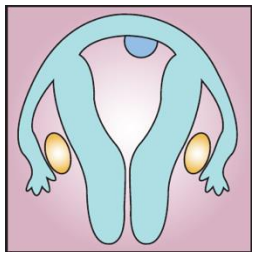
Καρκίνος ενδομητρίου

Χαράλαμπος Θεοφανάκης
Γυναικολόγος – Ογκολόγος (ESGO)
Επίκουρος Καθηγητής
Γ' Μαιευτική & Γυναικολογική
Κλινική ΕΚΠΑ
ΠΓΝ Αττικόν

Καρκίνος Ενδομητρίου



Ο πιο συχνός γυναικολογικός καρκίνος στην Ευρώπη

5-ετής εμφάνιση 34.7% (445.805 νέες περιπτώσεις)

7 % αφορά γυναίκες 20-44 ετών

8-14% σε γυναίκες αναπαραγωγικής ηλικίας

Παχυσαρκία, ΣΔ, καθυστέρηση τεκνοποίησης

World Health Organization. GLOBOCAN 2018: estimated cancer incidence, mortality and prevalence worldwide in 2018, 2018. Available: http://gco.iarc.fr/today/data/factsheets/cancers/24- Corpus-uteri-fact-sheet.pdf [Accessed 29 Jul 2020].

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Joint statement

ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma

Nicole Concin ,[1,2] Xavier Matias-Guiu,[3,4] Ignace Vergote,[5] David Cibula,[6] Mansoor Raza Mirza,[7] Simone Marnitz,[8] Jonathan Ledermann ,[9] Tjalling Bosse,[10] Cyrus Chargari,[11] Anna Fagotti,[12] Christina Fotopoulou ,[13] Antonio Gonzalez Martin,[14] Sigurd Lax,[15,16] Domenica Lorusso,[12] Christian Marth,[17] Philippe Morice,[18] Remi A Nout,[19] Dearbhaile O'Donnell,[20] Denis Querleu ,[12,21] Maria Rosaria Raspollini,[22] Jalid Sehouli,[23] Alina Sturdza,[24] Alexandra Taylor,[25] Anneke Westermann,[26] Pauline Wimberger,[27] Nicoletta Colombo,[28] François Planchamp,[29] Carien L Creutzberg[30]

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Risk Group	Molecular Classification Unknown	Molecular Classification Known[a],*
Low	• Stage IA endometrioid + low-grade** + LVSI negative or focal	• Stage I-II ***POLE*mut** endometrial carcinoma, no residual disease • Stage IA **MMRd/NSMP** endometrioid carcinoma + low-grade** + LVSI negative or focal
Intermediate	• Stage IB endometrioid + low-grade** + LVSI negative or focal • Stage IA endometrioid + high-grade** + LVSI negative or focal • Stage IA non-endometrioid (serous, clear cell, undifferentiared carcinoma, carcinosarcoma, mixed) without myometrial invasion	• Stage IB **MMRd/NSMP** endometrioid carcinoma + low-grade** + LVSI negative or focal • Stage IA **MMRd/NSMP** endometrioid carcinoma + high-grade** + LVSI negative or focal • Stage IA **p53abn** and/or non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) without myometrial invasion
High-intermediate	• Stage I endometrioid + substantial LVSI, regardless of grade and depth of invasion • Stage IB endometrioid high-grade**, regardless of LVSI status • Stage II	• Stage I **MMRd/NSMP** endometrioid carcinoma + substantial LVSI, regardless of grade and depth of invasion • Stage IB **MMRd/NSMP** endometrioid carcinoma high-grade**, regardless of LVSI status • Stage II **MMRd/NSMP** endometrioid carcinoma
High	• Stage III-IVA with no residual disease • Stage I-IVA non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) with myometrial invasion, and with no residual disease	• Stage III-IVA **MMRd/NSMP** endometrioid carcinoma with no residual disease • Stage I-IVA **p53abn** endometrial carcinoma with myometrial invasion, with no residual disease • Stage I-IVA **NSMP/MMRd** serous, undifferentiated carcinoma, carcinosarcoma with myometrial invasion, with no residual disease
Advanced Metastatic	• Stage III-IVA with residual disease • Stage IVB	• Stage III-IVA with residual disease of any molecular type • Stage IVB of any molecular type

[a]For stage III-IVA ***POLE*mut** endometrial carcinoma, and stage I-IVA MMRd or NSMP clear cell carcinoma with myometrial invasion, insufficient data are available to allocate these patients to a prognostic risk-group in the molecular classification. Prospective registries are recommended

* see text on how to assign double classifiers (e.g. patients with both *POLE*mut and p53abn should be managed as *POLE*mut)

** according to the binary FIGO grading, grade 1 and grade 2 carcinomas are considered as low-grade, and grade 3 carcinomas are considered as high-grade.

p53abn: p53 abnormal, MMRd: Mismatch Repair Deficient, NSMP: nonspecific molecular profile, *POLE*mut: polymerase Ɛ mutated

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SPECIAL ARTICLE

FIGO staging of endometrial cancer: 2023

Jonathan S. Berek[1] | Xavier Matias-Guiu[2] | Carien Creutzberg[3] | Christina Fotopoulou[4] | David Gaffney[5] | Sean Kehoe[6] | Kristina Lindemann[7] | David Mutch[8] | Nicole Concin[9,10] | Endometrial Cancer Staging Subcommittee, FIGO Women's Cancer Committee

