Google Scholar:	107
Number of citations on MTMT (independent):	67
H-index:	5

The detailed bibliography of the student can be found on pages 74-78.

2.3. Future plans

My future professional aspirations are closely connected to the clinical and scientific questions addressed in this thesis. As endometrial cancer care becomes increasingly personalized, I aim to further develop my gynecological ultrasound skills, particularly in oncological imaging and preoperative risk stratification. I also intend to place greater emphasis on surgical training, as imaging findings and tumor characteristics must ultimately be translated into appropriate operative decision-making.

From a scientific perspective, I plan to continue participating in multicenter studies and prospective research on novel biomarkers, including microRNAs and tumor-educated platelets. These approaches may contribute to earlier diagnosis, improved risk stratification, and more individualized treatment selection in endometrial cancer. Teaching will also remain an important part of my academic career. I aim to undertake clinical fellowships at international centers of excellence to further develop my diagnostic, surgical, and academic expertise.

After completing my PhD, my goal is to continue with postdoctoral research focused on clinically relevant translational questions that integrate imaging, molecular biomarkers, systemic therapy, and patient-centered outcomes. My long-term aspiration is to contribute to a more precise and individualized model of endometrial cancer care while continuing to develop as a clinician, researcher, surgeon, and educator.

3. SUMMARY OF THE THESIS

This PhD work addresses two complementary aspects of individualized endometrial cancer care: preoperative risk stratification and systemic treatment selection in advanced or recurrent disease. Endometrial cancer is a biologically heterogeneous disease with variable histopathological features, molecular profiles, clinical behavior, and treatment response. As a result, a uniform diagnostic or therapeutic approach is unlikely to provide optimal care for all patients. Modern management increasingly requires patient-centered decision-making, in which imaging findings, histological characteristics, molecular subtype, disease stage, fertility wishes, comorbidities, previous treatments, and expected treatment toxicity are integrated into a personalized strategy.

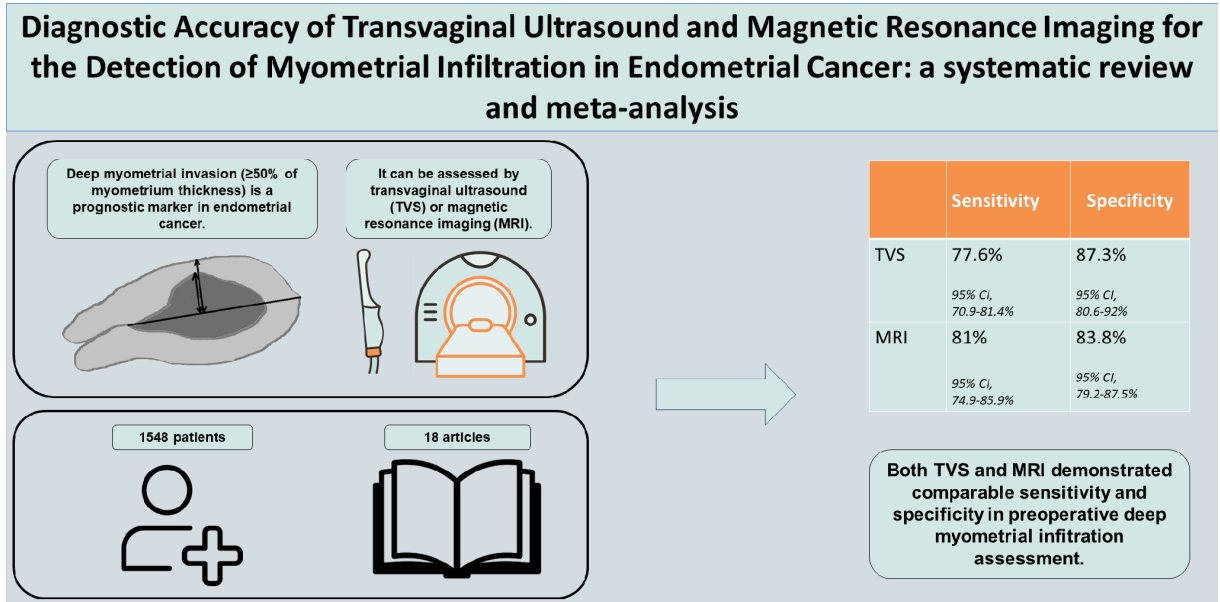
Within this framework, accurate preoperative assessment is essential for tailoring surgical management and avoiding both under- and overtreatment. The first study demonstrated that two-dimensional transvaginal ultrasound and magnetic resonance imaging have comparable diagnostic performance for detecting deep myometrial invasion. Our findings support the use of both imaging modalities in preoperative risk stratification, while also indicating that the optimal diagnostic pathway should be adapted to the clinical context and tumor characteristics. We also underline the future directions that should be addressed in the research.

Similarly, in recurrent or advanced disease, systemic therapy should be selected according to tumor biology and patient-specific factors rather than relying solely on conventional chemotherapy-based approaches. The second study showed that adding immune checkpoint inhibitors to chemotherapy seemed to result in the most favorable survival outcomes, especially in mismatch repair-deficient tumors. In contrast, the benefit was more modest in mismatch repair-proficient tumors. Exploratory analyses of hormonal therapy, lenvatinib plus pembrolizumab, PI3K/AKT/mTOR inhibitors, and combinations with aromatase inhibitors suggest that selected patients may benefit from other targeted systemic approaches, although the strength of evidence is limited by study heterogeneity and the lower methodological level of several included studies. These results highlight the importance of molecular classification in treatment selection and demonstrate that therapeutic benefit varies substantially across biologically distinct patient subgroups.

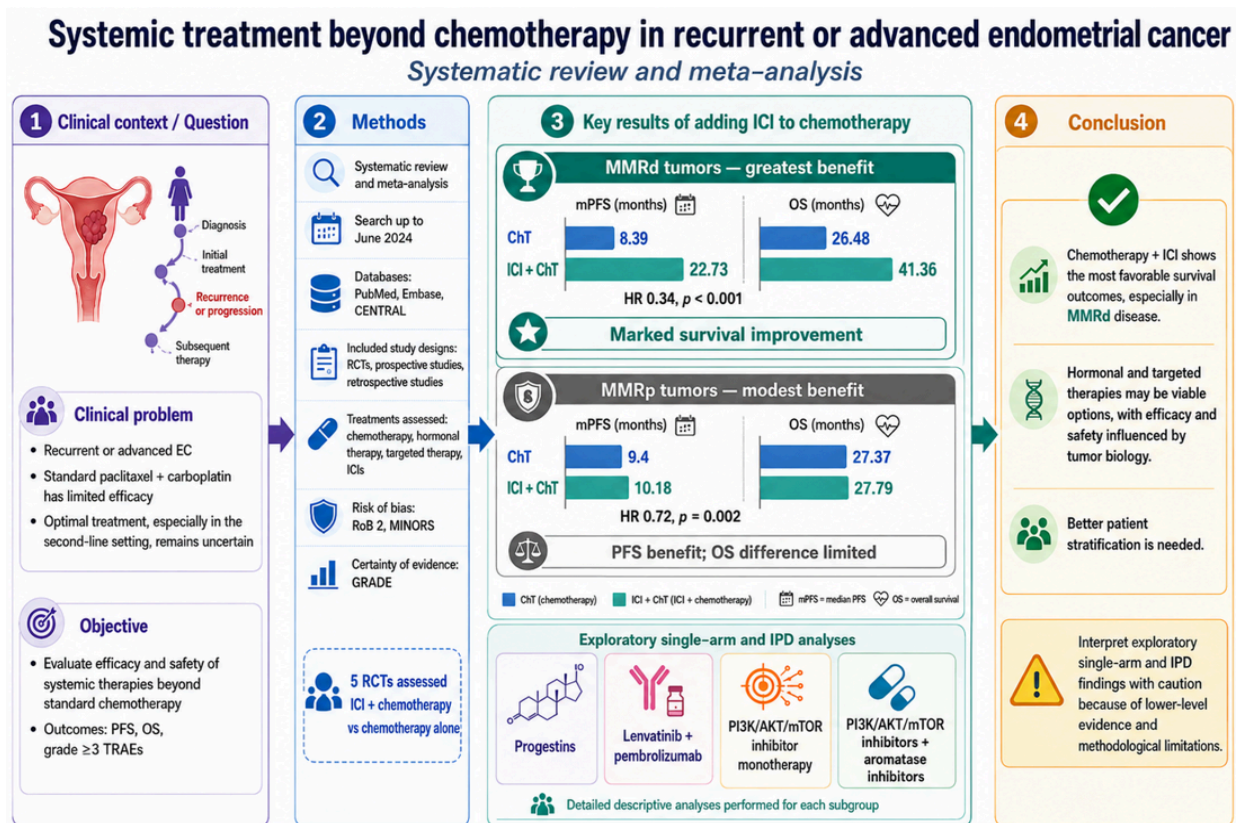
Therefore, the central aim of this PhD work was to evaluate diagnostic and therapeutic strategies that may support more individualized care for patients with endometrial cancer. Together, these studies emphasize that optimal management should be guided not only by disease stage, but also by imaging-based risk factors, histopathological characteristics, molecular subtype, expected treatment benefit, and patient-specific clinical priorities.

4. GRAPHICAL ABSTRACT

4.1. Study 1



4.2. Study 2



5. INTRODUCTION

5.1. Endometrial cancer

Endometrial cancer (EC) ranks among the most prevalent cancers in women globally, with its incidence steadily increasing (1). The lifetime risk of developing endometrial cancer for women is around 3%, with the median age of diagnosis being 61 years. Over the past three decades, the incidence of this cancer has increased by 132%, largely due to the growing prevalence of risk factors such as obesity and an aging population (2).

In early stage EC, hysterectomy and bilateral salpingo-oophorectomy are usually unavoidable. The extent of concomitant lymphadenectomy is determined by risk factors such as tumor grade, histological type, stage, myometrial infiltration depth, lymphovascular space invasion (LVSI) and molecular type. However, the choice of extended surgery is associated with an elevated risk of complications (3).

In recurrent or advanced EC, optimal systemic treatment remains uncertain, particularly in the second-line setting. While first-line chemotherapy with paclitaxel and carboplatin is widely used, its efficacy is limited. Recent evidence suggests that adding immune checkpoint inhibitors (ICIs) to chemotherapy (ChT) can improve progression-free survival (PFS). In addition, hormonal therapies (such as progestins and aromatase inhibitors), targeted therapies and ICIs used alone or in combination are emerging as potential treatment options.

5.2. What is the problem to solve?

5.2.1. *Myometrial invasion assessment in EC*

In early-stage EC, preoperative evaluation should determine the histopathologic type, grade, myometrial invasion, and LVSI, preferably with the addition of molecular classification. Based on these criteria, five prognostic risk groups were determined (low, intermediate, high-intermediate, high, and advanced), where the presence of deep myometrial invasion (DMI: more than 50% of myometrium is infiltrated by EC) plays an important role. In patients with low- or intermediate-risk disease, sentinel lymph node biopsy can be a viable option for staging. However, in patients with high-intermediate or high-risk disease, surgical lymph node staging should be performed (4).

For DMI assessment, a transvaginal or transrectal ultrasound performed by an expert or a pelvic magnetic resonance imaging (MRI) is recommended (4-7). Some authors suggest the usage of MRI only for patients in whom TVS, carried out by an expert, produces images of poor quality (8). Currently, there is no consensus on the imaging method of choice between the different guidelines (7).

Among individuals diagnosed with low-grade (grade 1 or 2 endometrioid) EC, approximately 15.4% are below the age of 50 years, while approximately 4.2% of women are diagnosed before the age of 40 years (9). In 2023, the ESGO/ESHRE/ESGE (European Society of Gynaecological Oncology, European Society of Human Reproduction and Embryology, European Society for Gynaecological Endoscopy) guidelines for the fertility-sparing treatment of patients with EC were published. Accordingly, in patients with endometrioid EC with grade 1, stage IA tumors, without myometrial invasion and without other risk factors, the option of fertility-sparing treatment can be considered (10). However, the assessment of transvaginal ultrasound or MRI in determining the absence of myometrial invasion or shallow myometrial invasion is based on extrapolation from data on diagnosing DMI (10).

5.2.2. Systemic therapy of recurrent or advanced EC beyond chemotherapy

Although specific molecular profiles show a better response to individualized therapies, the combination of carboplatin and paclitaxel serves as the standard systemic first-line chemotherapy for managing primary advanced or recurrent EC (11). Despite its widespread use, the long-term prognosis remains unfavorable (4, 12). In addition, standard combination chemotherapy (ChT) regimens are generally not as effective as second-line treatments, and they present high toxicity. Furthermore, standard monotherapy options yield only modest outcomes (13). Hence, other systemic therapies can be considered in specific patient groups. Emerging evidence suggests that the addition of immune checkpoint inhibitors (ICIs) to ChT may offer survival benefits. ICIs such as pembrolizumab, when combined with lenvatinib, a multi-kinase inhibitor, show consistent efficacy (14). While molecular profiling is a newer tool for guiding therapy, estrogen receptor (ER) and progesterone receptor (PR) positivity have long influenced treatment decisions in recurrent and advanced disease (2, 15). Although progestins and megestrol acetate therapy are widely used for advanced and recurrent endometrial cancer patients because of their low toxicity, the results among studies are

inconsistent (16). With proven benefits in breast cancer, aromatase inhibitors such as letrozole and anastrozole are involved in the blockage of natural synthesis of estrogen and demonstrate antitumor effects in EC (17).

Targeted therapies (TT) for EC exploit molecular aberrations to selectively inhibit tumor growth while preserving normal cells. The PI3K/AKT/mTOR (phosphatidylinositol-3 kinase/serine-threonine kinase/mammalian target of rapamycin) pathway is frequently dysregulated in EC and can be targeted by several inhibitors. These agents, used alone or in combination with chemotherapy or hormonal therapies, demonstrate efficacy in tumors harboring PIK3CA mutations, though resistance and toxicity remain challenges (18). Other possibilities include angiogenesis inhibition, such as with anti-VEGF agents, which disrupt angiogenesis, thus curbing tumor progression. A possible treatment of HER2-positive EC can be Trastuzumab, which, when combined with ChT, impedes HER2-mediated signaling. In tumors with MSI-H (microsatellite instability-high) and MMR deficiency, immune checkpoint inhibitors demonstrate clinical efficacy (19).

There is currently no universally agreed-upon standard of care for second-line treatment in advanced EC, as guidelines vary widely. Additionally, effective therapeutic options for managing recurrent disease remain limited (4). Despite these advances, treatment recommendations beyond first-line chemotherapy remain unclear, and comparative data across therapeutic strategies are limited. A detailed analysis of adverse events is lacking in literature.

5.3. What is the importance of the topic?

In EC, individualized patient care is essential, as a uniform diagnostic or therapeutic approach cannot adequately address its heterogeneity. Accurate preoperative risk stratification is important because it influences surgical planning, lymph node assessment, fertility-sparing decisions, and the need for adjuvant therapy. Inadequate stratification may lead to more complications, worse health-related quality of life, overtreatment, or unnecessary hysterectomies in fertile women who might otherwise be candidates for fertility-sparing management. Deep myometrial invasion is a key prognostic factor.

Individual patient care is also highly relevant in recurrent and advanced disease, where prognosis remains poor and optimal systemic therapy is still not fully defined. The

emergence of molecular classification and immune checkpoint inhibitors has changed treatment selection, especially for mismatch repair-deficient tumors, but the more limited benefit in mismatch repair-proficient disease and non-specific molecular profile tumors highlights the need for further therapeutic refinement. Health-related quality of life is also central, as treatment decisions should not focus only on survival outcomes but also on toxicity, long-term morbidity, functional status, and patient preferences.

