APPENDIX S4 ENDOMETRIAL CANCER

1.1. Standardized ultrasound report for endometrial cancer assessment

Ultrasound parameter	Description
Tumor identification	Yes/No. If yes, assess the tumor characteristics using IETA terms (Figure S2).[1]
Tumor location	▪ Anterior, posterior, fundal, right lateral or left lateral ▪ Localized (<25% of the endometrial surface) or extended (≥25% of the endometrial surface)
Tumor size (milimeters)	▪ Antero-posterior diameter (tumor thickness) ▪ Maximum craniocaudal diameter (tumor length) ▪ Latero-lateral diameter
Tumor echogenicity	▪ Uniform ▪ Non-uniform
Junctional (endo-myometrial) zone[1]	▪ Regular ▪ Irregular ▪ Interrupted ▪ Not defined
Myometrial invasion	**Subjective assessment:** Disruption to endometrial/myometrial border, subjective ratio of the width of healthy myometrium against the myometrial invasion of the tumor **Objective assessment** (Figure S4): ▪ Gordon's ratio: distance between the maximum tumor depth [d1] and the total myometrial thickness [d2] » d1/d2 > 0.5 indicates deep myometrial invasion[2, 3] ▪ Karlsson's ratio: the maximum anteroposterior [AP] thickness of the endometrial lesion measured in the sagittal plane [d1] divided by the AP uterine diameter [d2] » d1/d2 > 0.53 indicates deep invasion[2, 4]
Cervical stromal tumor invasion	**Subjective assessment:** ▪ Dynamic sliding test helps to differentiate the bulging or protrusion of the tumor into the endocervical canal from true cervical stromal invasion. ▪ Cervical stromal infiltration is characterised by the loss of clear demarcation of the endometrial lesion against the cervical stroma, accompanied by enhanced tumor perfusion. **Objective assessment** (Figure S5): ▪ Distance from the external cervical os to the lower tumor margin (cut-off value ≤ 20.5 mm is correlated to a high probability of cervical stromal invasion)[5]
Vascularization	▪ Colour Doppler score§ ▪ Vessel pattern[1]
Regional (pelvic and paraaortic) lymph nodes	Description of site, number, laterality Assessment by standardized **VITA terminology** using the classification LN1 – LN5[6]: ▪ LN1: Normal finding ▪ LN2: Benign finding ▪ LN3: Indeterminate, probably benign finding ▪ LN4: Probably malignant finding ▪ LN5: Malignant finding
Distant spread	▪ Distant lymph nodes (site, number, laterality if appropriate, lymph node status LN1-LN5, see above) ▪ Ovarian involvement ▪ Peritoneal infiltration ▪ Bladder and/or bowel involvement ▪ Other distant spread
Other findings	▪ Related / unrelated gynecologic/non-gynecologic pathologies
Staging system	▪ TNM and FIGO staging system[7, 8] ▪ Comments and recommendations to additional diagnostic tests to the referring specialist and to multidisciplinary team meeting

§Color score following IOTA (International Ovarian Tumor Analysis) terms and definitions (Color Score 1, no perfusion; Color Score 2, minimal perfusion; Color Score 3, moderate flow; Color Score 4, highly vascularized.[9]