Stage	Description
Stage I	Confined to the uterine corpus and ovary[c]
IA	Disease limited to the endometrium OR non-aggressive histological type, i.e. low-grade endometroid, 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 types involving less than half of the myometrium with no or focal LVSI
	IA3 Low-grade endometrioid carcinomas limited to the uterus and ovary[c]
IB	Non-aggressive histological types with invasion of half or more of the myometrium, and with no or focal LVSI[d]
IC	Aggressive histological types[e] limited to a polyp or confined to the endometrium
Stage II	Invasion of cervical stroma without extrauterine extension OR with substantial LVSI OR aggressive histological types with myometrial invasion
IIA	Invasion of the cervical stroma of non-aggressive histological types
IIB	Substantial LVSI[d] of non-aggressive histological types
IIC	Aggressive histological types[e] with any myometrial involvement
Stage III	Local and/or regional spread of the tumor of any histological subtype
IIIA	Invasion of uterine serosa, adnexa, or both by direct extension or metastasis
	IIIA1 Spread to ovary or fallopian tube (except when meeting stage IA3 criteria)[c] IIIA2 Involvement of uterine subserosa or spread through the uterine serosa
IIIB	Metastasis or direct spread to the vagina and/or to the parametria or pelvic peritoneum
	IIIB1 Metastasis or direct spread to the vagina and/or the parametria IIIB2 Metastasis to the pelvic peritoneum
IIIC	Metastasis to the pelvic or para-aortic lymph nodes or both[f]
	IIIC1 Metastasis to the pelvic lymph nodes IIIC1i Micrometastasis IIIC1ii Macrometastasis IIIC2 Metastasis to para-aortic lymph nodes up to the renal vessels, with or without metastasis to the pelvic lymph nodes IIIC2i Micrometastasis IIIC2ii Macrometastasis
Stage IV	Spread to the bladder mucosa and/or intestinal mucosa and/or distance metastasis
IVA	Invasion of the bladder mucosa and/or the intestinal/bowel mucosa
IVB	Abdominal peritoneal metastasis beyond the pelvis
IVC	Distant metastasis, including metastasis to any extra- or intra-abdominal lymph nodes above the renal vessels, lungs, liver, brain, or bone

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Table 2. FIGO endometrial cancer stage with molecular classification*

Stage designation	Molecular findings in patients with early endometrial cancer (Stages I and II after surgical staging)
Stage $IAm_{POLEmut}$	POLEmut endometrial carcinoma, confined to the uterine corpus or with cervical extension, regardless of the degree of LVSI or histological type
Stage $IICm_{p53abn}$	p53abn endometrial carcinoma confined to the uterine corpus with any myometrial invasion, with or without cervical invasion, and regardless of the degree of LVSI or histological type

FIGO, International Federation of Gynecology and Obstetrics; LVSI, lymphovascular space involvement; MMRd, mismatch repair deficient; NSMP, non-specific molecular profile; p53abn, p53 abnormal.

*When feasible, the addition of molecular subtype to the staging criteria allows a better prediction of prognosis in a staging/prognosis scheme. The performance of complete molecular classification (*POLEmut*, MMRd, NSMP, p53abn) is encouraged in all cases of endometrial cancer for prognostic risk-group stratification and as potential influencing factors of adjuvant or systemic treatment decisions. Molecular subtype assignment can be done on a biopsy, in which case it need not be repeated on the hysterectomy specimen. When performed, these molecular classifications should be recorded in all stages.

- Good prognosis: pathogenic *POLEmut*
- Intermediate prognosis: MMRd/microsatellite instability and NSMP
- Poor prognosis: p53abn When the molecular classification is known:
- FIGO Stages I and II are based on surgical/anatomical and histological findings. In case the molecular classification reveals *POLEmut* or p53abn status, the FIGO stage is modified in the early stage of the disease. This is depicted in the FIGO stage by the addition of "m" for molecular classification, and a subscript is added to denote *POLEmut* or p53abn status, as shown below. MMRd or NSMP status do not modify early FIGO stages; however, these molecular classifications should be recorded for the purpose of data collection. When molecular classification reveals MMRd or NSMP, it should be recorded as Stage Im_{MMRd} or Stage Im_{NSMP} and Stage IIm_{MMRd} or Stage IIm_{NSMP}.
- FIGO Stages III and IV are based on surgical/anatomical findings. The stage category is not modified by molecular classification; however, the molecular classification should be recorded if known. When the molecular classification is known, it should be recorded as Stage IIIm or Stage IVm with the appropriate subscript for the purpose of data collection. For example, when molecular classification reveals p53abn, it should be recorded as Stage $IIIm_{p53abn}$ or Stage IVm_{p53abn}.

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Recommendations

- Histopathologic tumor type and grade in endometrial biopsy is required (IV, A).
- Pre-operative mandatory work-up includes: family history; general assessment and inventory of co-morbidities; geriatric assessment, if appropriate; clinical examination, including pelvic examination; expert transvaginal or transrectal ultrasound or pelvic MRI (IV, C).
- Depending on clinical and pathologic risk, additional imaging modalities (thoracic, abdominal and pelvic CT scan, MRI, PET scan, or ultrasound) should be considered to assess ovarian, nodal, peritoneal, and other sites of metastatic disease (IV, C).