5.4. What would be the impact of our research results?

The results of this PhD work may contribute to a more individualized and evidence-based management of patients with endometrial cancer. By demonstrating that transvaginal ultrasound can provide diagnostic performance comparable to magnetic resonance imaging in the assessment of deep myometrial invasion, the findings support the broader clinical use of an accessible, cost-effective, and repeatable imaging method in preoperative risk stratification. This may be especially relevant in settings where MRI availability is limited, and in patients in whom rapid treatment planning is required. More accurate preoperative assessment of myometrial invasion may help avoid both undertreatment and overtreatment, thereby reducing unnecessary surgical morbidity, improving health-related quality of life, and supporting fertility-sparing decisions in carefully selected patients. It also suggests further research directions, like preoperative differentiation of no myometrial invasion and shallow myometrial invasion tumors, providing better stratification of patients with fertility wishes.

The second part of the work further supports individualized care by summarizing the evidence on systemic treatment strategies beyond conventional chemotherapy in recurrent or advanced endometrial cancer. As endometrial cancer is characterized by marked histopathological and molecular heterogeneity, treatment decisions should increasingly rely on tumor biology, molecular subtype, previous therapy, expected efficacy, and toxicity profile. The results highlight the growing role of immune checkpoint inhibitor-based strategies, while also defining the more limited but clinically relevant roles of hormonal therapy, targeted therapy, and combination regimens in selected patient groups. Overall, the impact of this PhD work lies in strengthening the transition toward a personalized, patient-centered decision-making, where diagnostic

accuracy, molecular stratification, treatment efficacy, safety, quality of life, and resource availability are considered together.

6. OBJECTIVES

6.1. Study I. – Diagnostic Accuracy of Transvaginal Ultrasound and Magnetic Resonance Imaging for the Detection of Myometrial Infiltration in Endometrial Cancer: A Systematic Review and Meta-Analysis

In our first study, we aimed to compare the diagnostic performance of two-dimensional transvaginal ultrasound (TVS) and magnetic resonance imaging (MRI) in the preoperative detection of DMI in patients with EC.

6.2. Study II. – Systemic Treatment Strategies Beyond Chemotherapy in Recurrent or Advanced Endometrial Cancer: A Systematic Review and Meta-Analysis

In our second study, our objective was to systematically evaluate the efficacy and safety of systemic therapies beyond standard ChT for patients with recurrent or advanced EC, focusing on progression-free survival (PFS), overall survival (OS), and treatment-related adverse events (TRAEs).

7. METHODS

7.1. Study I.

7.1.1. *Methodology and Protocol*

In accordance with the PRISMA 2020 guidelines (20), we presented our systematic review and meta-analysis following the methodological principles outlined in the Cochrane Handbook (21). Our study protocol was registered on PROSPERO, under registration number CRD42023426934.

7.1.2. *Eligibility Criteria*

We included prospective and retrospective cohort studies. The included population was EC patients who underwent hysterectomy and were examined preoperatively using both 2-dimensional (2D) TVS (Index Test 1) and MRI (Index Test 2), compared to definitive postoperative histology (Reference Test) as the gold standard for diagnosing myometrial invasion depth.

Studies (1) with inaccurate or inconsistent data or where data were presented in a way that could not be further processed, (2) conference abstracts, reviews, case series and case reports, (3) previous systematic reviews and meta-analyses, (4) articles containing data on patients screened exclusively with either TVS or MRI and (5) articles in which 3D ultrasound was the index test were excluded. Attempts were made to contact the authors of articles with inconsistent data.

Studies that reported on the level of myometrial invasion ($<50\%$ or $\geq 50\%$) were eligible for data processing. True positive, true negative, false positive and false negative values were all calculable or included in the articles.

No language or other restrictions were applied.

7.1.3. *Information Sources and Search Strategy*

Our systematic search was conducted in three databases: MEDLINE (Pubmed), Embase and Cochrane Library on 22 May 2023. The domains of the search key included endometrium, cancer, transvaginal sonography and magnetic resonance imaging. Full search key: (endometr* OR uter* OR womb OR UCEC) AND (neoplasm* OR tumor OR tumour OR carcinoma OR cancer* OR malign* OR UCEC) AND (ultraso* OR sonograph* OR TVS) AND (magnetic resonance imaging OR MRI)

7.1.4. Study Selection and Data Extraction

After duplicate removal, title-abstract and full-text selection processes were conducted by two independent authors (IM, GV). To assess inter-rater agreement, Cohen's kappa coefficients (κ) were calculated at each step (22). Disagreements were resolved by a third author (NÁ). Duplicate records were eliminated using EndNote 20 (Clarivate Analytics, Philadelphia, PA, USA), and the remaining articles were assessed using Rayyan (23). Data were extracted into a predefined sheet. Notably, if both expert and non-expert data were provided for the same patient cohort, expert data were included in the final analysis.

The following data were extracted: first author, year of publication, study population, study period, study type, settings (single/multicenter), patient data (total number, menopausal status, age), distribution of the patients with $<50\%$ or $\geq 50\%$ of myometrial involvement, whether data on patients with low-grade EC were available, data on TVS and MRI: number of true positive, true negative, false positive, false negative patients, data on sensitivity and specificity.

7.1.5. Risk of Bias and Quality of Evidence Assessment

The risk of bias assessment was performed independently by two authors (IM, GV), with disagreements resolved by a third author (GS). To evaluate the quality of the included studies, the modified version of the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) (24) tool was used.

7.1.6. Data Synthesis and Analysis

Statistical analyses were performed using R statistical software (version 4.1.2) and the R script of the online tool described by Freeman (25). For all statistical analyses, a p-value of less than 0.05 was considered significant.

Two by two contingency tables were directly extracted or calculated from the studies containing true positive, false positive, false negative and true negative values. To pool sensitivity and specificity, the bivariate models of Reitsma and Chu were fitted (26, 27). We used ROC (receiver-operating characteristic curve) plots to illustrate the sensitivities and specificities of the included studies, the summary estimates of sensitivity and specificity and the corresponding 95% confidence and prediction regions. The confidence region contained both pooled sensitivity and specificity (more specifically,

1-specificity) in 95% of the cases. The prediction region contained the true sensitivity and specificity (more exactly, 1-specificity) of a new study in 95% of the cases, thus providing excellent insight into heterogeneity. In these visualizations, the sizes of the ellipsoids reflected the weights of the studies, calculated according to the method described by Burke (28). Besides the prediction region, heterogeneity was assessed by performing separate univariate analyses of sensitivity. Specifically, we used the generalized mixed-effect approach of Stijnen et al. and calculated the I^2 measure and its confidence interval (29).

The statistical challenge was that the performance of the MRI and TVS was evaluated in the same population within each study, so we separately compared sensitivity and specificity as follows: Separately for the logit transformed sensitivity and specificity, we constructed a two-dimensional (with coordinates MRI logit sensitivity and TVS logit sensitivity, and for specificity analysis MRI logit specificity and TVS logit specificity) model using the `rma.mv()` function of the `metafor` R package. To circumvent the problem caused by the unknown correlations, we supplemented the method with the robust approach of Pustejovsky (30), implemented in the `coef_test()` function of the `clubSandwich` R package. Moreover, we repeated the approach under several within-study correlation assumptions. All sensitivity runs provided similar p-values. We assessed possible time trends in the sensitivity and specificity values by performing a random effect meta-regression using year as a continuous covariate. We visualized the results on regression plots.

Publication bias was assessed by performing the methodology of Deeks et al., including the modified funnel plot (31).

7.2. Study II.

7.2.1. Methodology and Protocol

This work was carried out as part of the Systems Education Program at Semmelweis University and conducted within the Translational Medicine (TM) Cycle Framework by the Academia Europaea (32, 33).

This systematic review and meta-analysis were performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (20, 33, 34). The study protocol was pre-registered on PROSPERO

(registration number CRD42023400040), and the analysis was conducted in strict compliance with the registered protocol.

7.2.2. Eligibility Criteria

We included randomized controlled trials (RCTs), non-randomized interventional studies, and prospective and retrospective observational studies that investigated systemic therapeutic agents in recurrent or advanced endometrial cancer (EC). Eligible interventions included immune checkpoint inhibitors (ICIs), targeted therapies (TT), and hormonal therapies (HT), either as a single therapy or in combination with chemotherapy.

Our clinical question was formulated based on the PICO framework. Eligible patients (P) were women aged ≥ 18 years with histologically confirmed recurrent or FIGO stage III–IV EC. We pooled and compared different systemic therapy schemes (I and C) in the case of randomized controlled trials. For single-arm studies, we pooled similar agents.

The primary outcomes (O) of our study were progression-free survival (PFS) and overall survival (OS). Secondary outcomes were efficacy and safety, including grade ≥ 3 treatment-related adverse events (TRAEs).

We excluded case reports, case series, reviews, conference abstracts, and non-English publications. The included articles contained data on PFS, and most of them also contained data on OS and adverse events. When multiple studies were conducted on the same cohort, the most recent article was included in our analysis. We did not include articles on chemotherapies other than paclitaxel and carboplatine/cisplatin. Where the reduced-dose therapy scheme and usual-dose therapy scheme were both within one study, the usual dose was included in the quantitative analysis. Data with patients on concurrent radiotherapy was excluded. In cases when systemic and non-systemic prior therapy groups were included, the data with prior chemotherapy were included in the quantitative analysis.

7.2.3. Information Sources and Search Strategy

A systematic search in MEDLINE (via PubMed), Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) was performed on 3 June 2024. A manual search on the reference lists of eligible articles was performed. No filters or restrictions were applied.

The following search key terms were used: endometrial cancer AND (recurrent OR advanced) AND systemic therapy. Full search key: (endometr* OR uter* OR womb) AND (canc* OR carcin* OR malign* OR neoplasm*) AND (recurren* OR advanced OR stage III OR stage 3 OR stage IV OR relapse* OR stage 4) AND (immune checkpoint* OR monoclonal antibod* OR mAB OR immunot* OR PD1 OR PD-1 OR PDL-1 OR PDL1 OR PD-L1 OR programmed cell death* OR programmed death-ligand-1 OR programmed death ligand-1 OR programmed death ligand 1 OR nivolumab OR opdivo OR pembrolizumab OR keytruda OR cemiplimab OR libtayo OR durvalumab OR imfinzi OR atezolizumab OR tecentriq OR avelumab OR bavencio OR PARP inhibit* OR poly ADP-ribose polymerase OR poly ADP-ribose polymerase OR poly ADP-ribose polymerase OR poly ADP-ribose polymerase OR olaparib OR lynparza OR rucaparib OR rubraca OR niraparib OR zejula OR talazoparib OR talzenna OR veliparib OR abt-888 OR vascular endothelial growth factor* OR VEGF OR bevacizumab OR avastin OR HER 2 OR HER-2 OR HER2 OR human epidermal growth factor OR trastuzumab OR herceptin OR cetuximab OR erbitux OR kinase inhibitor OR levatinib OR lenvima OR nintedanib OR ofev OR ridaforolimus OR pilaralisib OR progestin OR progestogen OR levonorgestrel OR LNG OR medroxy-progesterone acetate OR MPA OR Megestrol OR hormon* OR progesteron* OR aromatase inhibitor* OR tamoxifen OR fulvestrant OR letrozole OR everolimus OR mTOR OR mechanistic target of rapamycin OR Phosphoinositide 3-kinase OR PI3K).

7.2.4. Study Selection and Data Extraction

All records were imported into EndNote 20 (Clarivate Analytics, Philadelphia, PA, USA), followed by selection using Rayyan. After removing duplicate records, the title-abstract screening and full-text review were conducted independently by two authors (I.M. and G.V.). Cohen's kappa coefficient ($\kappa = 0.86$ for title-abstract and $\kappa = 0.92$ for full-text selection) was calculated to evaluate inter-rater agreement. Any disagreements were resolved through discussion with a third reviewer (N.Á.).

A standardized data extraction form was used. Data extraction was performed independently by two authors (I.M. and G.V.). In instances where multiple publications reported data from the same cohort, the most complete or expert-reviewed dataset was prioritized. Therapeutic agents with similar acting mechanisms, or combinations

containing similar therapeutic agents, with Kaplan–Meyer curves with data on PFS or OS available were pooled.

Given the limited availability of randomized controlled trials in this setting, single-arm data were included to provide a comprehensive overview of available therapeutic strategies; however, these analyses were considered exploratory and not intended for direct comparative inference.

The following data were extracted: first author, year of publication, study population, study period, study type, number of previous chemotherapy treatment lines, intervention chemotherapy agent, comparator chemotherapy agent (when data available), patients data (total number, histology, age, molecular classification data), data on PFS and OS for both groups, and data on efficacy and safety (duration of response, overall response rate, adverse events, grade ≥ 3 adverse events).

7.2.5. Risk of Bias and Quality of Evidence Assessment

Risk of bias was independently assessed by two reviewers (I.M. and G.V.) using the RoB 2 tool for randomized controlled trials and the MINORS tool for non-randomized and single-arm interventional studies. Disagreements were resolved by consensus or consultation with a third reviewer (N.Á.). Evidence quality was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework (35). Two reviewers (I.M. and G.V.) independently assessed each outcome and comparison, with disagreements resolved by a third reviewer (G.S.).

7.2.6. Data Synthesis and Analysis

Both qualitative and quantitative syntheses of the data were performed. The prespecified minimum number of clinically poolable studies for performing a meta-analysis was three. Hazard ratios from placebo-controlled RCTs were pooled in a separate analysis. The inverse variance method was used to calculate pooled HR, using the natural logarithm of HR and its SE from the available data following the methodology of Tierney et al. 2007 (36). To estimate the heterogeneity variance measure (tau-square), the restricted maximum-likelihood estimator was used with the Q profile method for confidence intervals (37, 38). The Hartung–Knapp adjustment was applied when estimating confidence intervals for the pooled effect (39). Heterogeneity was assessed by Higgins and Thompson I^2 statistics (40). Results were considered

statistically significant if the CI did not contain 1 for HR. Also, individual patient data (IPD) meta-analysis was performed for different treatment modalities separately. IPD was retrieved from published Kaplan–Meier (KM) curves using plot digitalization tools (WebPlotDigitizer version 4, Ankit Rohatgi, Pacifica, CA, USA, accessed on 12 December 2024) (41) and following the methodology of Liu et al. (42). Pooled survival probabilities for predefined time intervals and pooled median survival times (with 95% confidence intervals) were estimated for each treatment modality. To this end, the multivariate method described in Combescure et al. was implemented (43). The Greenwood formula was used to estimate confidence intervals for pooled survival probabilities. We summarized our findings in forest plots and tables. The statistical analysis was conducted in the R statistical environment (R Core Team) using the ‘meta’ (41), ‘dmetar’ (44), ‘IPDfromKM’ (42) and ‘metaSurvival’ packages. Due to limited access to original patient-level data, formal external validation of reconstructed datasets was not feasible; however, visual inspection and comparison with published survival summaries were performed to ensure consistency.

8. RESULTS

8.1. Study I: Diagnostic Accuracy of Transvaginal Ultrasound and Magnetic Resonance Imaging for the Detection of Myometrial Infiltration in Endometrial Cancer: A Systematic Review and Meta-Analysis

8.1.1. Study Search and Selection

Altogether 7649 citations were identified, and after duplicate removal and title–abstract selection, 89 were eligible for full-text screening. Of these, 18 articles (8, 45-61), including 1548 patients met the inclusion criteria. The selection process is detailed in Figure 1.

The included studies were published between January 1992 and September 2022. The number of patients with DMI ($\geq 50\%$ of myometrial infiltration) was 520 (33.6% of the total number of patients). The mean patient age was reported in nine studies, ranging from 54.4 to 69 years, the median age was reported in four further studies, ranging between 54 and 69 years. Most of the included studies were prospective ($n = 14$). Ten studies were single-center, whereas three had multicenter design. TVS was conducted in nine studies by a single expert examiner, while in six studies, it was performed by multiple examiners. However, MRI was generally interpreted by multiple examiners ($n = 10$) rather than a single examiner ($n = 5$). The basic characteristics of the enrolled studies are detailed in Table 1.