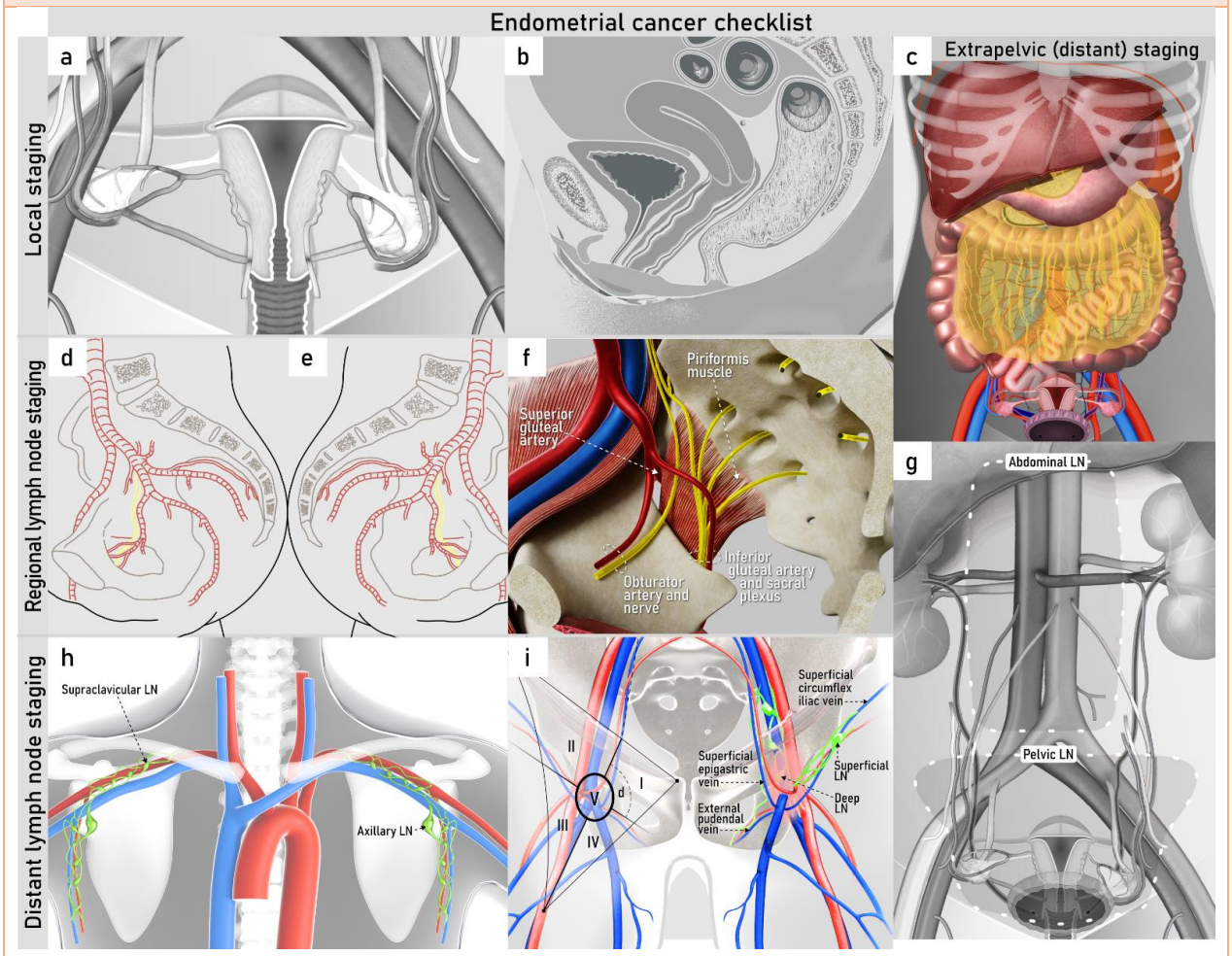

Figure S1 Schematic documentation of endometrial cancer staging by ultrasound. *Ultrasound documents the location and extension of primary tumor (a), local pelvic (b) and extrapelvic staging (c), and any suspicious lymph nodes (size of lymph node and intranodal metastasis, the number of lymph nodes involved, the presence or absence of extracapsular spread and others)(d-g). For local staging, schematics showing the coronal (a) and sagittal (b) views of pelvic anatomy; and the coronal view of abdominal anatomy (c). The regional pelvic lymph nodes can be plotted on a diagram of the right (d) and left (e) iliac vessels with the corresponding anatomical diagram (f). The regional pelvic and abdominal (paraaortic) lymph nodes are delineated by the dashed line in scheme (g). Distant lymph nodes (supraclavicular (scalene) and inguinofemoral lymph nodes) are demonstrated in diagrams (h, i).*

Table S1 *Ultrasound checklist on endometrial cancer based on the consensus of the authors*