Concin N, et al. Int J Gynecol Cancer 2021;**31**:12–39

EARLY STAGE DISEASE

Surgical management of apparent stage I/II endometrial carcinomas

Minimally invasive approach

Two randomized prospective studies comparing minimally invasive with open surgeries showed similar survival with quicker recovery with the minimally invasive approach.[104 105] More recently, pooled analyses of randomized prospective studies including, notably, these two studies and multiple retrospective and prospective studies also support the use of minimally invasive surgery for patients including those with high-risk endometrial carcinoma.[106–171]

Recommendations

- Minimally invasive surgery is the preferred surgical approach, including patients with high-risk endometrial carcinoma (I, A).
- Any intra-peritoneal tumor spillage, including tumor rupture or morcellation (including in a bag), should be avoided (III, B).
- If vaginal extraction risks uterine rupture, other measures should be taken (eg, mini-laparotomy, use of endobag) (III, B).
- Tumors with metastases outside the uterus and cervix (excluding lymph node metastases) are relative contra-indications for minimally invasive surgery (III, B).

ESGO Guidelines and Quality Indicators

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Recommendations

- Standard surgery is total hysterectomy with bilateral salpingo-oophorectomy without vaginal cuff resection (II, A).
- Staging infracolic omentectomy should be performed in clinical stage I serous endometrial carcinoma, carcinosarcoma, and undifferentiated carcinoma. It can be omitted in clear cell and endometrioid carcinoma in stage I disease (IV, B).
- Surgical re-staging can be considered in previously incompletely staged patients with high– intermediate-risk/high-risk disease if the outcome might have an implication for adjuvant treatment strategy (IV, B).
- If sentinel lymph node biopsy is performed (II, A):
  - Indocyanine green with cervical injection is the preferred detection technique.
  - Tracer re-injection is an option if sentinel lymph node is not visualized upfront.
  - Side-specific systematic lymphadenectomy should be performed in high–intermediate-risk/high-risk patients if sentinel lymph node is not detected on either pelvic side.
  - Pathologic ultrastaging of sentinel lymph nodes is recommended.
- When a systematic lymphadenectomy is performed, pelvic and para-aortic infrarenal lymph node dissection is suggested (III, B).
- Presence of both macrometastases and micrometastases (<2 mm, pN1(mi)) is regarded as a metastatic involvement (IV, C).
- The prognostic significance of ITCs, pN0(i+), is still uncertain (IV, C).
- If pelvic lymph node involvement is found intra-operatively, further systematic pelvic lymph node dissection should be omitted. However, debulking of enlarged lymph nodes and para-aortic staging can be considered (IV, B).

Concin N, et al. Int J Gynecol Cancer 2021;**31**:12–39

ESGO Guidelines and Quality Indicators

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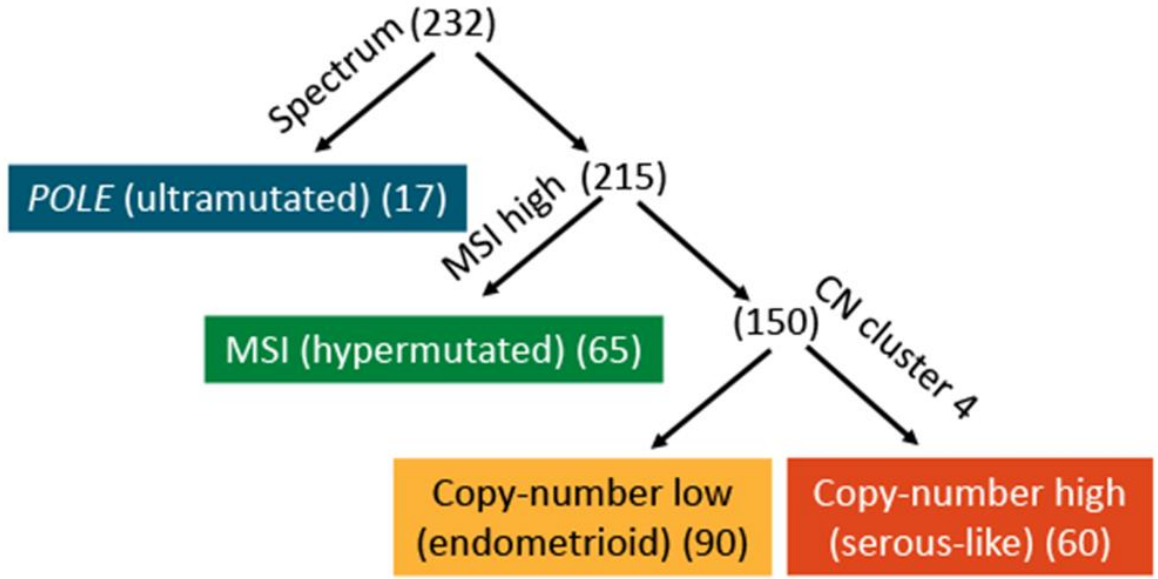
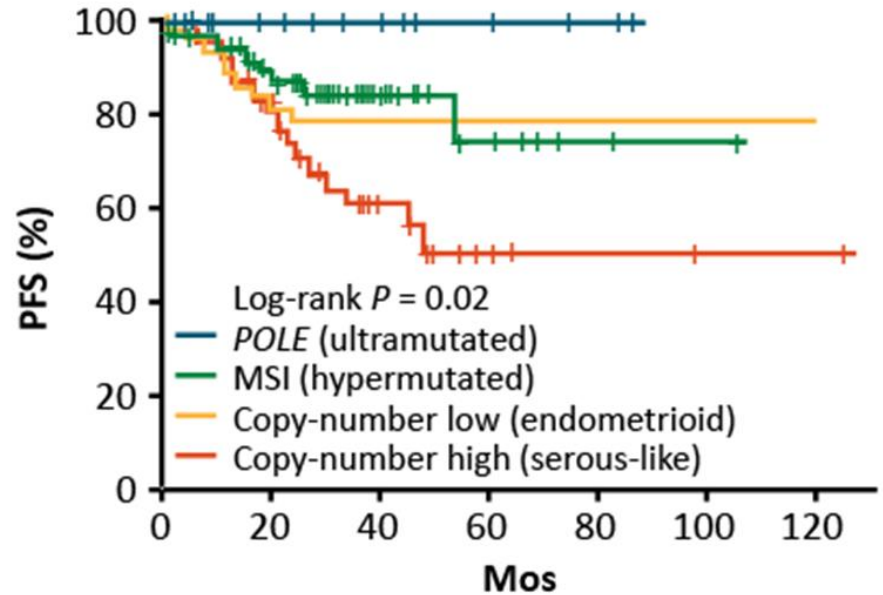
The "Modern" Molecular Classification: TCGA Classification