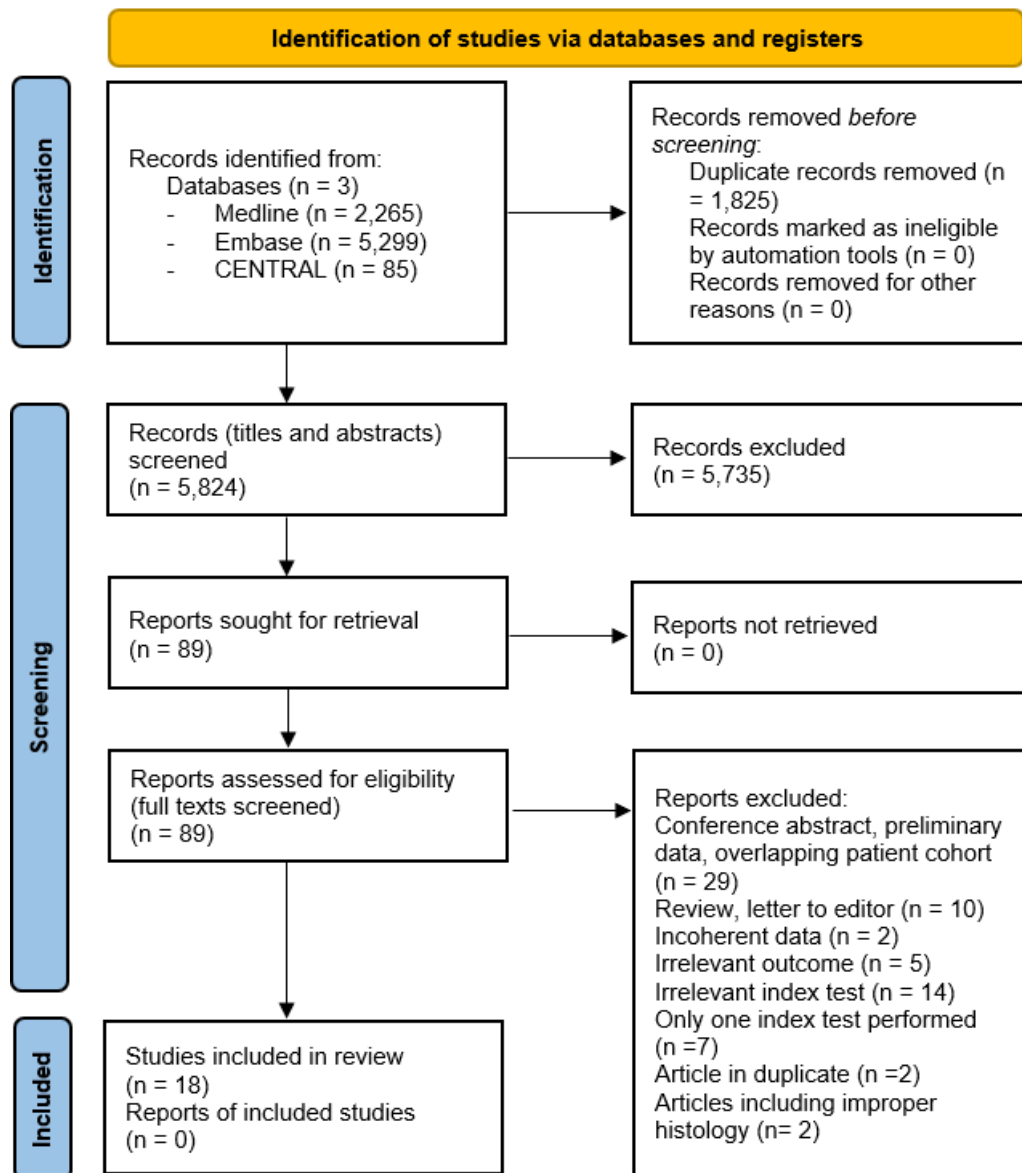


Figure 1. PRISMA 2020 flowchart representing the study selection process (20)

Table 1. Basic characteristics of the included studies.

Author	Study design	Study period	Number of centres	Number of patients	Number of DMI ($\geq 50\%$ myometrial infiltration)	Pathologist blinded to imaging	TVS Observer	MRI Observer
Cubo-Abert, 2021	prospective	2013.10.-2018.07.	single	131	45	NA	single	multiple
Gaston, 2022	prospective	2016.01.-2020.03.	single	156	20	yes	single	single
Palmer, 2023	prospective	2017.01.-2019.06.	multi	259	67	NA	multiple	multiple
Wong, 2022	prospective	2015.10.-2018.10.	single	51	22	yes	single	single
Perniola, 2022	prospective	2019.03.-2021.03.	single	56	32	NA	single	single
Cerovac, 2022	prospective	2019.07.-2021.04.	single	60	26	NA	single	single
Rahmani, 2018	prospective	2009.10.-2012.12.	single	45	16	NA	single	single
Dueholm, 2021	prospective	2013.11.-2015.12.	single	122	47	NA	multiple	multiple

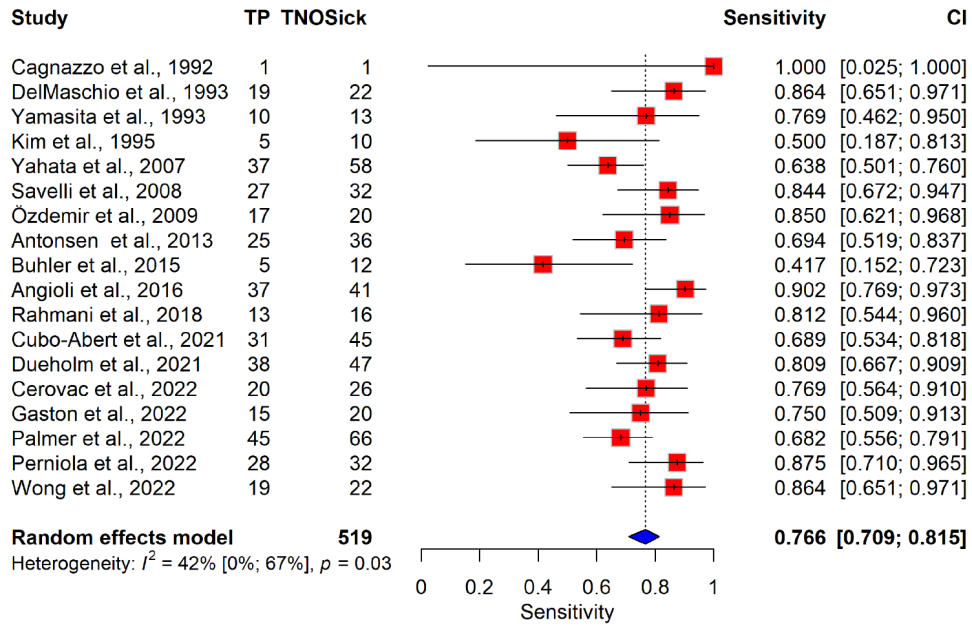
Cagnazzo, 1992	NA	NA	NA	14	1	NA	NA	NA
DelMaschio, 1993	prospective	NA	NA	42	22	yes	single	multiple
Yamasita, 1993	prospective	NA	NA	40	13	yes	single	multiple
Kim, 1995	prospective	1991.01.-1 994.04	NA	26	10	NA	multiple	multiple
Yahata, 2007	retrospective	1995.01.-2 004.04.	NA	177	58	NA	NA	NA
Savelli, 2008	prospective	2000.02.-2 004.05.	multi	74	32	NA	multiple	multiple
Özdemir, 2009	prospective	2007.01.-2 008.11.	single	64	20	NA	single	multiple
Antonsen, 2013	prospective	2009.09.-2 012.01.	multi	123	36	NA	multiple	multiple
Buhler, 2015	retrospective	2012.07.-2 014.07.	single	29	12	NA	multiple	multiple
Angioli, 2016	prospective	2012.01.-2 015.02.	single	79	41	NA	NA	NA

DMI: deep myometrial invasion. TVS: transvaginal ultrasound. MRI: magnetic resonance imaging. NA: no data available.

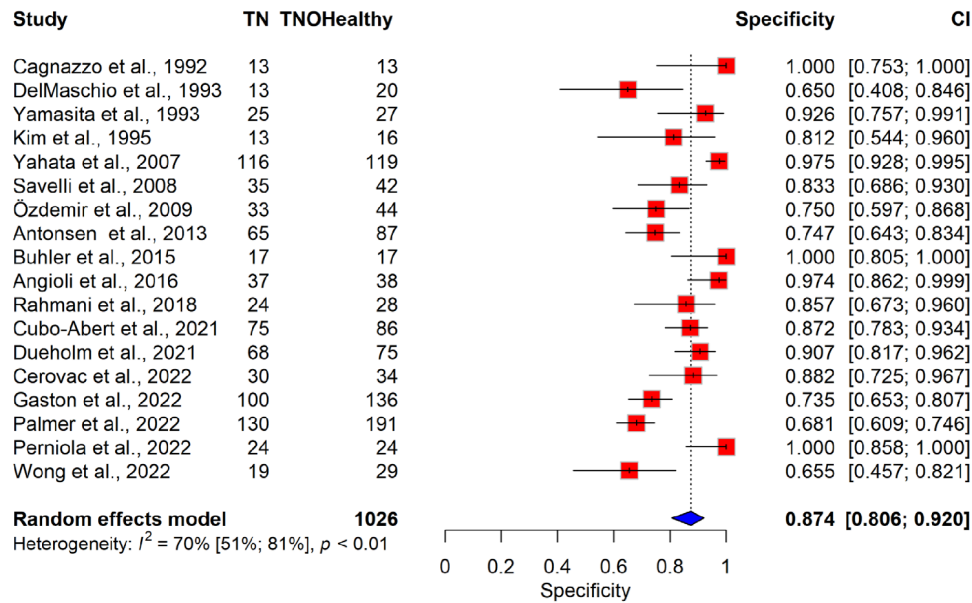
8.1.2. Primary Outcomes

8.1.2.1. Diagnostic Performance of TVS vs. MRI

The pooled sensitivity for DMI sensitivity was 76.6% (95% CI, 70.9–81.4%) for TVS and 81.1% (95% CI, 74.9–85.9%) for MRI, respectively. The pooled specificity was 87.4% (95% CI, 80.6–92%) for TVS and 83.8% (95% CI, 79.2–87.5%) for MRI. The difference between the specificity and sensitivity of the two imaging methods was not significant (sensitivity: $p = 0.116$, specificity: $p = 0.707$). The pooled sensitivity and specificity are presented in forest plots (Figure 2).



(A)



(B)

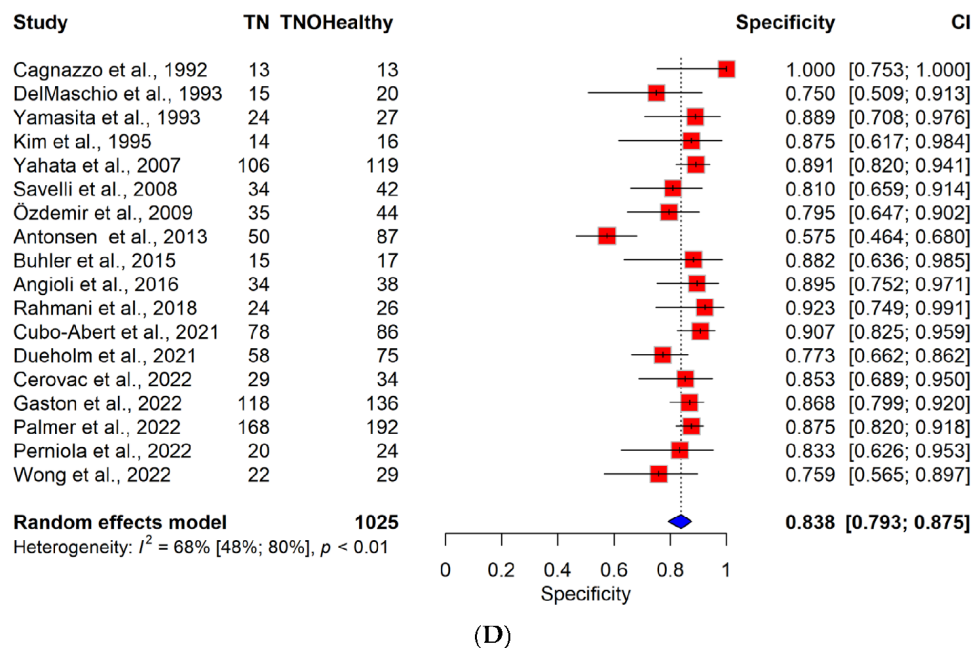
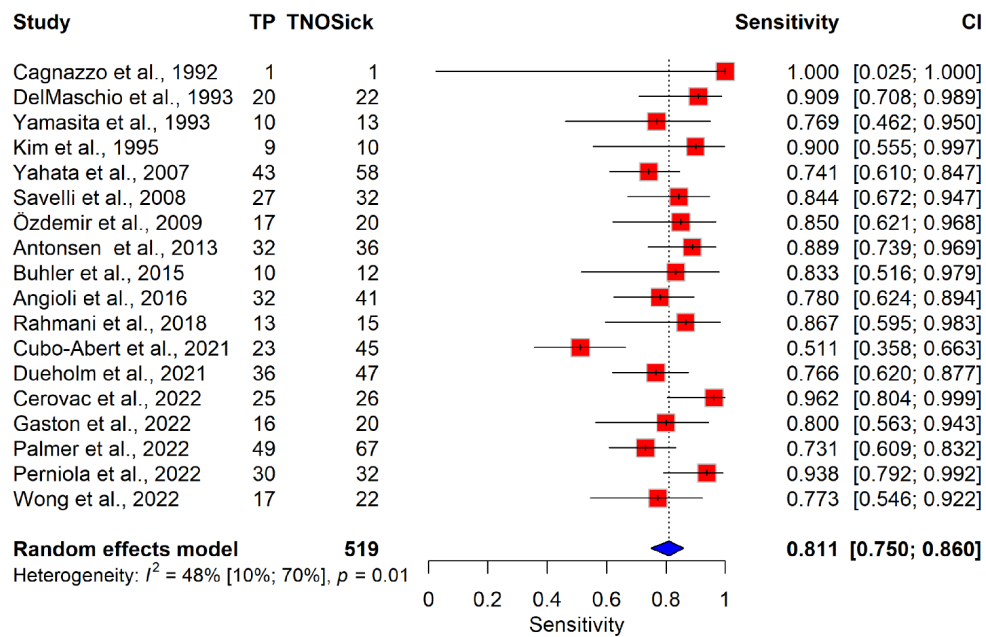


Figure 2. (A) Forest plot of TVS for sensitivity across all articles included. Abbreviations: TP: number of true positive patients. TN: number of true negative patients. TNOHealthy: total number of healthy patients. TNOSick: total number of patients diagnosed with endometrial cancer. CI: confidence interval. TVS: transvaginal sonography. MRI: magnetic resonance imaging. The results of the pooled model are visualized as well. Each red square represents the point estimate of the effect size for a specific study, and the horizontal line through the square indicates the 95% confidence

interval (CI). The blue diamond at the bottom represents the overall pooled effect size, with its width representing the 95% CI. Heterogeneity is indicated by I^2 and p -values, representing the variability between the included studies. **(B)** Forest plot of TVS for specificity across all articles included. **(C)** Forest plot of MRI for sensitivity across all articles included. **(D)** Forest plot of MRI for specificity across all articles included.

8.1.3. Secondary Outcomes

8.1.3.1. Diagnostic Performance of TVS vs. MRI in a Cohort of Patients with Low-Grade Endometrial Cancer

Four studies (51, 54, 57, 59) were included in the low-grade subgroup, and three of these enrolled exclusively low-grade EC patients. This subgroup consisted of 577 patients.

A separate analysis of low-grade EC patients resulted in a sensitivity of 71.9% (95% CI, 64.2–78.4%) for TVS and 70.1% (95% CI, 56.9–80.6%) for MRI, respectively. The difference between these values was not statistically significant ($p = 0.495$). On the other hand, a statistically significant difference ($p = 0.044$) was observed between the specificity of the two groups: a 74.7% (95% CI, 65.3–82.1%) specificity for TVS and an 87.2% (95% CI, 83.1–90.4%) specificity for MRI. Clinically, this result is particularly relevant in patients with low-grade endometrial cancer, where the higher sensitivity of MRI allowed for a more careful assessment of fertility-sparing operations. Figure 3 shows forest plots for TVS and MRI for low-grade EC.