1.2. 2023 FIGO staging for endometrial cancer

STAGE	T	N	M	DESCRIPTION
I	T1	N0	M0	Confined to the uterus corpus and ovary[c]
IA	T1a	N0	M0	Disease limited to the endometrium OR non-aggressive histological type, i.e low grade endometrioid, with invasion of less than half of myometrium with no or focal lymphovascular space involvement (LVSI) OR good prognosis disease IA1 Non-aggressive histological type limited to an endometrial polyp OR confined to the endometrium IA2 Non-aggressive histological type involving less than a half of the myometrium with no or focal LVSI IA3 Low grade endometrioid carcinomas limited to the uterus and ovary[c]
IB	T1b	N0	M0	Non-aggressive histological types with invasion of half or more of the myometrium and with no or focal LVSI[d]
IC	T1c	N0	M0	Aggressive histological types[e] limited to a polyp or confined to the endometrium
II	T2	N0	M0	Invasion of cervical stroma without extrauterine extension OR with substantial LVSI OR aggressive histological types with myometrial invasion
IIA	T2a	N0	M0	Invasion of the cervical stroma of non-aggressive histological types
IIB	T2b	N0	M0	Substantial LVSI[d] of non-aggressive histological types
IIC	T2c	N0	M0	Aggressive histological types[e] with any myometrial involvement
III	T3	N0	M0	Local and/or regional spread of the tumor of any histological subtype
IIIA	T3a	N0	M0	Invasion of uterine serosa, adnexa, or both by direct extension or metastasis IIIA1 Spread to ovary or fallopian tube (except when meeting stage IA3 criteria) [c] IIIA2 Involvement of uterine subserosa or spread through the uterine serosa
IIIB	T3b	N0	M0	Metastasis or direct spread to the vagina and/or to the parametria or pelvic peritoneum IIIB1 Metastasis or direct spread to the vagina and/or the parametria IIIB2 Metastasis to the pelvic peritoneum
IIIC	T1-T3	N1, N1mi or N1a N2, N2mi or N2a	M0	Metastasis to the pelvic or para-aortic lymph nodes or both[f] IIIC1Metastasis to the pelvic lymph nodes IIIC1i Micrometastasis IIIC1ii Macrometastasis IIIC2 Metastasis to the para-aortic lymph nodes up to the renal vessels, with or without metastasis to the pelvic lymph nodes IIIC2i Micrometastasis IIIC2ii Macrometastasis
IV	Any T	Any N	M0 or M1	Spread to the bladder mucosa and/or intestinal mucosa and/or distant metastasis
IVA	T4	Any N	M0	Invasion of the bladder mucosa and/or intestinal/bowel mucosa
IVB	Any T	Any N	M1	Abdominal peritoneal metastasis beyond the pelvis
IVC	Any T	Any N	M1	Distant metastasis, including metastasis to any extra- or intra- abdominal lymph nodes above the renal vessels, lungs, liver, brain or bone

Table S2 *2023 FIGO staging of cancer of endometrium[(10)]*
Abbreviations: EEC, endometrioid carcinoma; LVSI, lymphovascular space involvement.
[a]Endometrial cancer is surgically staged and pathologically examined. In all stages, the grade of the lesion, the histological type and LVSI must be recorded. If available and feasible, molecular classification testing (POLEmut, MMRd, NSMP, p53abn) is encouraged in all patients with endometrial cancer for prognostic risk-group stratification and as factors that might influence adjuvant and systemic treatment decisions.
[b]In early endometrial cancer, the standard surgery is a total hysterectomy with bilateral salpingo-oophorectomy via a minimally invasive laparoscopic approach. Staging procedures include infracolic omentectomy in specific histological subtypes, such as serous and undifferentiated endometrial carcinoma, as well as carcinosarcoma, due to the high risk of microscopic omental

metastases. Lymph node staging should be performed in patients with intermediate-high/ high-risk. Sentinel lymph node (SLN) biopsy is an adequate alternative to systematic lymphadenectomy for staging proposes. SLN biopsy can also be considered in low−/low-intermediate- risk patients to rule out occult lymph node metastases and to identify disease truly confined to the uterus. Thus, the ESGO-ESTRO-ESP guidelines allow an approach of SLN in all patients with endometrial carcinoma, which is endorsed by FIGO. In assumed early endometrial cancer, an SLN biopsy in an adequate alternative to systematic lymphadenectomy in high-intermediate and high-risk cases for the purpose of lymph node staging and can also be considered in low– intermediate-risk disease to rule out occult lymph node metastases. An SLN biopsy should be done in association with thorough (ultrastaging) staging as it will increase the detection of low-volume disease in lymph nodes.