- **POLE (ultramutated malignancies):**
  - Their hallmark are mutations in the exonuclease domain of POLE
  - POLE encodes the catalytic subunit of DNA polymerase epsilon which plays a relevant role in DNA repair.
- **MSI-High: Tumors that harbor a high rate of mutations resulting from impaired DNA MMR pathway:**
  - A DNA repair system that corrects errors such as single-base mismatches or short insertions and deletions that spontaneously occur during DNA replications
  - The most implicated genes are: MLH1, MSH2, MSH6, PMS2

Cancer Genome Atlas Research Network. Nature. 2013;497:67.

Slide credit: clinicaloptions.com

- **Leiden/PORTEC group**: *όλα τα δείγματα εξετάστηκαν για όλους τους μοριακούς δείκτες => δείγματα που ανήκουν σε περισσότερες από μία ομάδες: multiple classifiers*
- **Vancouver/ProMisE group**: *τα δείγματα εξετάστηκαν σταδιακά*
- Επικύρωσαν την προγνωστική αξία της μοριακής ταξινόμησης καθιστώντας την κλινικά εφαρμόσιμη με τη χρήση «υποκατάστατων/surrogates»
- Ανοσοϊστοχημική ανίχνευση των πρωτεϊνών mismatch repair (MMR) proteins και του p53
- surrogate για την POLE sequencing δεν υπάρχει μέχρι στιγμής

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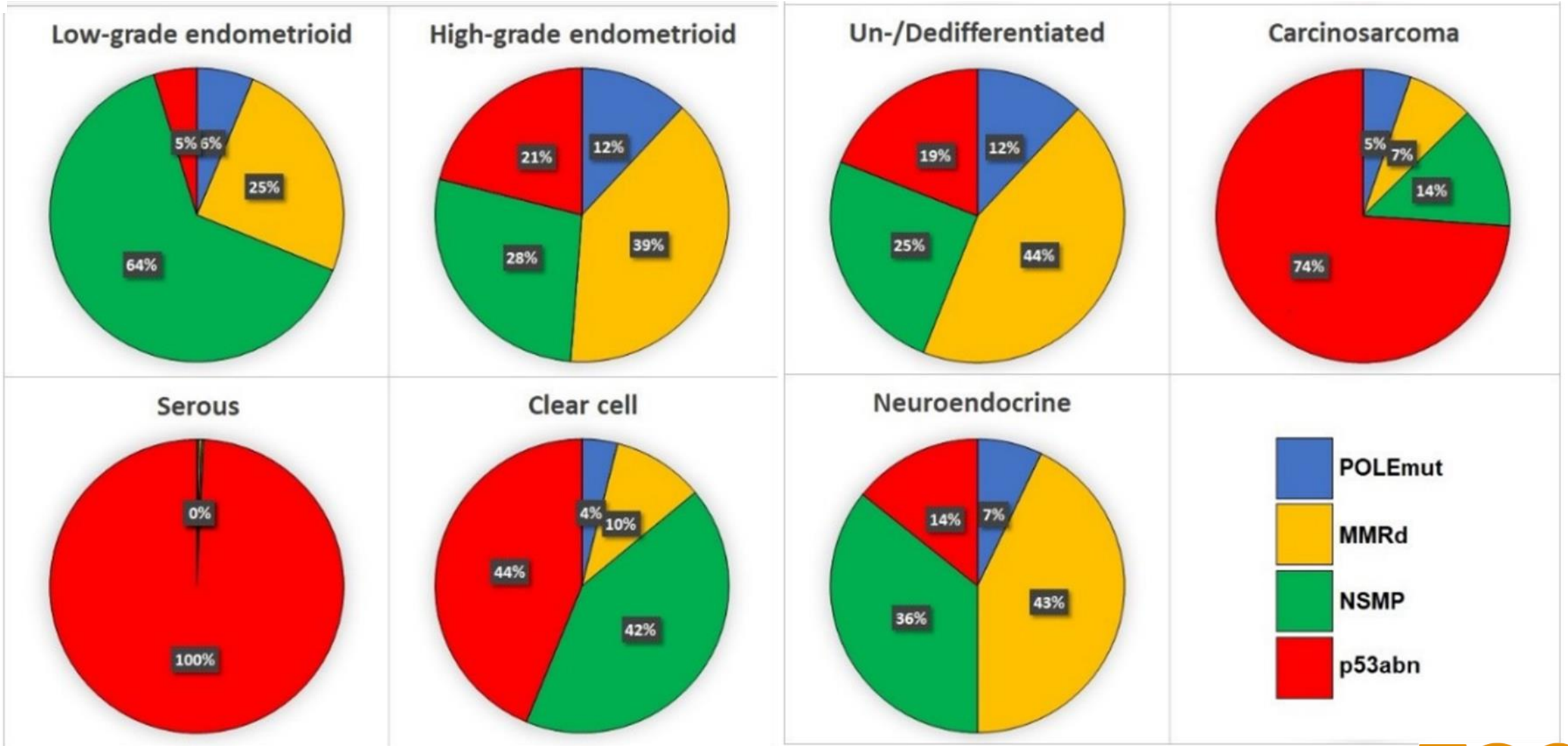