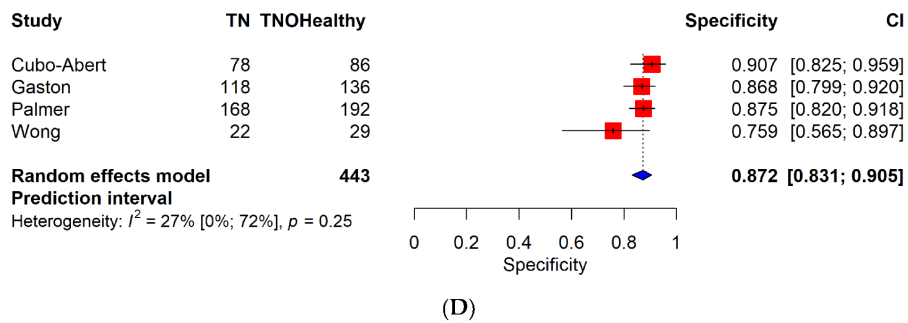
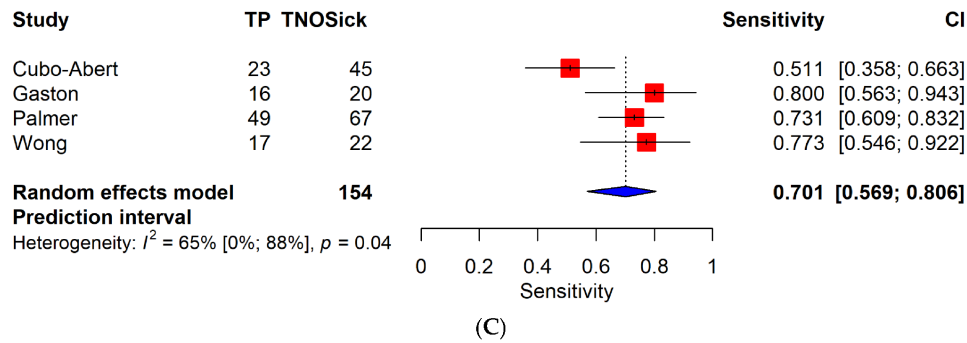
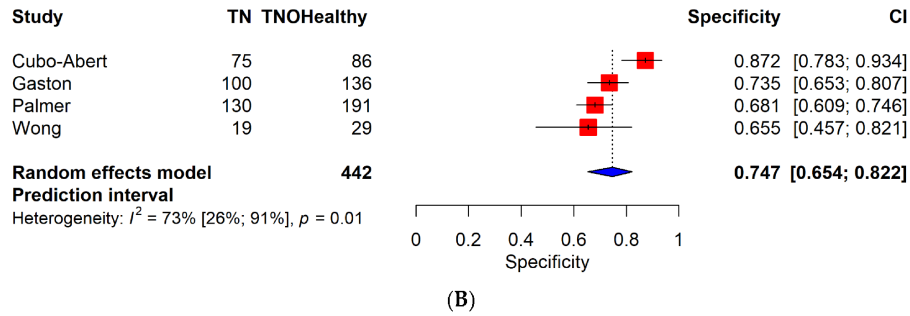
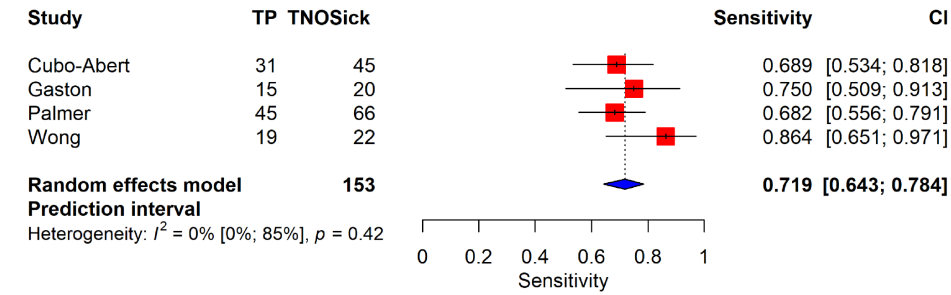


Figure 3. (A) Forest plot of TVS for sensitivity; only low-grade EC articles are included. Abbreviations: TP: number of true positive patients. TN: number of true negative patients. TNOHealthy: total number of healthy patients. TNOSick: total number of patients diagnosed with endometrial cancer. CI: confidence interval. TVS: transvaginal sonography. MRI: magnetic resonance imaging. The results of the pooled model are visualized as well. Each red square represents the point estimate of the effect size for a specific study, and the horizontal line through the square indicates the 95%

confidence interval (CI). The blue diamond at the bottom represents the overall pooled effect size, with its width representing the 95% CI. Heterogeneity is indicated by I^2 and p -values, representing the variability between the included studies. **(B)** Forest plot of TVS for specificity, with only low-grade EC articles included. **(C)** Forest plot of MRI for sensitivity, with only low-grade EC articles included. **(D)** Forest plot of MRI for specificity, with only low-grade EC articles included.

8.1.3.2. No Myometrial Invasion vs. Invasion of Any Depth

In five articles, including 329 patients (45, 49, 52, 60, 61), it was possible to compare TVS and MRI for no myometrial invasion vs. myometrial invasion of any depth. The pooled sensitivity for the detection of myometrial invasion was 89.9% (95% CI, 76.8–95.9%) for TVS and 91.1% (95% CI, 78.4–96.6%) for MRI, respectively. The pooled specificity was 42.6% (95% CI, 30.9–55.1%) for TVS and 46.1% (95% CI, 35.6–56.9%) for MRI. No significant difference was observed (sensitivity: $p = 0.911$, specificity: $p = 0.145$).

8.1.4. Risk of Bias Assessment

For the domain Patient Selection, most of the articles clearly defined inclusion criteria. The overall risk of bias was moderate to low. Articles excluding high-grade EC patients were not considered to be at a high risk of bias (51, 54, 57).

For the index test domain, we performed separate assessments of TVS and MRI. Most of the studies were considered to be at a low risk of bias.

In three studies (47, 56, 57), the exact method adopted to assess DMI with the TVS or the infiltration depth was not clearly defined, leaving the risk of bias unclear. In one study (48), none of the previous criteria were well defined, and the study was therefore considered to be at a high risk of bias.

For MRI examination, most of the studies were considered to have low risk of bias. In seven articles (45–48, 56–58), either the exact methodology or a clear description of how DMI was assessed were missing. These studies were considered to be at an unclear risk of bias.

For the reference test domain, four studies (52, 56, 59, 61), clearly reported that the pathologist performing the final histopathology was blinded to the results of the imaging procedures. These were considered to be at a low risk of bias.

For the flow and timing domain, the overall risk of bias was low to moderate. Eleven studies clearly identified the time between the index test and surgery; therefore, these were considered to be at a low risk of bias. In the rest of the studies, these data were missing, making the risk of bias unclear.

The results of the risk of bias assessment are presented in Table 2.

In terms of applicability, patient selection and reference standard domains were considered to have low risk of bias across all articles.

Table 2. Risk of bias (Quality Assessment of Diagnostic Accuracy Studies 2)

First author	Publication year	Risk of bias					Applicability concerns			
		Patient selection	Index test TVS	Index test MRI	Reference standard	Flow and timing	Patient selection	Index test TVS	Index test MRI	Reference standard
Cubo-Abert et al.	2021	😊	😊	😊	😐	😊	😊	😞	😊	😊
Gaston et al.	2022	😊	😊	😊	😐	😐	😊	😊	😊	😊
Palmer et al.	2023	😊	😐	😐	😐	😐	😊	😐	😐	😊
Wong et al.	2022	😊	😊	😊	😊	😊	😊	😊	😊	😊
Perniola et al.	2022	😊	😊	😐	😐	😐	😊	😊	😊	😊
Cerovac et al.	2022	😊	😊	😊	😐	😊	😊	😊	😊	😊
Rahmani et al.	2018	😊	😊	😐	😐	😐	😊	😊	😐	😊
Dueholm et al.	2021	😞	😊	😊	😐	😐	😊	😊	😊	😊
Cagnazzo et al.	1992	😞	😊	😊	😐	😊	😊	😊	😊	😊
DelMaschio et al.	1993	😊	😊	😊	😊	😊	😊	😊	😊	😊
Yamashita et al.	1993	😊	😊	😊	😊	😊	😊	😊	😊	😊
Kim et al.	1995	😊	😊	😊	😐	😊	😊	😊	😊	😊
Yahata et al.	2007	😞	😊	😊	😐	😊	😊	😊	😊	😊
Savelli et al.	2008	😞	😊	😊	😐	😐	😊	😊	😊	😊
Özdemir et al.	2009	😞	😐	😐	😊	😊	😊	😐	😐	😊
Antonsen et al.	2013	😊	😐	😐	😐	😊	😊	😐	😐	😊
Buhler et al.	2015	😞	😞	😐	😐	😐	😊	😊	😐	😊
Angioli et al.	2016	😞	😊	😐	😐	😊	😊	😊	😐	😊

TVS: transvaginal ultrasound. MRI: magnetic resonance imaging. Green sign: low risk of bias. Blue sign: intermediate risk of bias. Red sign: high risk of bias.

8.1.5. Publication bias and heterogeneity

On the basis of the funnel plot, no evidence of serious publication bias could be observed for the diagnostic accuracy of the two methods (TVS: $p = 0.214$, MRI: $p = 0.052$).

Moderate heterogeneity was observable for sensitivity (TVS: $I^2 = 42\%$ [0–67%], MRI: $I^2 = 48\%$ [10–70%]) for all-grade EC patients. Specificity was moderate for both imaging methods (TVS: $I^2 = 70\%$ [51–81%], MRI: $I^2 = 68\%$ [48–80%]).

8.2. Study II: Systemic Treatment Strategies Beyond Chemotherapy in Recurrent or Advanced Endometrial Cancer: A Systematic Review and Meta-Analysis

8.2.1. Study Search and Selection

A total of 16,488 records were identified. After the removal of 2656 duplicates, 13,832 titles and abstracts were screened. Of these, 498 articles were retrieved for full-text review; a total of 112 studies met the eligibility criteria and were included in the final analysis. The selection process is illustrated in the PRISMA flow diagram (Figure 4).

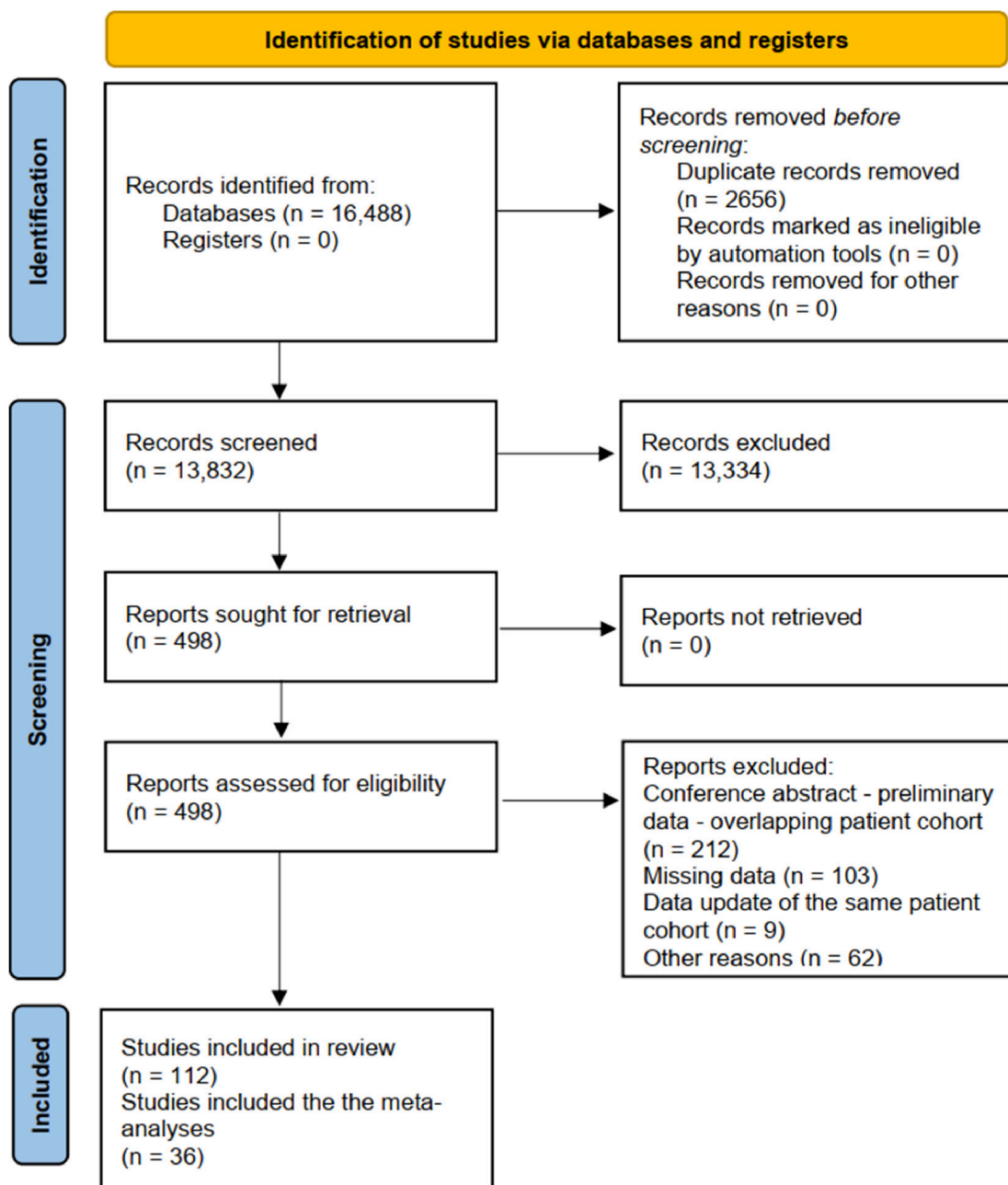


Figure 4. *PRISMA 2020 flowchart representing the study selection process (20).*

Studies included a range of systemic therapies for recurrent or advanced endometrial cancer, which were categorized into three main groups: hormonal therapy, immune checkpoint inhibitors and other targeted therapies. These agents were evaluated either as monotherapies or in combination with chemotherapy or one another. Study designs included both randomized controlled trials and prospective or retrospective cohort studies. The number of patients included in the studies ranged from 6 to 927, and the median age of the patients ranged between 53 and 71 years.

8.2.2. Primary Outcomes

8.2.2.1. Immune Checkpoint Inhibitors (ICIs) Combination with Chemotherapy (Paclitaxel and Carboplatin)

Five RCTs (phase II and III trials) compared ChT (1149 patients) groups with ChT+ICIs (including pembrolizumab, dostarlimab, avelumab, durvalumab and atezolizumab) (1311 patients) (62-66). In three studies, these therapies were applied as first-line treatment (64-66); in the other two studies (62, 63), prior systemic and local treatments were permitted.

In the all-comer populations, ICIs combined with ChT resulted in a pooled mPFS of 12.98 months (9.72–20.57) and an mOS of 33.98 months (29.18–39.07). ChT alone resulted in an mPFS of 9.37 months (7.96–9.87) and an mOS of 28.57 months (24.53–31.17). The combination therapy group had better PFS (HR: 0.63, CI 0.48–0.83); however, heterogeneity was high ($I^2 = 68\%$), primarily reflecting variability in the magnitude of treatment effect rather than inconsistency in direction, as all studies favored the intervention. OS proved to be better as well (HR: 0.76, CI 0.65–0.89). Heterogeneity was low, as visible in Figure 5 and Figure 6. Notably, the addition of avelumab to ChT resulted in worse OS rates in the all-comer population; mPFS was better when avelumab was added to the ChT regime.