[c]*Low-grade EECs involving both the endometrium and the ovary are considered to have a good prognosis, and no adjuvant treatment is recommended if all the below criteria are met. Disease limited to low-grade endometrioid carcinomas involving the endometrium and ovaries (Stage IA3) must be distinguished from extensive spread of the endometrial carcinoma to the ovary (Stage IIIA1), by the following criteria: (1) no more than superficial myometrial invasion is present (<50%); (2) absence of extensive/substantial LVSI; (3) absence of additional metastases; and (4) the ovarian tumor is unilateral, limited to the ovary, without capsule invasion/rupture (equivalent to pT1a).*

[d]*LVSI as defined in WHO 2021: extensive/substantial, ≥5 vessels involved.*

[e]*Grade and histological type*

- *Serous adenocarcinomas, clear cell adenocarcinomas, mesonephric-like carcinomas, gastrointestinal-type mucinous endometrial carcinoma, undifferentiated carcinomas, and carcinosarcomas are considered high-grade by definition. For EECs, grade is based on the proportion of solid areas: low grade = grade 1 (≤5%) and grade 2 (6%–50%); and high grade = grade 3 (>50%). Nuclear atypia excessive for the grade raises the grade of a grade 1 or 2 tumor by one. The presence of unusual nuclear atypia in an architecturally low-grade tumor should prompt the evaluation of p53 and consideration of serous carcinoma. Adenocarcinomas with squamous differentiation are graded according to the microscopic features of the glandular component.*
- *Non-aggressive histological types are composed of low-grade (grade 1 and 2) EECs. Aggressive histological types are composed of high-grade EECs (grade 3), serous, clear cell, undifferentiated, mixed, mesonephric-like, gastrointestinal mucinous type carcinomas, and carcinosarcomas.*
- *It should be noted that high-grade EECs (grade 3) are a prognostically, clinically, and molecularly heterogenous disease, and the tumor type that benefits most from applying molecular classification for improved prognostication and for treatment decision-making.[(11)] Without molecular classification, high-grade EECs cannot appropriately be allocated to a risk group and thus molecular profiling is particularly recommended in these patients. For practical purposes and to avoid undertreatment of patients, if the molecular classification is unknown, high-grade EECs were grouped together with the aggressive histological types in the actual FIGO classification.*

[f]*Micrometastases are considered to be metastatic involvement (pN1 (mi)). The prognostic significance of isolated tumor cells (ITCs) is unclear. The presence of ITCs should be documented and is regarded as pN0(i+). According to TNM8, macrometastases are >2 mm in size, micrometastases are >0.2–2 mm and/or >200 cells, and isolated tumor cells are≤0.2 mm and ≤200 cells.[(12)]*

1.3. 2009 FIGO / TNM staging

FIGO	T	N	M	DEFINITION
I	T1	N0	M0	The cancer is growing inside the uterus. It may also be growing into the glands of the cervix, but not into the supporting connective tissue of the cervix (T1). It has not spread to nearby lymph nodes (N0) or to distant sites (M0).
IA	T1a	N0	M0	The cancer is in the endometrium (inner lining of the uterus) and may have grown less than halfway through the underlying muscle layer of the uterus (the myometrium) (T1a). It has not spread to nearby lymph nodes (N0) or to distant sites (M0).
IB	T1b	N0	M0	The cancer has grown from the endometrium into the myometrium. It has grown more than halfway through the myometrium, but has not spread beyond the body of the uterus (T1b). It has not spread to nearby lymph nodes (N0) or to distant sites (M0).
II	T2	N0	M0	The cancer has spread from the body of the uterus and is growing into the supporting connective tissue of the cervix (called the cervical stroma). But it has not spread outside the uterus (T2). It has not spread to nearby lymph nodes (N0) or to distant sites (M0).
III	T3	N0	M0	The cancer has spread outside the uterus, but has not spread to the inner lining of the rectum or urinary bladder (T3). It has not spread to nearby lymph nodes (N0) or to distant sites (M0).
IIIA	T3a	N0	M0	The cancer has spread to the outer surface of the uterus (called the serosa) and/or to the fallopian tubes or ovaries (the adnexa) (T3a). It has not spread to nearby lymph nodes (N0) or to distant sites (M0).
IIIB	T3b	N0	M0	The cancer has spread to the vagina or to the tissues around the uterus (the parametrium) (T3b). It has not spread to nearby lymph nodes (N0) or to distant sites (M0).
IIIC1	T1-T3	N1, N1mi or N1a	M0	The cancer is growing in the body of the uterus. It may have spread to some nearby tissues, but is not growing into the inside of the bladder or rectum (T1 to T3). It has also spread to pelvic lymph nodes (N1, N1mi, or N1a), but not to lymph nodes around the aorta or distant sites (M0).
IIIC2	T1-T3	N2, N2mi or N2a	M0	The cancer is growing in the body of the uterus. It may have spread to some nearby tissues, but is not growing into the inside of the bladder or rectum (T1 to T3). It has also spread to lymph nodes around the aorta (para-aortic lymph nodes) (N2, N2mi, or N2a), but not to distant sites (M0).
IVA	T4	Any N	M0	The cancer has spread to the inner lining of the rectum or urinary bladder (called the mucosa) (T4). It may or may not have spread to nearby lymph nodes (Any N), but has not spread to distant sites (M0).
IVB	Any T	Any N	M1	The cancer has spread to inguinal (groin) lymph nodes, the upper abdomen, the omentum, or to organs away from the uterus, such as the lungs, liver, or bones (M1). The cancer can be any size (Any