Cancers **2021**, 13, 2623. https://doi.org/10.3390/cancers13112623

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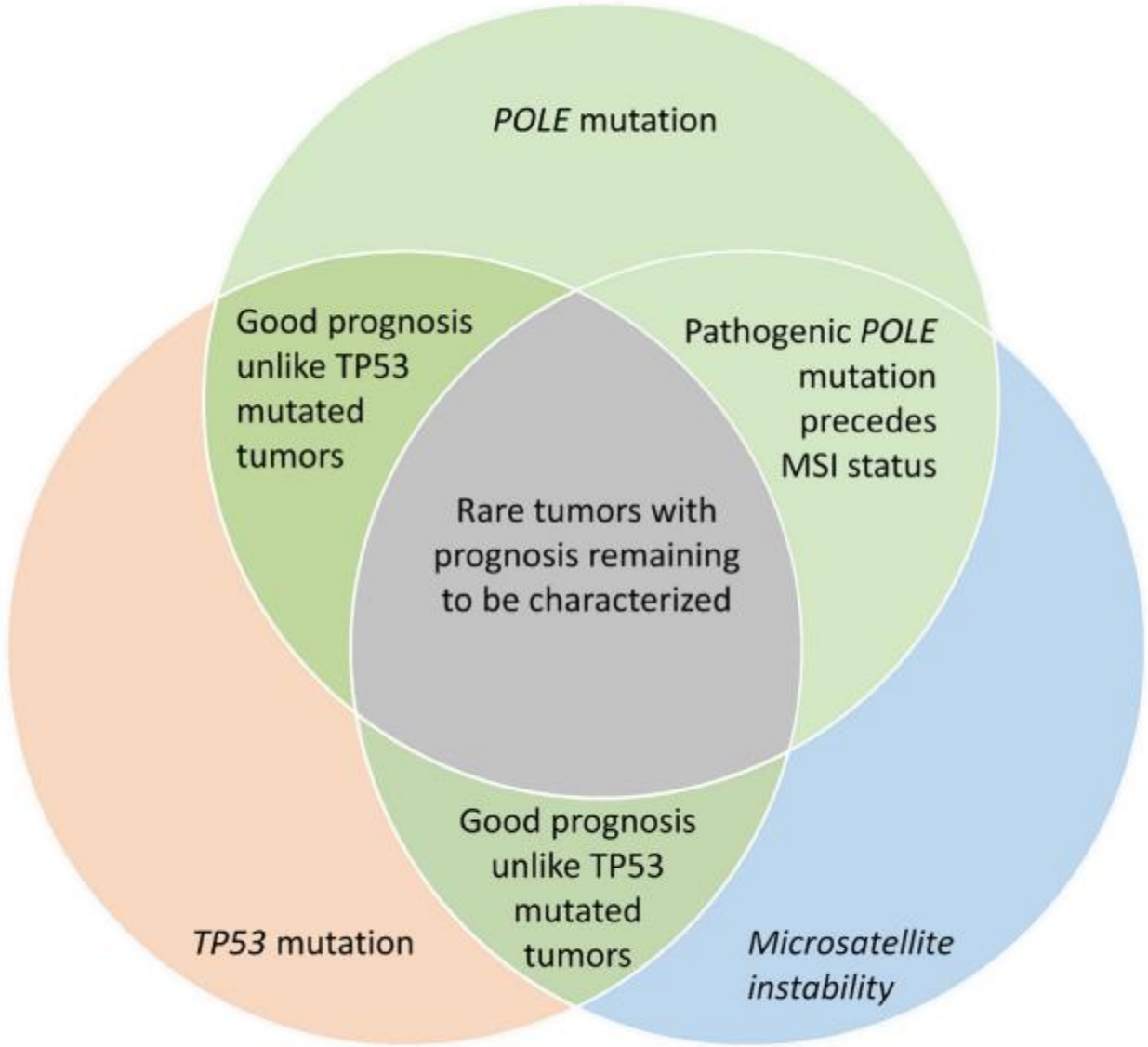
‘multiple classifier’ ενδομητρικά καρκινώματα:

Καρκινώματα με >από 1 μοριακό τύπο=>
POLEmut+MMRd, POLEmut+TP53 mutation, MMRd+TP53 mutation

Δευτερογενείς/όψιμες μεταλλάξεις: Subclonal MMRd κυρίως επί υπερμεθυλίωσης του MLH1 subclonal p53=>passenger mutation