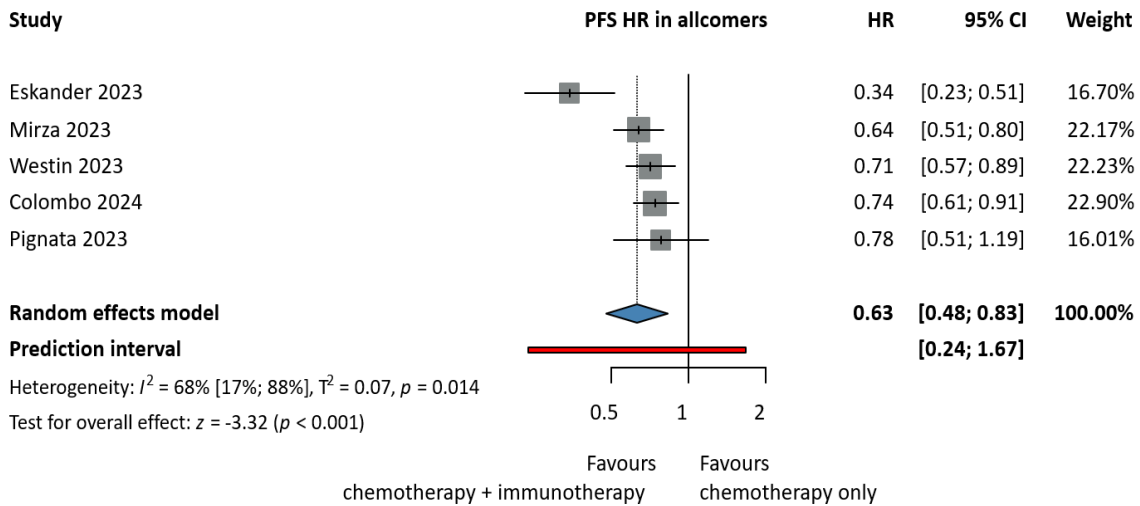


Figure 5. Forest plot of progression-free survival (PFS) hazard ratios (HR) comparing chemotherapy plus immunotherapy versus chemotherapy alone in all comers. Articles cited: Eskander et al.(62), Mirza et al.(63), Westin et al.(65), Colombo et al.(66), Pignata et al.(64). Abbreviations: PFS: progression-free survival. HR: hazard ratio. CI: confidence interval.

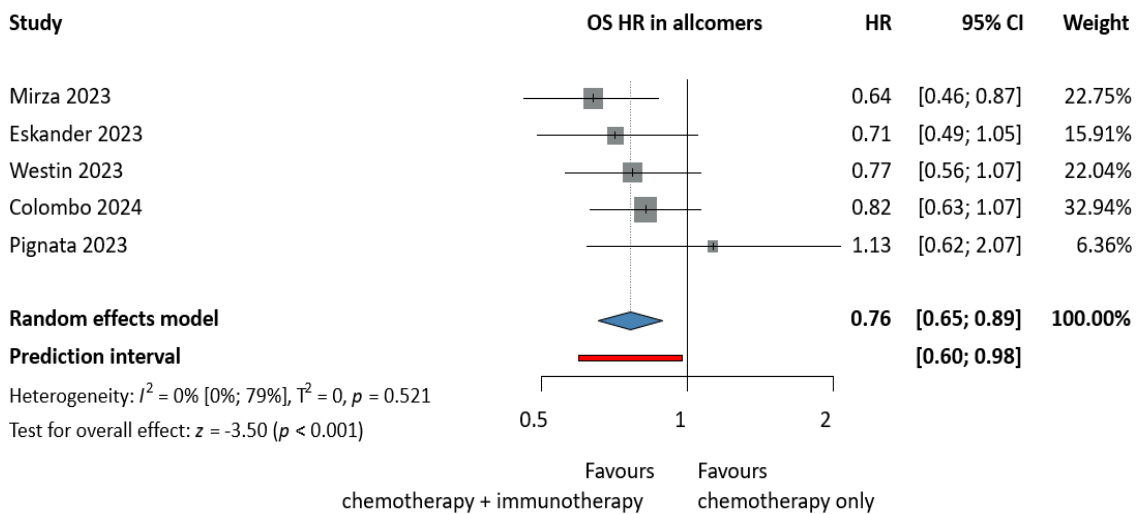


Figure 6. Forest plot of overall survival (OS) hazard ratios (HR) comparing chemotherapy plus immunotherapy versus chemotherapy alone in all comers. Articles cited: Eskander et al.(62), Mirza et al.(63), Westin et al.(65), Colombo et al.(66), Pignata et al.(64). Abbreviations: OS: overall survival. HR: hazard ratio. CI: confidence interval.

In the MMRd population, a significantly better mPFS (22.73 months, 15.03–28.03) was obtained in therapy regimes involving ICIs than in ChT groups (8.39 months,

6.92–9.79), HR: 0.34 (0.27–0.44), $p < 0.001$ with low heterogeneity. With regard to OS, the addition of ICIs resulted in better OS (41.36 months vs. 26.48 months (18.45–28.76)), HR: 0.38 (0.25–0.56), $p < 0.001$. Figures 7 and 8 contain the forest plots of this subgroup.

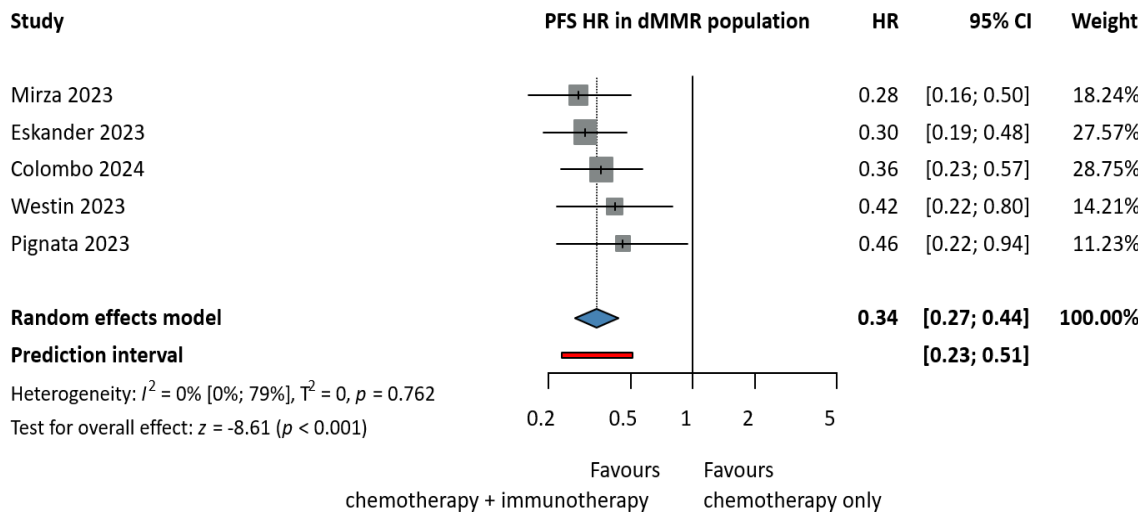


Figure 7. Forest plot of progression-free survival (PFS) hazard ratios (HR) comparing chemotherapy plus immunotherapy versus chemotherapy alone in mismatch repair-deficient patients (dMMR). Articles cited: Eskander et al.(62), Mirza et al.(63), Westin et al.(65), Colombo et al.(66), Pignata et al.(64). Abbreviations: PFS: progression-free survival. HR: hazard ratio. CI: confidence interval. dMMR: mismatch repair-deficient.

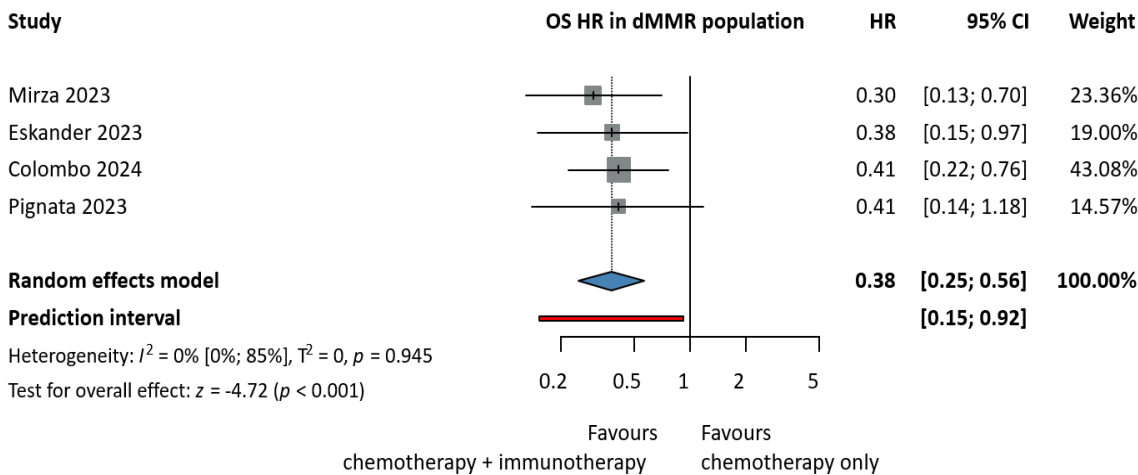


Figure 8. Forest plot of overall survival (OS) hazard ratios (HR) comparing chemotherapy plus immunotherapy versus chemotherapy alone in mismatch repair-deficient patients (dMMR). Articles cited: Eskander et al.(62), Mirza et al.(63),

Colombo et al. (66), Pignata et al.(64). Abbreviations: OS: overall survival. HR: hazard ratio. CI: confidence interval. dMMR: mismatch repair-deficient.

In MMRp populations, mPFS was superior in the population receiving ICIs as well (mPFS 10.18 (9.19–11.45) vs. 9.4 months (8.27–9.87) in the ChT group), HR: 0.77 (0.62–0.97), $p = 0.031$. Heterogeneity was moderate to high (62%), warranting cautious interpretation of the pooled estimate despite its statistical significance. In the study concerning avelumab, analysis based on MMR status showed that the PFS benefit was driven by the dMMR population, whereas patients with a pMMR tumor did not benefit from the addition of avelumab. Figures 9 and 10 contain the forest plot of this subgroup.

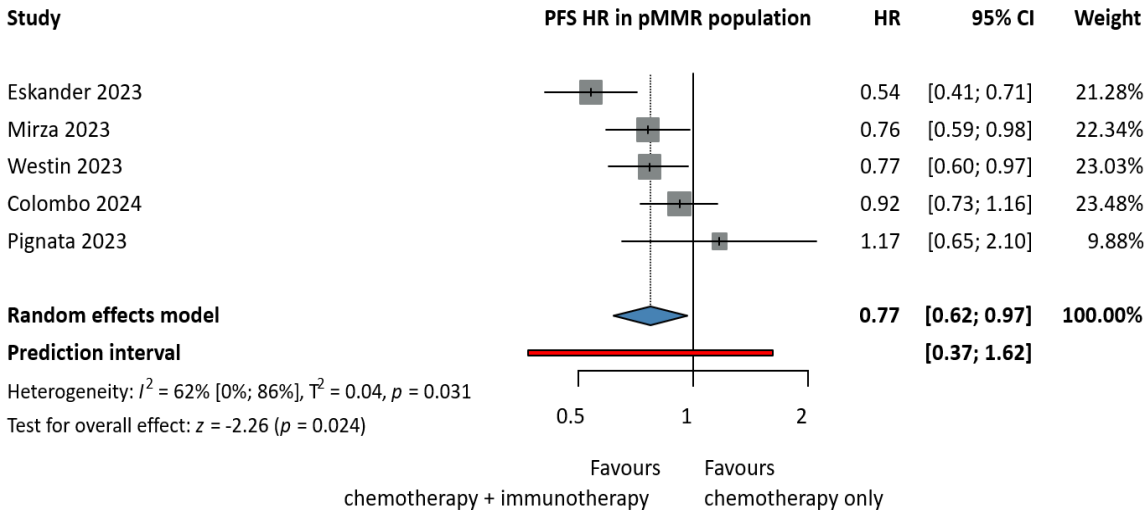


Figure 9. Forest plot of progression-free survival (PFS) hazard ratios (HR) comparing chemotherapy plus immunotherapy versus chemotherapy alone in mismatch repair-proficient (pMMR) patients. Articles cited: Eskander et al. (62), Mirza et al. (63), Westin et al. (65), Colombo et al. (66), Pignata et al. (64). Abbreviations: PFS: progression-free survival. HR: hazard ratio. CI: confidence interval. pMMR: mismatch repair-proficient.

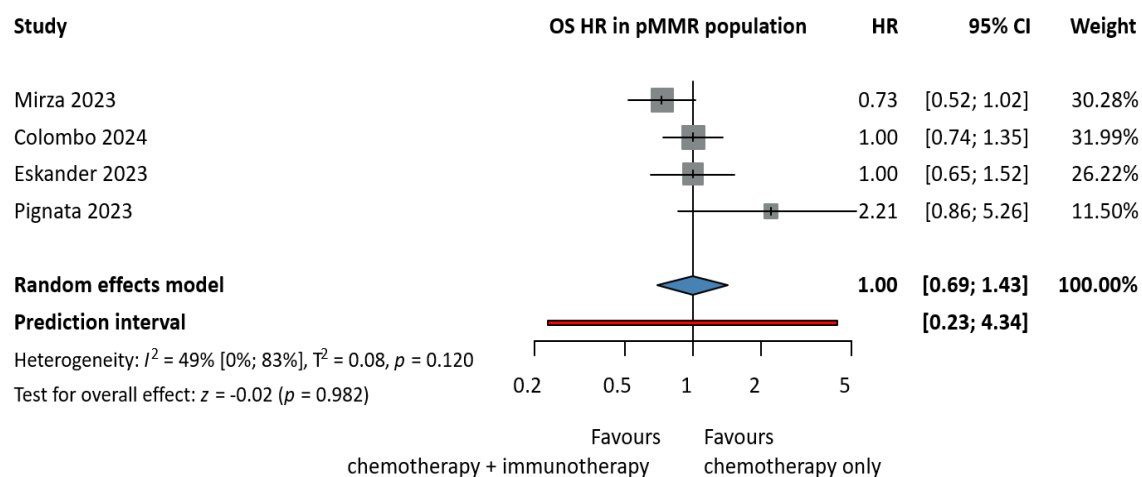


Figure 10. Forest plot of overall survival (OS) hazard ratios (HR) comparing chemotherapy plus immunotherapy versus chemotherapy alone in mismatch repair-proficient (pMMR) patients. Articles cited: Eskander et al.(62), Mirza et al.(63), Colombo et al.(66), Pignata et al.(64). Abbreviations: OS: overall survival. HR: hazard ratio. CI: confidence interval. dMMR: mismatch repair-proficient.

With regard to the TRAEs, these trials collectively indicate that integrating immune checkpoint inhibitors into platinum–taxane chemotherapy regimens maintain a broadly comparable safety profile to chemotherapy alone. While the addition of immunotherapy slightly expands the spectrum of severe adverse events, it does not fundamentally shift the overall toxicity landscape, which continues to be dominated by hematologic complications inherent to cytotoxic chemotherapy.

Risk of bias as assessed by the ROB 2 tool was low.

8.2.2.2. ICI Combined with Angiogenesis Inhibitors

Nine studies (67-75) matched the inclusion criteria in this subgroup. In all the studies, every patient had received at least one line of ChT prior to lenvatinib and pembrolizumab treatment.

This subgroup included prospective trials and retrospective cohorts evaluating lenvatinib plus pembrolizumab in advanced or recurrent endometrial cancer. Studies included early-phase and pivotal clinical trials (67, 71, 75)(Taylor et al., 2020; Makker et al., 2023 - KEYNOTE-146; Makker et al., 2023 KEYNOTE-775), as well as retrospective or real-world analyses (68-70, 72-74)(How et al., 2021; Kim et al., 2022; Zammarrelli et al., 2023; Chiba et al., 2024; Tochigi et al., 2024; Shang et al., 2024).