Table S3 *2009 FIGO staging and TNM of endometrial cancer*[7, 8, 12]

1.4 Methodology of endometrial cancer ultrasound staging

A methodologic approach to describe endometrial findings on ultrasound was developed by the International Endometrial Tumor Analysis (IETA) group (Figure S2).[1]

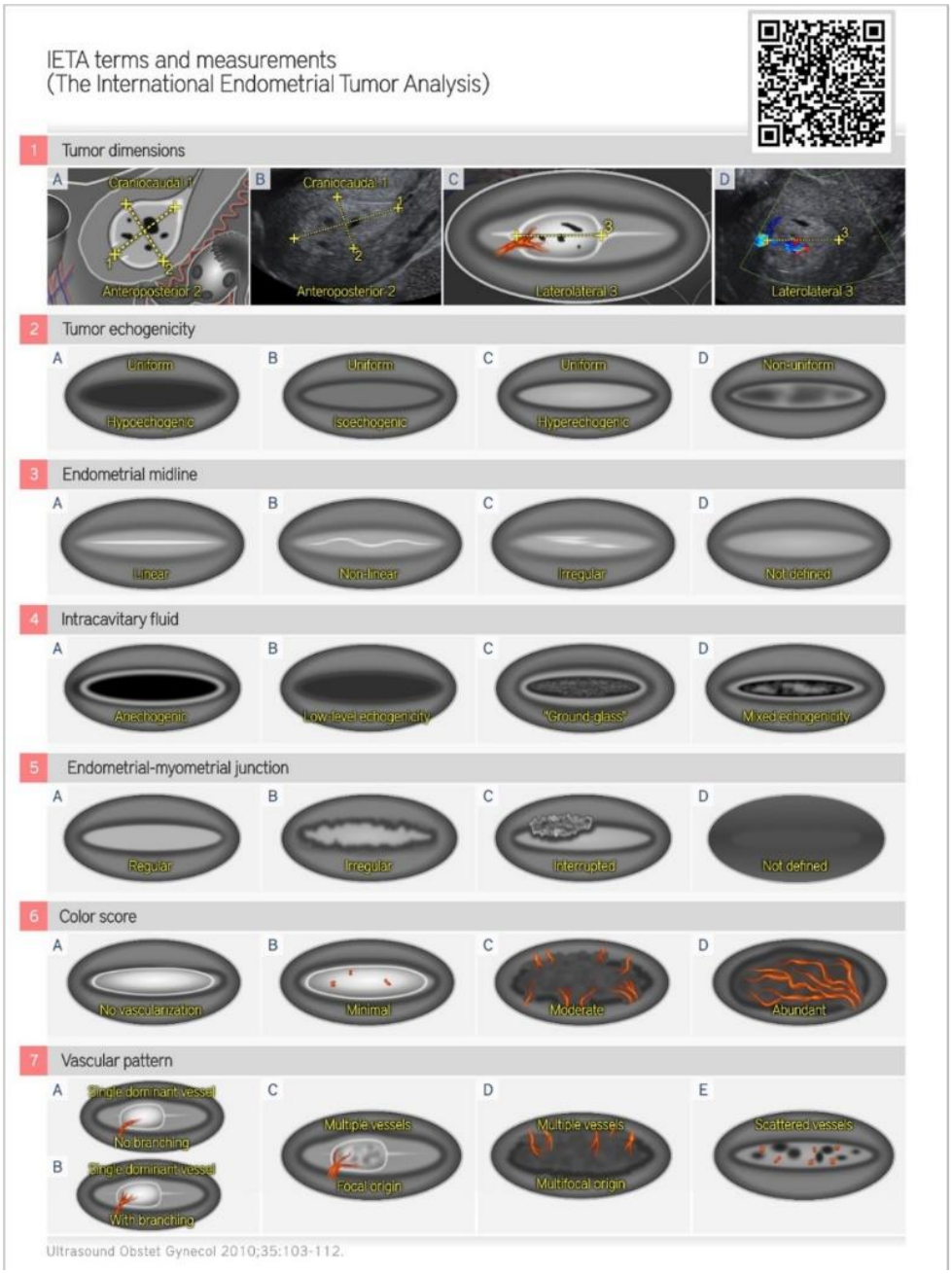

Figure S2 IETA terms to describe the sonographic features of the endometrium and intrauterine lesions

IETA, the International Endometrial Tumor Analysis.[1]

Additionally, the identification of ultrasound features on grayscale and power Doppler may be used to predict low and high-risk endometrial cancer phenotypes (Figure S3).

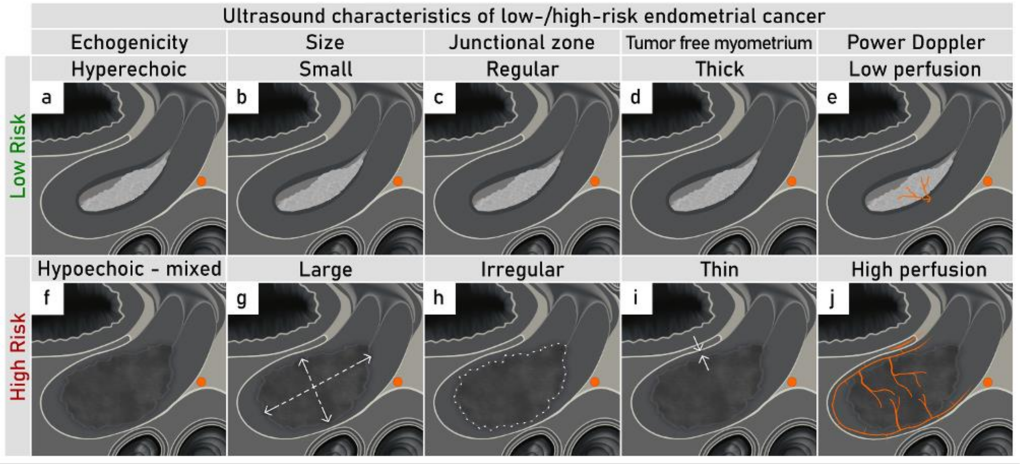

Figure S3 Ultrasound characteristics of low-/high-risk endometrial cancer
Low-risk tumors are usually hyperechoic, smaller, with regular endometrial-myometrial junction, greater tumor free myometrium, and exhibit less perfusion, with single vessel with branching or multiple vessels with a focal origin (a-e). High-risk tumors are usually larger with irregular endometrial-myometrial junction, non-uniform echogenicity and more often exhibit multiple, multifocal vessel patterns with moderate or high colour score on power Doppler (f-j).

Myometrial invasion and the cervical stromal infiltration are the main features that must be assessed in the ultrasound pre-operative work-up as they influence the treatment strategy. Myometrial invasion can be assessed either by a subjective or an objective approach. Subjective assessment based on estimated correlation of the width of unaffected myometrium with the depth of myometrial invasion by the tumor is superior compared to the objective assessment.[2, 13] Among the objective measurements, there are two most frequently used ratios (Figure S4). Gordon's ratio measures the distance between endometrium-myometrium interface and maximum tumour depth to the total myometrial thickness.[3] Karlsson's ratio measures the anteroposterior endometrial tumour thickness in relation to anteroposterior uterine diameter.[4] Using the Karlsson's approach the cut-off value of 0.53 achieved similar sensitivity and specificity as subjective evaluation, which was validated in a prospective IETA (International Endometrial Tumor Analysis)-4 cohort.[2, 5, 13]