Surgical Pathology 15 (2022) 277–299

Leon-Castillo et al. J Pathol 2020; 250: 312–322

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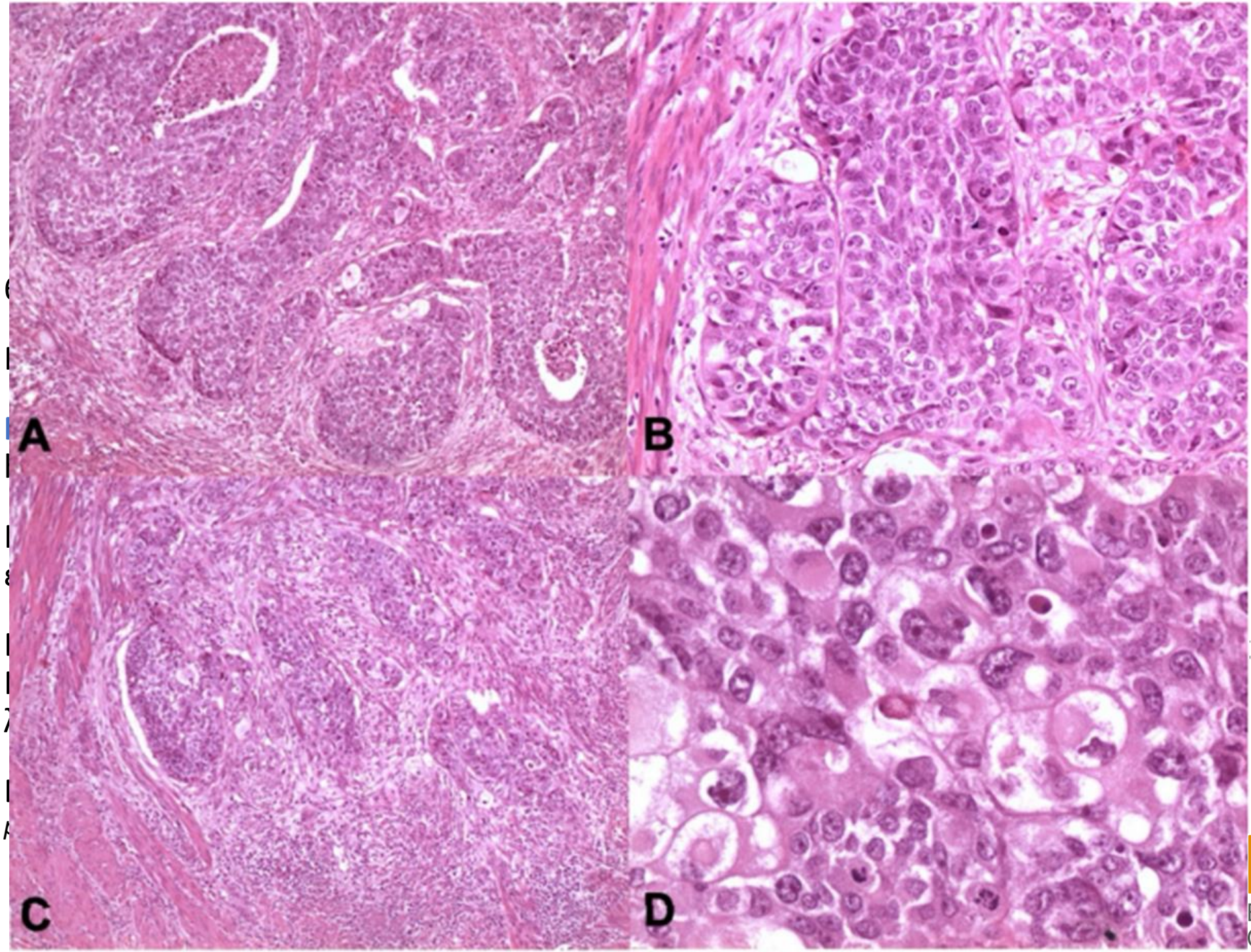