Overall, lenvatinib plus pembrolizumab demonstrated clinically meaningful activity across prospective and real-world datasets. In the early-phase study, lenvatinib plus pembrolizumab (Taylor et al., 2020 (67)) showed promising antitumor activity, with a median PFS of 9.7 months; median OS was not reached at the time of analysis. However, toxicity was substantial, with grade ≥ 3 treatment-related adverse events reported in 67% of patients.

Subsequent retrospective studies reported more variable outcomes. Lenvatinib plus pembrolizumab (How et al., 2021 (69); Kim et al., 2022 (68); Zammarrelli et al., 2023 (74)) was associated with median PFS values ranging from 4.6 to 6.0 months. In Zammarrelli et al., median OS was 18.3 months, similar to the OS reported in the pivotal KEYNOTE-775 trial, although high-grade treatment-related adverse events occurred in 84% of patients.

The pivotal randomized phase III trial confirmed the efficacy of this regimen. Lenvatinib plus pembrolizumab (Makker et al., 2023; KEYNOTE-775 (71)) achieved a median PFS of 7.3 months and median OS of 18.7 months in 411 patients, outperforming chemotherapy with doxorubicin or paclitaxel. Benefits in PFS and OS were observed across molecular subgroups, regardless of mismatch repair status. However, grade ≥ 3 treatment-related adverse events were frequent, occurring in 90.1% of patients compared with 73.7% in the chemotherapy control group.

Additional evidence supported the durability and real-world relevance of these findings. Lenvatinib plus pembrolizumab (Makker et al., 2023; KEYNOTE-146 (75)) demonstrated sustained efficacy and acceptable tolerability in previously treated advanced endometrial cancer. Lenvatinib plus pembrolizumab (Tochigi et al., 2024 (73)) showed a median PFS of 8.47 months, consistent with clinical trial outcomes. In Chiba et al. (2024) (70), median PFS was 11.6 months, with grade ≥ 3 adverse events in 80% of patients. This study also suggested that the p53abn molecular subgroup had a poorer prognosis despite treatment with lenvatinib plus pembrolizumab.

The toxicity profile was clinically relevant and distinct from chemotherapy-based regimens. Across studies, grade ≥ 3 adverse events were mainly characterized by hypertension, fatigue, gastrointestinal toxicity, endocrine or metabolic abnormalities, anemia, weight loss, hypothyroidism, and thrombocytopenia. Hypertension was the most consistent high-grade toxicity, reported at high frequency in several real-world

cohorts. Fatigue, diarrhea or mucositis, hepatic dysfunction, proteinuria, and immune-related events were also observed. Although hematologic adverse events occurred, they were generally less dominant than in platinum-based chemotherapy.

Explorative quantitative analysis was performed.

Seven studies (68-71, 73-75) with 684 patients were included in the quantitative analysis; of note, in one study (67), only mPFS was reported. Pooled mPFS in the seven included articles was 7.03 months (95% confidence interval (CI) 5.66–8.82). Median OS was 18.02 months (95% CI 13.99–19.73). Both MMRd and MMRp patients were included. Five studies (68, 70, 73-75) were of single-arm design. The heterogeneity of the included studies was low ($I^2=0$).

The combination of ICI with anti-angiogenesis inhibitors yielded improved survival data compared to single-agent therapy.

Risk of bias as assessed by the MINORS tool was moderate to low.

8.2.3. Secondary Outcomes

8.2.3.1. ICI-Only Therapy Protocols

Seven articles (76-82) assessed the PD-1 or PD-L1 inhibitors (durvalumab, pembrolizumab, avelumab, nivolumab, retifanlimab) as monotherapies, out of which six studies (76-79, 81, 82) were of single-arm, phase II design. In all studies, except for one (79), all the patients had undergone at least one first-line therapy regime.

In this group of studies evaluating immune checkpoint inhibitors mostly in mis-match repair-deficient (dMMR) or microsatellite instability-high (MSI-high) endometrial cancer, median PFS and OS varied across agents (6–23.5 and 30.2–40 months, respectively) but consistently favored immunotherapy in MMRd molecular subtypes. Overall, ICI monotherapy was associated with a favorable and manageable safety profile, with grade ≥ 3 TRAEs under 16% in all studies.

8.2.3.2. Anti-Angiogenic Agent-Only Therapies

Across 12 phase II (14, 83-94) trials evaluating anti-angiogenic agents, efficacy and toxicity profiles were variable. PFS varied between 1.97 and 4.6 months, whereas OS varied between 6.3 and 20.2 months. In most studies, the anti-angiogenic therapies were applied after at least one prior therapy line; however, in two studies (92, 93), a mixed cohort of patients with no or one prior chemotherapy line was included.

8.2.3.3. *PI3K/AKT/mTOR Inhibitor Monotherapies*

This subgroup included 11 studies, including 4 randomized phase II trials, evaluating inhibitors of the PI3K/AKT/mTOR pathway in predominantly pretreated populations. Agents included temsirolimus (Oza et al., 2011(95); Fleming et al., 2014(96); Emons et al., 2015(97)), everolimus (Ray-Coquard et al., 2013(98)), ridaforolimus (Oza et al., 2015(99)), pilaralisib (Matulonis et al., 2015(100)), gedatolisib and PF-04691502 (del Campo et al., 2016(101)), apitolisib (Makker et al., 2016(102)), buparlisib (Heudel et al., 2017(103)), LY3023414 (Rubinstein et al., 2020(104)), and MK-2206 (Myers et al., 2020(105)).

Overall efficacy was modest. Median progression-free survival ranged from approximately 2.0 to 7.33 months, with the longest PFS observed for temsirolimus in chemotherapy-naïve patients (Oza et al., 2011(95)). In chemotherapy-pretreated patients, PFS with temsirolimus was shorter, at 3.25 months (Oza et al., 2011). Most other agents produced median PFS values of approximately 2.5–4.5 months, while gedatolisib reached 5.9 months (del Campo et al., 2016(101)). Median overall survival, where reported, ranged from 8.1 months with everolimus (Ray-Coquard et al., 2013(98)) to 21.3 months with temsirolimus (Emons et al., 2015(97)).

Among randomized studies, ridaforolimus (Oza et al., 2015(99)) showed a statistically significant PFS benefit over control therapy (hormonal therapy and chemotherapy), with a hazard ratio of 0.53 and $p = 0.008$, although this was accompanied by frequent grade ≥ 3 adverse events. Several other studies showed limited activity or failed to meet predefined efficacy thresholds, including temsirolimus (Emons et al., 2015(97)), pilaralisib (Matulonis et al., 2015(100)), apitolisib (Makker et al., 2016(102)), LY3023414 (Rubinstein et al., 2020(104)), and MK-2206 (Myers et al., 2020(105)). Available biomarker analyses did not demonstrate a clear relationship between outcomes and PTEN status or other PI3K/Akt/mTOR pathway markers (Oza et al., 2011(95)).

Treatment-related adverse events were consistent with PI3K/AKT/mTOR pathway inhibition. The toxicity profile was mainly characterized by metabolic disturbances such as hyperglycemia and hyperlipidemia, gastrointestinal and mucosal events including diarrhea and stomatitis, and hematologic toxicity such as anemia and thrombocytopenia. Fatigue, anorexia, hepatic enzyme elevations, pneumonitis, and thromboembolic events

were also reported. Some regimens had substantial grade ≥ 3 toxicity, including apitolisib (Makker et al., 2016(102)) and ridaforolimus (Oza et al., 2015(99)), and the temsirolimus plus megestrol acetate combination arm was closed because of excess venous thromboses (Fleming et al., 2014(96)).

8.2.3.4. *PI3K/AKT/mTOR Combined with Aromatase Inhibitors*

This subgroup included 4 phase II studies, evaluating mTOR-pathway inhibition combined with endocrine therapy in advanced, recurrent, or metastatic endometrial cancer. Treatments included everolimus plus letrozole (Slomovitz et al., 2015(106)), everolimus plus letrozole plus metformin (Soliman et al., 2020(107)), vistusertib plus anastrozole (Heudel et al., 2022(108)), and everolimus plus letrozole versus tamoxifen plus medroxyprogesterone acetate (Slomovitz et al., 2022(109)).

Overall efficacy was modest to clinically meaningful, with the strongest signals seen in selected endocrine-sensitive populations. Everolimus plus letrozole (Slomovitz et al., 2015(106)) produced a clinical benefit rate of 40% and an objective response rate of 32%, including several complete responses. Median PFS was 3.0 months, OS 14 months, although a subset of responders had prolonged disease control. Serous histology predicted lack of response, while patients with endometrioid tumors and CTNNB1 mutations appeared to respond favorably.

Everolimus plus letrozole plus metformin (Soliman et al., 2020(107)) showed a clinical benefit rate of 50% and an objective response rate of 28% in recurrent endometrioid endometrial cancer. Median PFS was 5.7 months, and median OS was 19.6 months. Positive progesterone receptor expression was associated with a higher likelihood of clinical benefit.

In the randomized VICTORIA trial, vistusertib plus anastrozole (Heudel et al., 2022(108)) improved the 8-week progression-free rate compared with anastrozole alone: 67.3% versus 39.1%. Overall response rates were 24.5% versus 17.4%, and median PFS was 5.2 months versus 1.9 months, respectively. These findings support the activity of adding mTOR inhibition to endocrine therapy in hormone receptor-positive recurrent or metastatic disease.

In the randomized GOG Foundation study, everolimus plus letrozole (Slomovitz et al., 2022(109)) and tamoxifen plus medroxyprogesterone acetate both demonstrated clinical activity. Response rates were 22% and 25%, respectively, while median PFS was 6

months with everolimus plus letrozole and 4 months with hormonal therapy. Notably, chemotherapy-naïve patients treated with everolimus plus letrozole had a median PFS of 28 months, compared with 4 months in patients with prior chemotherapy.

Treatment-related adverse events were consistent with mTOR inhibition and endocrine therapy. Across studies, toxicity was mainly characterized by metabolic effects, particularly hyperglycemia, together with mucositis, fatigue, anemia, gastrointestinal symptoms, and laboratory abnormalities. In vistusertib plus anastrozole (Heudel et al., 2022(108)), fatigue, lymphopenia, hyperglycemia, and diarrhea were the most common reported vistusertib-associated events. In everolimus plus letrozole (Slomovitz et al., 2022(109)), grade ≥ 3 adverse events were more frequent than with hormonal therapy, while thromboembolic events (11% of patients) were observed in the hormonal therapy arm but not in the everolimus plus letrozole arm.

Explorative quantitative analysis was performed. This included four studies (106-109) comprising a total of 96 patients with recurrent or advanced endometrial cancer treated with a combination of mTOR inhibitors and aromatase inhibitors.

The pooled mPFS was 5.56 months (CI 95% 4.03-8.31), indicating moderate disease control with the combination therapy. The mOS was 15.89 months (CI 3.52–22.14), although survival estimates varied significantly among the included studies, reflecting heterogeneity in patient populations and treatment protocols.

8.2.3.5. *Progestines*

This subgroup included studies evaluating progestins, estrogen receptor antagonists, aromatase inhibitor-based combinations, GnRH analogs, progesterone receptor antagonists, LHRH-targeted agents, CDK4/6 inhibitors, and chemotherapy–hormonal therapy combinations in recurrent or advanced endometrial cancer.

Overall, single-agent hormonal therapies showed modest but generally well-tolerated activity. Medroxyprogesterone acetate and megestrol acetate (Thigpen et al., 1999(110); Thigpen et al., 2001(111); Whitney et al., 2004(112)) produced median PFS values of approximately 3.0–3.2 months and median OS values of 8.8–13 months, with generally low rates of grade ≥ 3 adverse events. More recent retrospective data suggested that benefit may be greater in selected lower-grade tumors: progestin therapy (Kulkarni et al., 2023(113)) was associated with median PFS of 15.7 months and OS of 25.9 months

in grade 1–2 recurrent endometrial cancer, compared with 5 months and 12.5 months, respectively, in grade 3 disease. In patients with at least 1 prior line of chemotherapy, PFS was 6.2 months, while OS was 23 months.

Fulvestrant (Covens et al., 2011(114); Emons et al., 2013(115)) demonstrated limited efficacy, with median PFS of 1.6–2.3 months and median OS of 9–13.2 months, although toxicity was minimal. Similarly, GnRH analogs, including leuprolide, goserelin, and triptorelin (Covens et al., 1996(116); Asbury et al., 2002(117); Lhommé et al., 1999(118)), showed limited activity, with median PFS of 1.9–2.8 months and median OS of 7.2–9 months, but were associated with few severe adverse events. Mifepristone (Ramondetta et al., 2009(119)) also showed very limited activity, with fatigue and dyspnea reported as notable toxicities.

Among investigational or targeted hormonal approaches, AEZS-108 (Emons et al., 2014(120)), a doxorubicin-linked LHRH agonist, achieved a median PFS of 7 months and median OS of 15 months in LHRH receptor–positive patients. Severe toxicity was mainly hematologic, particularly neutropenia and leukopenia. CDK4/6 inhibitor–based approaches appeared more promising. Ribociclib (Colon-Otero et al., 2020(121)) was reported as safe and active in estrogen receptor–positive endometrial cancer, with median PFS of 5.4 months and OS of 18.9 months. Letrozole plus abemaciclib (Konstantinopoulos et al., 2023(122)) showed encouraging activity in estrogen receptor–positive disease, with median PFS of 9.1 months and manageable hematologic toxicity.

Combination strategies using chemotherapy with hormonal therapy showed variable efficacy. Regimens such as chemotherapy plus hormonal therapy (Ayoub et al., 1988(123); Hoffman et al., 1989(124); Bafaloukos et al., 1999(125); Karagol et al., 2006(126)) produced median PFS values of approximately 4–6 months in most studies and were commonly associated with hematologic and gastrointestinal toxicity. In hormonal therapy versus chemotherapy(126), median PFS was 5 months and 4 months, and median OS was 16 months and 11 months, respectively, although the difference was not statistically significant.

The toxicity profile of hormonal therapy was generally milder than that of chemotherapy or modern targeted combinations, but thromboembolic and metabolic events were recurrent safety signals. Severe events were uncommon with several

hormonal agents, but pulmonary embolism, thrombophlebitis, arterial thrombosis, hyperglycemia, hypertension, edema, hepatic toxicity, and anemia were reported across progestin-containing regimens (110, 112, 127-129). Targeted combinations had a broader toxicity profile, including metabolic, hematologic, hepatic, and fatigue-related adverse events (96, 106).

Explorative quantitative analysis was performed. A total of nine studies (96, 109, 110, 112, 113, 127-130) with recurrent or advanced EC were included in the quantitative analysis of progestin-containing therapy protocols.

Eight studies (96, 109, 110, 112, 113, 127, 129, 130) including 503 patients reported data on PFS, which yielded an mPFS of 3.58 months (95% CI 2.32–5.14).

The mOS reported by all nine included articles was 12.06 months, which ranged from 8.83 to 14.63 months across the included studies, with 523 patients included.

Adverse effects related to progestin treatment were reported in one-third of patients, with the majority classified as mild. The incidence of severe toxicity was low, with thromboembolic events (approximately 1–5% across studies) being the most frequently reported severe adverse effect. Importantly, the risk of thromboembolic complications was comparable to that seen with standard first-line chemotherapy using carboplatin and paclitaxel.

The overall quality of studies was low, with the risk of bias for patient selection being moderate. Heterogeneity was also low.

9. DISCUSSION

9.1. Summary of Findings, International Comparisons (including all studies)

In our first study, we found no significant difference between the diagnostic performance of TVS and MRI when both low- and high-grade EC patients were included. On the other hand, when only low-grade cases were analyzed, the specificity of MRI proved to be significantly higher. This might highlight the potential benefits of MRI, interpreted by expert examiners, in patients with low-grade EC, when TVS has limited diagnostic abilities due to different factors affecting visibility.