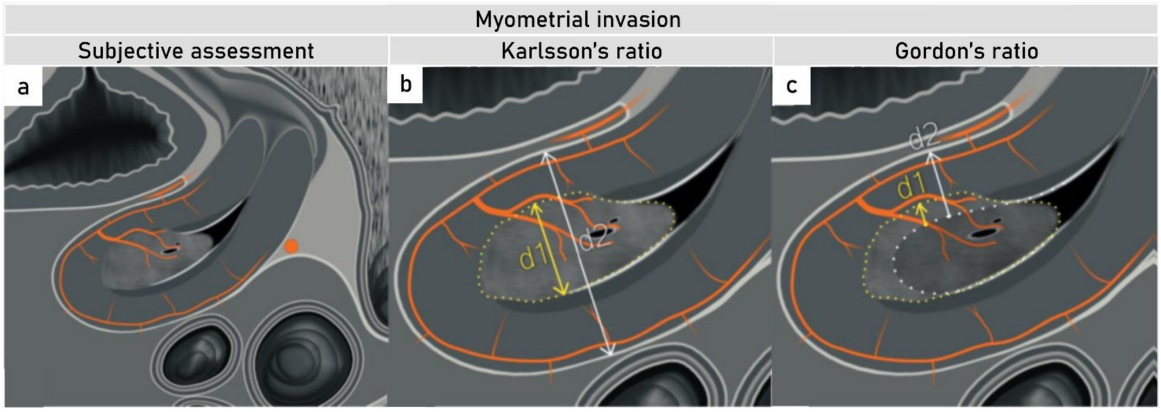

Figure S4 Subjective and objective evaluation of myometrial invasion
Subjective assessment of myometrial invasion based on evaluation of disrupted endometrial/myometrial border and a subjective correlation of the width of myometrium along with the depth of tumor invasion (a). Karlsson's ratio (the maximum anteroposterior [AP] thickness of the endometrial lesion measured in the sagittal plane [d1] divided by the AP uterine diameter [d2] indicates deep invasion if d1/d2>0.53 (b).[5] Gordon's ratio (the distance between the maximum tumor depth [d1] and the total myometrial thickness [d2]) with d1/d2>0.50 indicates deep myometrial invasion (c).[3]

Similarly to myometrial invasion, cervical stromal invasion may be assessed objectively or subjectively (more accurate).[13] Using subjective assessment, the dynamic ultrasound test helps to differentiate the bulging or protrusion of the tumor into the endocervical canal from true cervical stromal invasion (Figure S5).

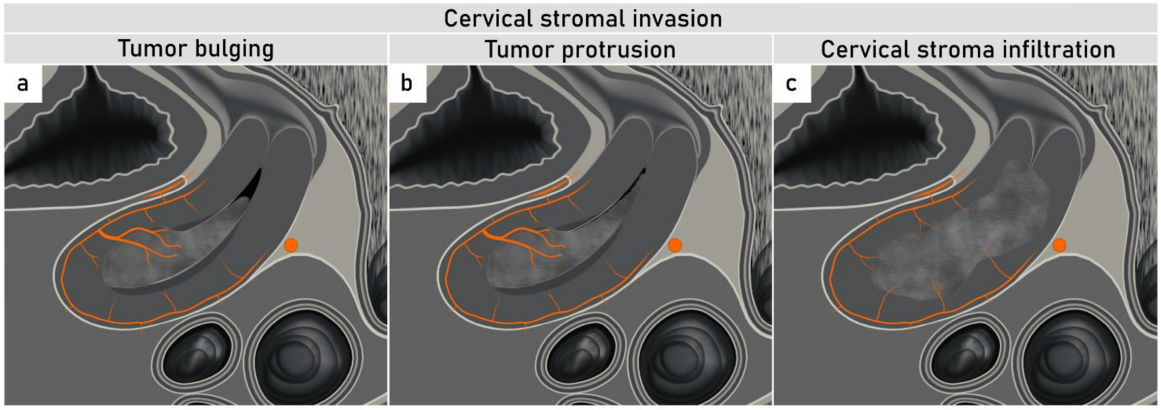

Figure S5. Cervical stroma invasion
Absence of cervical stromal invasion is demonstrated on schematic drawings as bulging or protrusion of endometrial tumor (a, b), while cervical invasion is suspected if there is no clear demarcation of the endometrial lesion against the cervical canal (c). Note: objective measurement of the distance from the external cervical os to the lower margin of the tumor with cut-off of ≤ 20.5 mm was correlated to high probability of cervical stromal invasion, but subjective assessment of cervical stromal invasion performed significantly better.[5]