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- **Lync**
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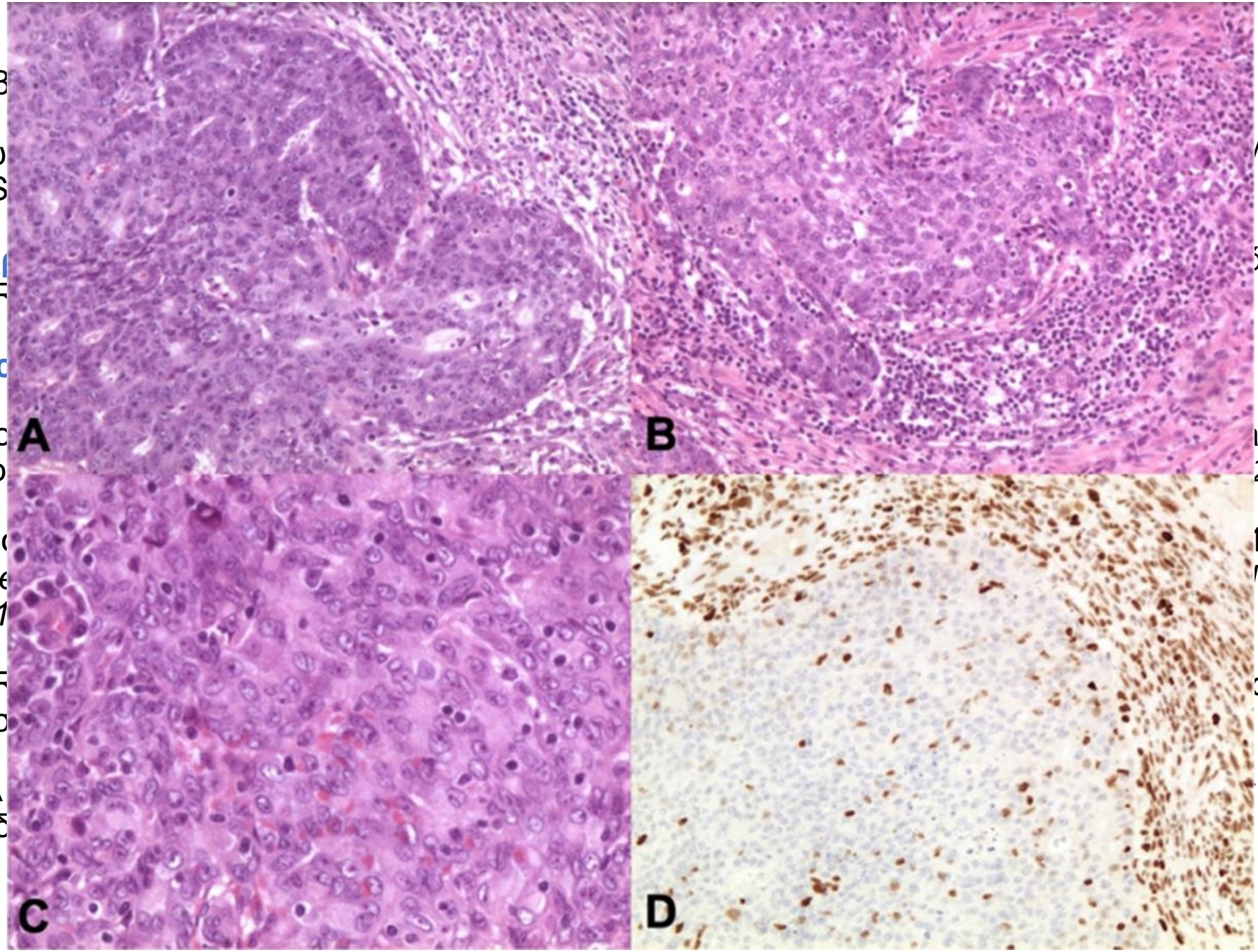

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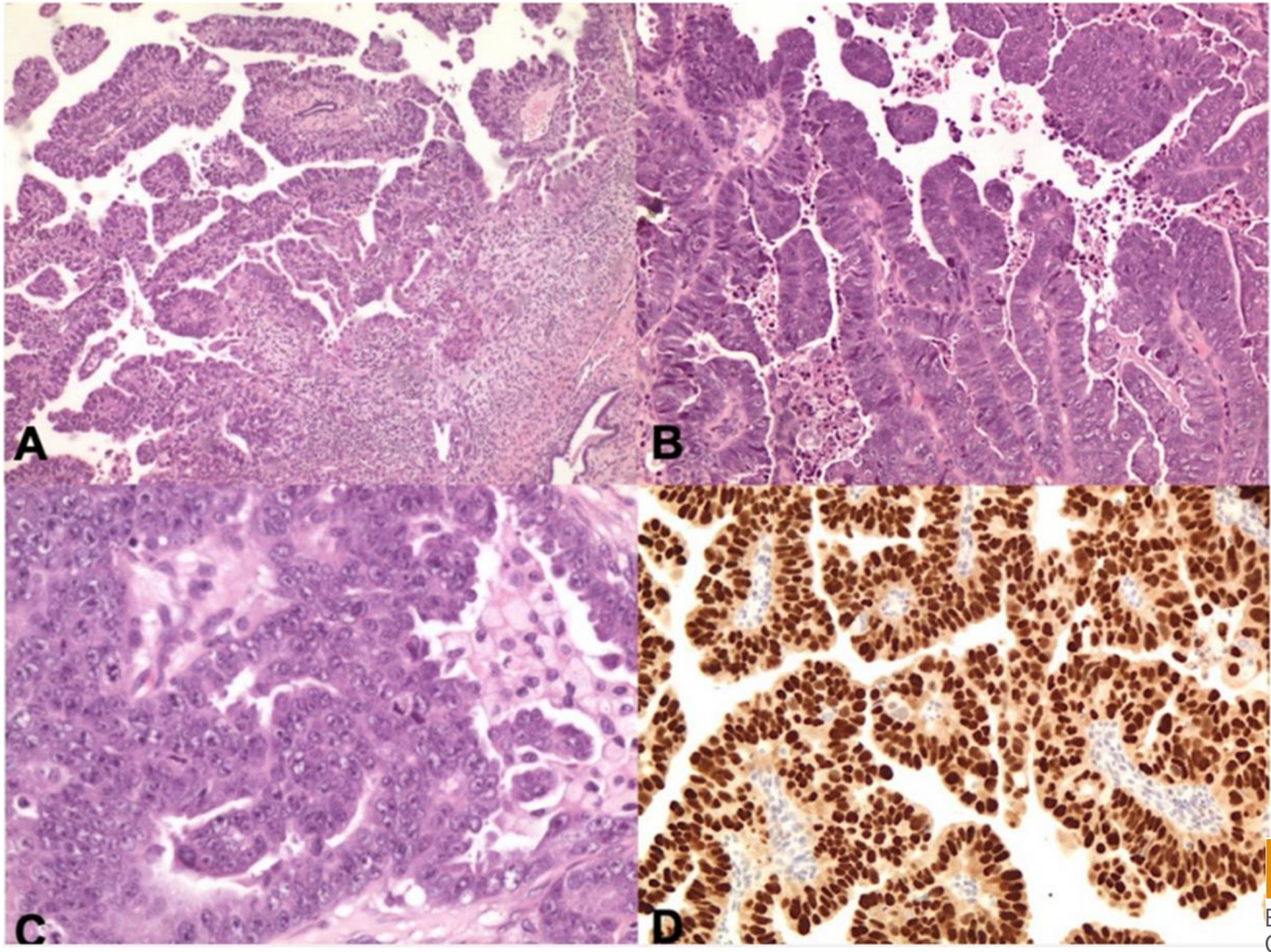