In 2017, Alcazar et al. published a meta-analysis on the assessment of DMI, including studies on 560 patients, published before 2013 (131). They concluded that MRI showed superior sensitivity compared to TVS in detecting DMI in women with EC. However, the difference between the two imaging modalities was not statistically significant. The elaboration of studies conducted after 2013 showed a slightly better TVS sensitivity and specificity, as well as MRI specificity. However, the pooled sensitivity of MRI was reduced.

Ultrasound imaging has advantages, such as being more accessible, repeatable and time-efficient, and it can be performed without the use of a contrasting agent. However, disadvantages include the fact that it is operator-dependent, and accuracy is affected by tumor size, tumor vascularization density, tumor vessel architecture and histological grading (132, 133). In a recent meta-analysis by Tameish et al., conducted exclusively on patients with low-grade EC, neither sensitivity nor specificity was significant between TVS and MRI in the assessment of DMI (134). However, in our subgroup analysis on the same articles, we observed a significantly better specificity of MRI. This difference can be attributed to the different data used in our study. In one article, two different radiologists evaluated MRI examinations (57). We included data from more experienced examiners, in agreement with the recommendations of the ESGO/ESTRO/ESP guidelines (4).

The addition of clinical data and radiomics to ultrasound can result in promising models, able to discriminate between different EC risk groups. In 2022, Moro et al. demonstrated that radiomics exhibits a capacity to differentiate low-risk endometrial cancer from other forms and demonstrates superior discrimination between high-risk

endometrial cancer and alternative types. Nevertheless, the integration of radiomics features into clinical ultrasound models did not yield a significant enhancement in overall performance (135). Radiomics applied to ultrasound images and machine learning models demonstrated promising performance in other female genital tumors, such as ovarian and myometrial lesions (136, 137).

Spagnol et al. reported comparable diagnostic accuracy of 3D-TVS to MRI for the detection of DMI (138). In this meta-analysis, which includes five studies, with a total of 450 patients, the pooled sensitivity was 77% (95% CI, 66–85%) for 3D-TVS and 80% (95% CI, 73–86%) for MRI, with a specificity of 74% vs. 83% for detecting DMI. In our study, the pooled sensitivity was similar to these data, and TVS specificity was better. In a recent meta-analysis by Ziogas et al., no significant difference was observed between 2D-TVS and 3D-TVS in terms of sensitivity and specificity (80.4% vs. 77.6% and 82.8% vs. 81.6%, respectively, $p = 0.960$ and $p = 0.733$) (139). Perniola et al. reported that tumor volume estimation on 2D-TVS, 3D-TVS and MRI showed correlations among all three methods, indicating that 2D-TVS can be sufficient for myometrial infiltration assessment (45). However, Costas et al. conducted a meta-analysis on the predictive value of 3D-TVS in DMI assessment, which resulted in a pooled sensitivity of 84% (95% CI, 73–90%) and a specificity of 82% (95% CI, 75–88%). These findings were superior to the outcomes of our investigation (140).

MRI, the other imaging technique of interest, provides detailed information on soft tissues. However, MRI images are more expensive to obtain, are not tolerated by many patients due to claustrophobia, are time consuming, are not suitable for patients who are very obese or have metal implants, foreign bodies or impaired kidney functions (141, 142). In contrast to TVS, MRI is considered as less reliant on operator skills. Nevertheless, a multicenter network study suggests the use of the European Society of Urogenital Radiology (ESUR) guidelines (143). Radiomics applied to MRI and artificial intelligence are valuable tools that can aid clinicians in the proper diagnosis and management of EC (144). These tools have shown promising results in other gynecological tumors as well (145-147).

Our study highlighted the role of TVS in the preoperative assessment of patients with EC, emphasizing the need of personalized care.

Our second study provided a broad overview of systemic therapeutic possibilities, concentrating on the role of targeted therapies, immune checkpoint inhibitors, hormonal therapies and their combinations in recurrent or advanced EC. EC is a heterogeneous disease, with several histological and molecular subtypes; therefore, numerous therapeutic choices are available. Based on our meta-analyses, currently, the best PFS and OS in recurrent or advanced EC appears to be provided by ChT combined with ICIs in MMRp patients. However, we must point out that our study is based on significantly heterogeneous data and levels of evidence, making the clinical interpretability limited. The absence of direct comparative studies among the different treatment approaches limits the ability to make reliable conclusions regarding their relative efficacy. The addition of ICIs slightly increases the prevalence of TRAEs; these are manageable. MMRd/MSI-H patients clearly benefited from the addition of ICIs. In combination therapy, the PFS and OS of MMRd patients surpassed those of MMRp patients, except when avelumab was used. Notably, in one study, two different protocols of follow-up therapy were compared: follow-up therapy with a PARP inhibitor yielded the best PFS and OS (Durva-Olap-CP) in the overall population (65). Also of note, in the included RCTs, the analysis was based mostly on patients receiving therapy as first-line treatment or more than 6 months after the first-line treatment. This could have led to better PFS and OS because of the patients' better general condition. ICI combinations showed slightly higher rates of grade 3–4 TRAEs versus chemotherapy alone. Yet, the overall toxicity burden remained primarily driven by chemotherapy and is not substantially exacerbated by the addition of checkpoint inhibitors. Hematologic toxicities consistently represent the principal grade ≥ 3 adverse events across all regimens. While immunotherapy introduces additional adverse events, these are generally low in frequency and include immune-related and systemic complications such as hypertension, thromboembolism, and infections. Importantly, differences between intervention and comparator arms are modest and inconsistent across trials, with no clear indication of a markedly increased risk of severe toxicity associated with the incorporation of checkpoint inhibitors. Heterogeneity varied substantially across endpoints and subgroups, with direct implications for the strength of evidence. In the overall population, PFS showed moderate-to-high heterogeneity ($I^2 = 68\%$) with a wide prediction interval crossing unity, limiting confidence in the generalizability of the

effect despite consistent direction. In contrast, OS demonstrated no detectable heterogeneity ($I^2 = 0\%$), supporting a more robust and consistent survival benefit. In subgroup analyses, findings diverged markedly. The dMMR population showed no heterogeneity ($I^2 = 0\%$) for both PFS and OS, with consistent effect sizes and prediction intervals entirely below unity, indicating a stable and reproducible benefit. Conversely, the pMMR subgroup exhibited moderate heterogeneity for both PFS ($I^2 = 62\%$) and OS ($I^2 = 49\%$), with wide prediction intervals crossing unity and, for OS, a null pooled effect, reflecting substantial uncertainty and inconsistency across studies. Overall, these results indicate that the observed treatment benefit is driven primarily by the dMMR population, while evidence in pMMR remains heterogeneous and less conclusive, warranting cautious interpretation. The wide prediction intervals crossing the null value indicate substantial uncertainty regarding the effect expected in an individual future study.

We also reviewed other systemic therapy possibilities and performed exploratory pooling of the single-arm studies. The best pooled second-line therapies in our study were the lenvatinib and pembrolizumab combination and mTOR inhibitors combined with aromatase inhibitors. However, findings derived from single-arm pooled estimates should be interpreted with caution, as they do not allow for direct comparison between treatment modalities. As these estimates are derived from lower-level evidence, their generalizability may be limited. The exploratory nature of the results, particularly those based on single-arm data from the four subgroup analyses, should be emphasized.

The lenvatinib and pembrolizumab combination was superior to the physicians' choice chemotherapy protocol in a randomized controlled study including 827 patients (411 vs. 416 patients) (71) (PFS in intention to treat population: 7.2 vs. 3.8 months, $p < 0.001$, OS 18.3 vs. 11.4 months, $p < 0.001$) with an increased $\geq$ grade 3 TRAE rate. Of note, the benefits of this treatment were observed regardless of MMR status, and the majority of patients exhibited tumor regression, irrespective of histological subtype. To reduce side effects, dose reduction was investigated in a study by How et al. (69), concluding that a reduced dose results in similar PFS and OS. This study provided the worst PFS in our cohort (3.2 in the recommended dose vs. 5.5 months in the reduced dose cohort), which can be attributed to a lower proportion of endometrioid tumors, more patients with ≥ 2 prior ChT lines and the inclusion of patients with worse performance status. Most

real-world studies (68, 70, 73, 74) showed similar PFS and OS rates to those in our analysis. Of note, a study conducted by Kim et al. (68) showed lower treatment response rates but concluded that this protocol is feasible as it offers acceptable treatment response and manageable TRAEs. Zammarelli et al. (74) reported significantly better 1-year PFS in patients with reduced lenvatinib doses and similar OS, with no difference in PFS and OS in black patients compared to other racial groups. Across trials, the toxicity profile differed from chemotherapy-based regimens and was dominated by hypertension, fatigue, and gastrointestinal adverse events, along with endocrine and hepatic effects. Hypertension was the most consistent and prominent grade ≥ 3 adverse event, occurring in roughly 25–50% of patients in several studies. Other frequent toxicities included fatigue, diarrhea/colitis, liver dysfunction, and proteinuria, with occasional serious immune-related or organ-specific events. The role of lenvatinib and pembrolizumab following first-line chemoimmunotherapy remains unclear, as no studies included in our analysis have specifically evaluated lenvatinib–pembrolizumab in this setting.

PI3K/AKT/mTOR inhibitors combined with aromatase inhibitors provided an exploratory pooled median PFS of 5.33 months and OS of 15.89 months in the four included studies. In addition to substantial heterogeneity, the single-arm design of the included studies warrants careful consideration when interpreting these results. In the randomized phase II trial of Slomowitz et al. (109), chemotherapy-naïve patients treated with letrozole and everolimus showed better PFS than the ChT group of the pivotal GOG-209 trial (12) (28 vs. 14 months). This finding suggests a need for more clinical trials involving everolimus combined with letrozole as a first-line treatment. Patients with endometrial histology showed better response rates. In the other included study, the addition of metformin to letrozole and everolimus resulted in a 50% clinical benefit rate and a 28% overall response in women with recurrent EC (107). Studies highlight the need for novel biomarkers for predicting response.

MMRd/MSI-H tumor patients provided outstanding response rates, PFS and OS across the included trials. The best PFS was obtained by pembrolizumab, durvalumab and retifanlimab monotherapy protocols. Real-world data by Colomba et al. (78) confirmed that the efficacy of immunotherapy remained consistent across both first-line and later-line settings, suggesting that patients may derive benefit irrespective of the line of

systemic therapy. The combination of immunotherapy and systemic therapies offers modest results, with PFS ranging from 1.4 to 7.4 months. Real-world data from Cui et al. (148) concerning amlotinib combined with pembrolizumab demonstrated a similar effect.

Progestin therapy represents another option, particularly for patients with low-grade, hormone receptor-positive disease. These have been utilized in the treatment of recurrent or advanced EC for several decades. In our exploratory pooled analysis, limited by the low-level evidence studies and methodological shortcomings, progestin therapy resulted in an mPFS of 3.6 months in a heterogeneous study population. By contrast, data from Kulkarni et al. (113) (retrospective study, with the inherent limitations of selection bias but reflecting real-world practice) demonstrated a substantially longer median PFS of 14.3 months. Notably, chemotherapy-naïve patients in this cohort achieved a PFS of 17.9 months, whereas those previously treated with chemotherapy exhibited a significantly shorter PFS of 6.2 months. Most of the patients received megestrol acetate. The superior outcomes reported in this study may be explained by the relatively homogeneous composition of the patient population, which was characterized by favorable prognostic features such as endometrioid histology, low tumor grade, and hormone receptor positivity. Comparable results have been reported in the GOG 209 trial (12), where chemotherapy-naïve patients achieved a PFS of 13–14 months, although overall survival (OS) was higher, ranging between 37 and 41 months. Similarly, Pautier et al. (129) reported consistent findings with hormonal therapy, further supporting its clinical relevance in selected patient groups. Other medications targeting the hormonal cascade, such as fulvestrant, irosustat, anastrozole, leuprolide, exametastane, triptorelin, tamoxifen, danazole, goserelin or combined with other substances resulted in an mPFS between 1 and 9.1 months. Of note, patients were usually not selected based on their hormonal status. A combination of abemaciclib and letrozole (122) resulted in the best PFS (9.1 months).

9.2. Strengths (including all studies)

Regarding the strengths of our analyses, we followed our protocols, registered in advance in both studies. We adhered to PRISMA guidelines, enhancing methodological transparency and reproducibility.

In our first study, further strengths were the rigorous methodology, meticulous analysis of data, several subgroup analyses, such as a low-grade only patient group. MRI and TVS were performed on the same cohort of patients, which allowed a better comparison of the two methods. Finally, the studies generally showed a moderate-to-good quality in terms of the index test and reference standard definition.

In our second systematic review, several updated meta-analyses were performed, providing a comprehensive synthesis of the evolving literature on systemic therapy for recurrent or advanced endometrial cancer. Most included studies confirmed progression using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria (149), offering consistency in outcome measurement.

9.3. Limitations (including all studies)

The generalization of our first study's results is problematic for low-grade tumors, due to the low number of patients enrolled and the barely significant difference between the specificity of TVS and MRI. For a non-expert examiner, this difference was not statistically significant. Different interpretations of the imaging data were applied in the articles. The presence of moderate and high risks of bias in some of the domains is an additional limitation.

Heterogeneity might be attributed to different scanning and interpretation methods, as well as to the different proportions of EC types in the study populations. In addition, operator experience might also play a role.

Our second article also has some limitations. The included studies exhibited significant heterogeneity in patient populations, treatment protocols, and study designs, which may limit the comparability of results. A substantial proportion of the analyses was based on single-arm studies, which inherently limit comparative interpretation due to the absence of control groups. Such designs are susceptible to selection bias, confounding, and heterogeneity in patient populations, prior treatments, and outcome definitions.

Therefore, pooled estimates from single-arm analyses should be regarded as descriptive and hypothesis-generating rather than as definitive evidence of comparative efficacy. In many cases, direct comparisons between therapies were lacking, which reduces the strength of conclusions drawn from pooled estimates. We acknowledge that the

available evidence did not provide a sufficiently connected and homogeneous network of studies with common comparators to permit a robust network meta-analysis.

Reconstruction of individual patient data from Kaplan–Meier curves is subject to potential inaccuracies, including digitization errors and variability in curve resolution. The method relies on assumptions regarding the distribution of censoring and events over time, which may not fully reflect the original data. Consequently, survival estimates derived from reconstructed IPD should be interpreted as approximations rather than exact representations of original patient-level data. These limitations may introduce estimation bias, particularly in studies with sparse reporting or complex survival patterns.

We acknowledge that several other subgroup analyses could have been performed based on tumor and patient characteristics. However, the available studies frequently lacked sufficiently detailed molecular, histopathological, and treatment-sequencing data, preventing robust interpretation of these subgroups.

Publication bias could not be reliably assessed, as most analyses included a small number of studies, rendering funnel plot interpretation and statistical tests unreliable. Therefore, the potential influence of publication bias on the pooled estimates cannot be excluded.

Follow-up durations were generally short, limiting the ability to evaluate long-term outcomes. Several studies also presented a moderate to high risk of bias, particularly in allocation concealment and outcome reporting. In analyses of ICI+ChT combinations, differences in trial design—such as the inclusion of carcinosarcoma cases, treatment duration, and varying proportions of recurrent or heavily pretreated cases and different distributions of high-grade cases across studies—hinder direct cross-trial comparisons. Furthermore, molecular subgroup data beyond MMR status were often incomplete, limiting stratified analyses by TCGA classification.

10. CONCLUSIONS

10.1. Study 1.

In conclusion, our study showed that ultrasound maintains its diagnostic performance in the detection of deep myometrial infiltration in endometrial cancer. Thus, it provides a better patient stratification, enhancing the individualized patient care.

For all-grade tumors, TVS showed higher sensitivity, whereas MRI had higher specificity. Further research should be conducted on the performance of TVS and MRI to assess the presence or absence of myometrial infiltration and to provide valuable information, especially in fertility-sparing wishes.

Furthermore, there is a need to explore how artificial intelligence and radiomics can improve the diagnostic performance and predictive values of ultrasound and MRI. External validation of prognostic models would also be reasonable.