Cervical stromal infiltration is characterized by the loss of clear demarcation of the endometrial lesion against the cervical stroma, accompanied by enhanced tumor perfusion. Objective assessment of cervical stroma invasion is based on the measurement of the distance from the external cervical os to the lower margin of the tumor with a validated cut-off value of ≤ 20.5.[5, 13] Preoperative assessment must include a systematic search for ovarian pathologies, peritoneal infiltration, lymphadenopathies, etc. For these reasons, transabdominal ultrasound always complements pelvic ultrasound examination (Figure S6).

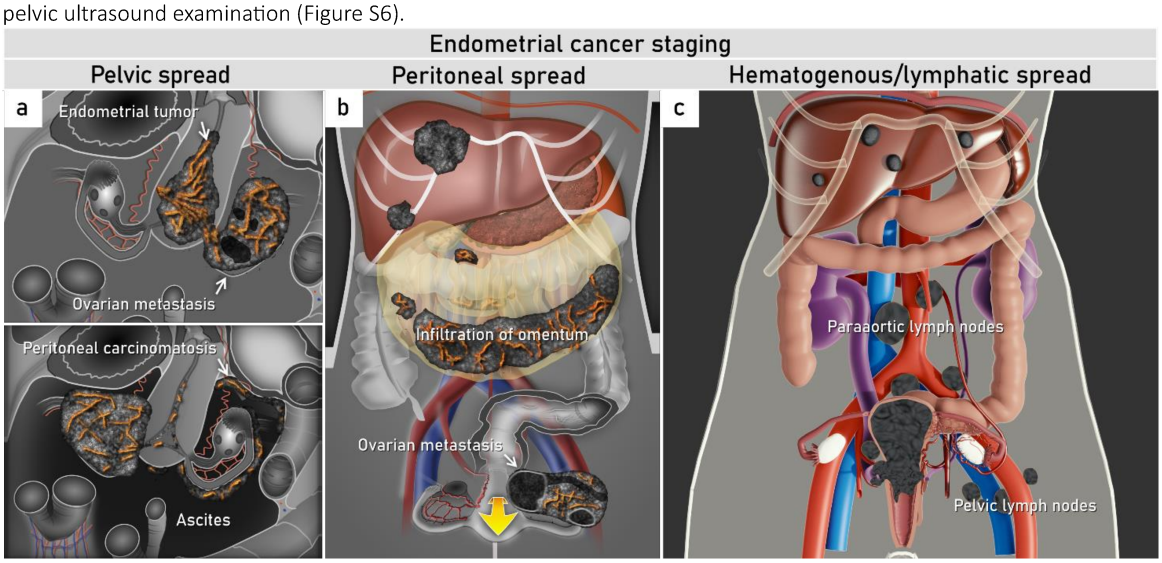

Figure S6 Systematic approach to assess pelvic and abdominal spread using ultrasound
Demonstration of pelvic spread using transvaginal scan (a), abdominal spread on the peritoneum including omentum (b) and infiltration of regional lymph nodes and distant intraparenchymal spread (c) in endometrial cancer.

On ultrasound, ovarian metastases originating from endometrial tumor present as either solid hyperechogenic tumors (consistent with the echogenicity of endometrial tumor), unilocular-solid or multilocular-solid tumors. Their solid portion is highly vascularized and the intracystic fluid is of low-level or ground glass echogenicity.[14] Tumor staging should be documented in a schematic drawing (Figure S1) within a standardized systematic checklist (Table S1).

Supplemental references

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[11] Bosse T, Nout RA, McAlpine JN et al. Molecular Classification of Grade 3 Endometrioid Endometrial Cancers Identifies Distinct Prognostic Subgroups. *The American journal of surgical pathology*. 2018;**42**: 561-8.

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