10.2. Study 2.

Chemotherapy combined with immune checkpoint inhibitors appears to provide the best PFS and OS, with manageable TRAEs for recurrent or advanced endometrial cancer, with the greatest benefit in MMRd tumors. Endometrial cancer is a heterogeneous disease, studies on further biomarkers are needed to provide a more personalized treatment strategy. Further randomized studies should be directed toward the application of ICIs, hormonal therapies, aromatase inhibitors and their combinations based on careful patient selection. Treatment options for NSMP and p53-abnormal subtypes remain limited, and optimal treatment sequencing is still unclear. Further prospective studies are needed to optimize subtype-specific, personalized therapy.

11. IMPLICATIONS FOR PRACTICE

The findings of the first article support the clinical role of both transvaginal ultrasound and magnetic resonance imaging in the preoperative stratification of endometrial cancer. Since deep myometrial invasion is an important prognostic factor and directly influences surgical planning, reliable preoperative imaging can help clinicians select the most appropriate operative strategy. The results indicate that expert transvaginal ultrasound may provide diagnostic performance comparable to MRI for the detection of deep myometrial invasion, while MRI may offer higher specificity in selected subgroups, particularly in low-grade tumors. These findings suggest that transvaginal ultrasound should not be considered only as a preliminary examination, but as a potentially valuable method for structured preoperative risk assessment when performed by experienced examiners. Accurate imaging-based stratification may reduce both undertreatment and overtreatment, including unnecessary extensive surgery or lymph node assessment in selected patients. Further clinical attention should be directed toward the ability of imaging to distinguish absence from superficial myometrial invasion, especially in patients considered for fertility-sparing treatment.

The findings of the second article have direct implications for the systemic treatment of recurrent or advanced endometrial cancer. Chemotherapy combined with immune checkpoint inhibitors appears to provide the most favorable progression-free and overall survival outcomes, with the greatest benefit observed in mismatch repair-deficient tumors. This supports the integration of molecular classification into routine therapeutic decision-making, as treatment benefit differs substantially between molecular subgroups. Hormonal therapies, aromatase inhibitors, targeted therapies, and their combinations may remain relevant options for selected patients, particularly when treatment goals, toxicity profile, tumor biology, and prior therapy exposure are carefully considered. In clinical practice, systemic therapy should therefore be individualized rather than selected according to a uniform treatment algorithm. The limited treatment options for NSMP and p53-abnormal tumors, together with the uncertainty regarding optimal treatment sequencing, highlight the need for further randomized studies and real-world validation.

12. IMPLICATIONS FOR RESEARCH

12.1. Study 1.

12.1.1. Methodology and Study Design

There is a lack of standardization of myometrial invasion measurement methods in endometrial cancer. Different methods of measuring myometrial invasion should be standardized. As demand for fertility sparing treatment increases, there is an urgent need of studies comparing TVS and MRI for no myometrial invasion vs. shallow myometrial invasion. Large scale prospective, multicenter, head-to-head analysis studies with standardized imaging approach can provide data on the most suitable imaging method in endometrial cancer.

12.1.2. New Areas

Involving novel ultrasound methods, such as elastography and 3D imaging, radiomics and integration of molecular characteristics in patient preoperative stratification could be an important step into personalized patient care.

12.2. Study 2.

12.2.1. Methodology and Study Design

Current evidence in comparing different systemic treatment methods is lacking. Large scale, prospective, multicenter studies comparing different systemic treatment methods are needed, especially studies where patient stratification is based on novel molecular characteristics. Important emphasis should be placed on health-related quality of life of the patients suffering from advanced disease, attention should be shifted in that direction.

12.2.2. New areas

Biomarker-based patient selection in the evaluation of novel targeted therapies could result in significant improvement of efficacy. Studies comparing different therapy combinations are needed. Clinical trials on further medications applied in other tumors (especially gastrointestinal and gynecologic) with promising result should be conducted based on molecular profile in EC.

13. IMPLICATIONS FOR POLICY MAKERS

13.1. Study 1.

The findings of the first study have important implications for the organization of preoperative diagnostic pathways in endometrial cancer. Since transvaginal ultrasound and magnetic resonance imaging showed comparable diagnostic performance for the assessment of deep myometrial invasion, policy makers should recognize expert gynecological ultrasound as a valuable component of structured preoperative risk stratification. This is particularly relevant because transvaginal ultrasound is widely available, relatively inexpensive, and may support timely clinical decision-making when performed by trained examiners. Health systems should therefore invest in standardized ultrasound training, quality assurance programs, and structured reporting protocols to improve the reliability and reproducibility of preoperative assessment. At the same time, MRI should remain accessible for selected patients, especially in complex cases, uncertain ultrasound findings, low-grade tumors, or when detailed pelvic evaluation is required. A rational diagnostic policy should aim to use imaging resources efficiently while maintaining high-quality risk stratification, thereby reducing unnecessary interventions, avoiding undertreatment, and supporting individualized surgical planning.

13.2. Study 2

The findings of the second study highlight the need for policy frameworks that support molecularly informed and equitable access to modern systemic treatment in recurrent or advanced endometrial cancer. The demonstrated benefit of immune checkpoint inhibitor-based treatment, particularly in mismatch repair-deficient tumors, underlines the importance of routine molecular testing as a prerequisite for appropriate treatment selection. Policy makers should therefore ensure broad access to validated molecular diagnostics, including mismatch repair status and other clinically relevant biomarkers, so that therapeutic decisions are guided by tumor biology rather than by histology or stage alone. Because novel systemic therapies may be costly and associated with substantial toxicity, reimbursement decisions should consider molecular subtype, expected clinical benefit, safety profile, quality of life, and real-world effectiveness. Health systems should also support national registries and prospective data collection to evaluate treatment outcomes outside clinical trials and to clarify optimal treatment

sequencing. Such policies may promote more efficient use of healthcare resources while improving survival, reducing inequities, and supporting personalized care for patients with recurrent or advanced endometrial cancer.

14. FUTURE PERSPECTIVES

14.1. General future directions

Taken together, future progress in endometrial cancer care will depend on the integration of accurate preoperative imaging, molecular classification, proper treatment selection, and patient-centered outcomes. The next step is not only to improve individual diagnostic or therapeutic tools, but to combine them into clinically useful pathways that guide personalized decision-making from diagnosis to advanced disease. This approach may help reduce overtreatment, avoid undertreatment, improve survival, and preserve quality of life. Future research should therefore prioritize prospective, multicenter, and multidisciplinary studies that reflect real-world clinical practice while maintaining methodological rigor. Such efforts may support the development of more precise and equitable care strategies for patients with endometrial cancer.

14.2. Personal aspirations

My future professional aspirations are closely connected to the clinical and scientific questions addressed in this thesis. As endometrial cancer care becomes increasingly personalized, I aim to further develop the skills that are essential for accurate diagnosis, appropriate treatment selection, and high-quality patient care. A central goal of my professional development is the continuous improvement of my gynecological ultrasound skills, particularly in the field of oncological imaging and preoperative risk stratification. I consider expert ultrasound not only a diagnostic technique, but also an important clinical tool that can directly influence surgical planning, patient counseling, and individualized decision-making.

In addition to diagnostic expertise, I would like to place greater emphasis on surgical training in the coming years. The integration of imaging findings, tumor characteristics, and surgical strategy is especially important in gynecologic oncology, and therefore I aim to strengthen my operative skills alongside my diagnostic and academic work. I believe that a clinician involved in endometrial cancer research should also understand the practical surgical consequences of preoperative stratification and treatment planning. From a scientific perspective, I intend to continue participating in multicenter studies, as collaborative research is essential for generating clinically meaningful and generalizable evidence. I am particularly interested in prospective studies investigating novel

biomarkers, including microRNAs and tumor-educated platelets, which may contribute to earlier diagnosis, more accurate risk stratification, and improved treatment selection in endometrial cancer. These approaches may help bridge the gap between molecular research and everyday clinical practice.

Teaching will remain an important part of my academic career. I would like to further develop my role in medical education, especially in the fields of gynecological ultrasound, gynecologic oncology, and evidence-based medicine. In parallel, I aim to participate in foreign study trips and international training opportunities, which can broaden my clinical perspective, strengthen professional collaborations, and support the transfer of advanced diagnostic and therapeutic approaches into local practice.

After completing my PhD, my goal is to continue with postdoctoral research that builds on the foundations of this thesis. I intend to focus on clinically relevant, translational research questions that combine imaging, molecular biomarkers, systemic therapy, and patient-centered outcomes. My long-term aspiration is to contribute to a more precise and individualized model of endometrial cancer care, while developing as a clinician, researcher, surgeon, and educator.

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16.1. Publications Related to the Thesis

1.

Madár, István ; Szabó, Anett ; Cavalcante, Bianca Golzio Navarro ; Vleskó, Gábor ; Hegyi, Péter ; Ács, Nándor ; Kói, Tamás ; Kálovics, Emma ; Szabó, Gábor

Systemic Treatment Strategies Beyond Chemotherapy in Recurrent or Advanced Endometrial Cancer: A Systematic Review and Meta-Analysis

CANCERS 18 : 13 Paper: 2091 , 36 p. (2026)

DOI 10.3390/cancers18132091

Journal subject: Scopus - Oncology Rank: Q1

IF: 4.8 (2026)

2.

Madár, István ; Szabó, Anett ; Vleskó, Gábor ; Hegyi, Péter ; Ács, N ; Fehérvári, Péter ; Kói, Tamás ; Kálovics, Emma ; Szabó, Gábor ✉

Diagnostic Accuracy of Transvaginal Ultrasound and Magnetic Resonance Imaging for the Detection of Myometrial Infiltration in Endometrial Cancer : A Systematic Review and Meta-Analysis

CANCERS 16 : 5 Paper: 907 , 16 p. (2024)

DOI 10.3390/cancers16050907

Journal subject: Scopus - Oncology Rank: Q1

IF: 4.4 (2024)

16.2. Publications not Related to the Thesis

3.

Szabó, G. ✉ ; Bokor, A. ; Fancsovits, V ; Madár, I. ; Darici, E. ; Pashkunova, D. ; Arányi, Z. ; Fintha, A. ; Rigó, J. Jr. ; Lipták, L. et al.

Clinical and ultrasound characteristics of deep endometriosis affecting sacral plexus

ULTRASOUND IN OBSTETRICS AND GYNECOLOGY 64 : 1 pp. 104-111. , 8 p.
(2024)

DOI 10.1002/uog.27602

Journal subject: Scopus - Obstetrics and Gynecology Rank: D1

IF: 6.3 (2024).

4.

Szabó, Gábor ✉ ; Hudelist, Gernot ; Madár, István ; Rigó, János Jr. ; Dobó, Noémi ;
Fintha, Attila ; Lipták, Laura ; Kalovics, Emma ; Fancsovits, Veronika ; Bokor, Attila

**Diagnostic accuracy of the IDEA protocol for non invasive diagnosis of
rectosigmoid DE – a prospective cohort study**

ULTRASCHALL IN DER MEDIZIN 45 : 1 pp. 61-68. , 8 p. (2024)

DOI 10.1055/a-2034-2022

Journal subject: Scopus - Radiology, Nuclear Medicine and Imaging Rank: Q2

IF: 2.9 (2024).

5.

Szabó, Gábor ; Madár, István ; Lipták, L. ; Pete, B. ; Kálovics, E. ; Fancsovits, V.

A mélyen infiltráló endometriosis ultrahang-diagnosztikája.

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6.

Szabó, G. ✉ ; Madár, I. ; Hudelist, G. ; Arányi, Z. ; Turtóczki, K. ; Rigó, J. ; Ács, N. ;
Lipták, L. ; Fancsovits, V. ; Bokor, A.

**Visualization of sacral nerve roots and sacral plexus on gynecological transvaginal
ultrasound: feasibility study**

ULTRASOUND IN OBSTETRICS AND GYNECOLOGY 62 : 2 pp. 290-299. , 10 p.
(2023)

DOI 10.1002/uog.26204

Journal subject: Scopus - Obstetrics and Gynecology Rank: D1

IF: 6.1 (2023)

7.

Szabó, G. ; Madár, I. ; Hudelist, G. ; Arányi, Z. ; Mázsár, B. ; Rigó, J. ; Ács, N. ; Lipták, L. ; Fancsovits, V. ; Kálovics, E. et al.

OC09.03: Identification and characteristics of deep endometriosis infiltrating the sacral plexus with transvaginal ultrasound

ULTRASOUND IN OBSTETRICS AND GYNECOLOGY 62 : S1 pp. 20-21. Paper:

OC09.03, 2 p. (2023)

DOI 10.1002/uog.26377

8.

Artner, Attila ; Szatmári, Erzsébet ; Madár, István

Képalakotói megnyilvánulás (Endometrium carcinoma)

NŐGYÓGYÁSZATI ONKOLÓGIA 27 pp. 18-21. , 4 p. (2022)

9.

Szabó, Gábor ✉ ; Madár, István ; Rigó, János ; Dobó, Noémi ; Ács, Nándor ; Bokor, Attila

A novel complementary method for ultrasonographic screening of deep endometriosis: a case series of 5 patients diagnosed with transvaginal strain elastography

CLINICAL & EXPERIMENTAL OBSTETRICS & GYNECOLOGY 49 : 1 Paper: 002

, 9 p. (2022)

DOI 10.31083/j.ceog4901002

Journal subject: Scopus - Obstetrics and Gynecology Rank: Q4

IF: 0.2

10.

Szabó, Gábor ✉ ; Madár, István ; Bokor, Attila ; Rigó, János

Transvaginal Strain Elastosonography May Help in the Differential Diagnosis of Endometriosis?

DIAGNOSTICS 11 : 1 Paper: 100 , 3 p. (2021)

DOI 10.3390/diagnostics11010100

Journal subject: Scopus – Clinical biochemistry Rank: Q2

11.

Szabó, G. ; Madár, I. ; Ács, N. ; Rigó, J. ; Dobó, N. ; Csibi, N. ; Brubel, R. ; Bokor, A.

VP62.21: Quantitative shear wave ultrasound elastography in patients with deep endometriosis

ULTRASOUND IN OBSTETRICS AND GYNECOLOGY 56 : S1 pp. 342-342. , 1 p. (2020)

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Szabó, Gábor ✉ ; Madár, István ; Bokor, Attila ; Rigó, János Jr.

Az elasztográfós ultrahangvizsgálatok szülészeti-nőgyógyászati alkalmazási lehetőségei

NŐGYÓGYÁSZATI ONKOLÓGIA 25 : 2-3 pp. 76-82. , 7 p. (2020)

13.

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Evaluation of IOTA simple rules and IOTA ADNEX model in the hands of expert examiners at the diagnosis of the adnexal tumors

Australasian Journal of Ultrasound in Medicine 22 : 2 pp. 147-147. , 1 p. (2019)

DOI 10.1002/ajum.12151

14.

Szabó, G. ; Madár, I. ; Bokor, A. ; Brubel, R. ; Csibi, N. ; Rigó, J.

OC20.01: Preoperative mapping of deep infiltrating endometriosis in the posterior compartment using transvaginal strain elastography and IDEA classification

ULTRASOUND IN OBSTETRICS AND GYNECOLOGY 54 : S1 p. 50 (2019)

DOI 10.1002/uog.20557

15.

Szabó, G. ; Madár, I. ; Bokor, A. ; Bokor, R. ; Csibi, N. ; Rigó, J.

Usefulness of transvaginal strain elastography in the diagnosis of deep infiltrating endometriosis in the posterior compartment

Australasian Journal of Ultrasound in Medicine 22 : 2 pp. 144-145. , 2 p. (2019)

DOI 10.1002/ajum.12145

16.

Madár, I ✉ ; Szabó, G ; Szabó, B

A IOTA Simple Rules és az IOTA ADNEX Model alkalmazása a petefészek-daganatok kórismézésében

NŐGYÓGYÁSZATI ONKOLÓGIA 22 : 1 pp. 3-8. , 6 p. (2017)

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