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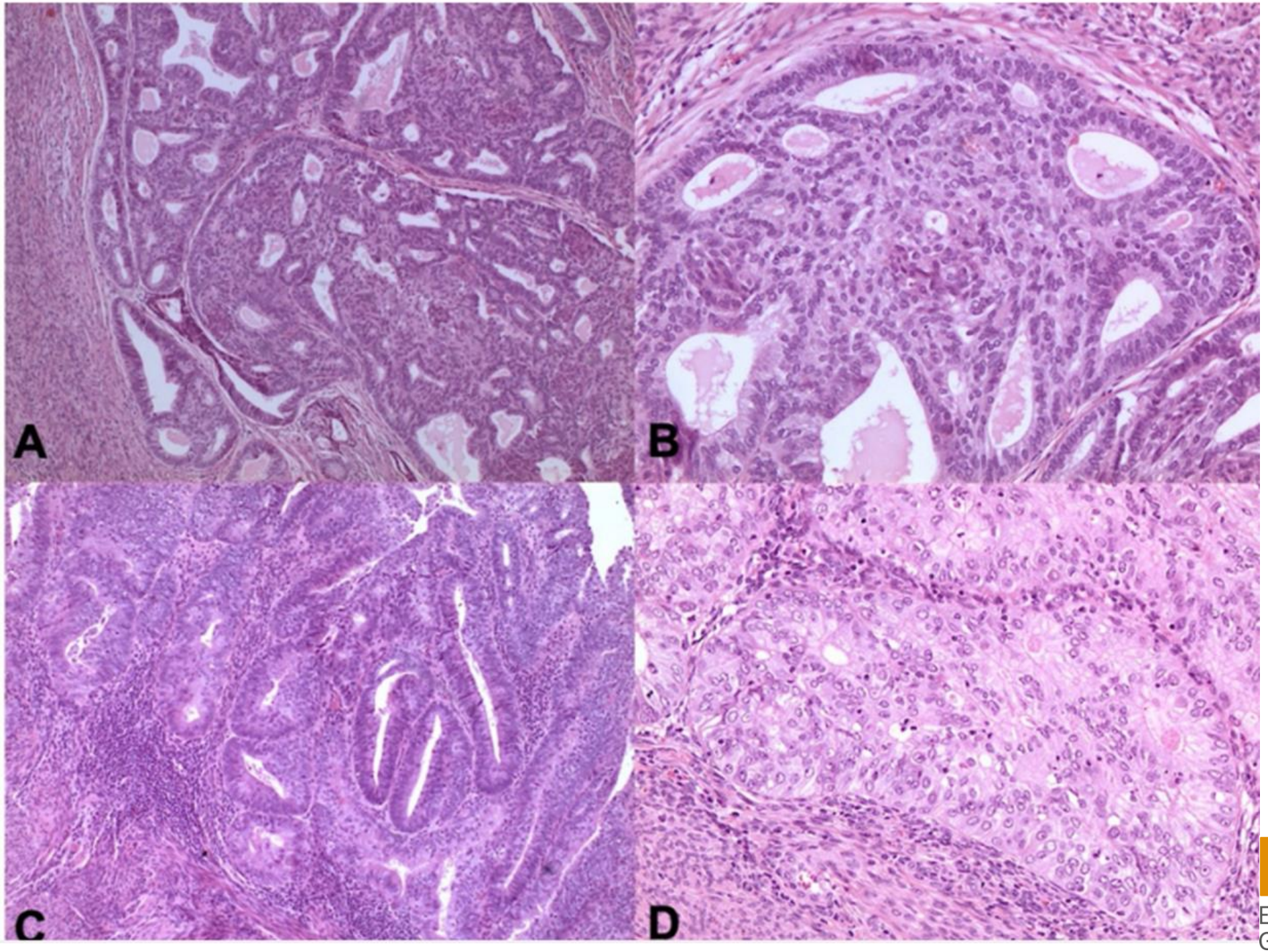

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Ιστολογικός τύπος

Μη επιθετικός

- Ανώτερης/μέτριας διαφοροποίησης ενδομητριοειδές καρκίνωμα (G1,2)

Επιθετικός

- Χαμηλής διαφοροποίησης ενδομητριοειδές καρκίνωμα (G3)
- Μη ενδομητριοειδής ιστότυπος:

Ορώδες/διαυγοκυτταρικό/καρκινοσάρκωμα/αδιαφοροποίητο/μεσονεφρικού τύπου/γαστρικού τύπου

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Μη επιθετικός ιστολογικός τύπος

- Ενδοβλεννογονική ανάπτυξη **IA1**
- Διήθηση <50% του μυομητρίου **IA2**
- Αν πληρούνται τα κριτήρια «σύγχρονης» ανάπτυξης στην ωοθήκη **IA3**
- Διήθηση >50% του μυομητρίου **IB**
- Διήθηση στρώματος τραχήλου **IIA**
- Ικανός αριθμός εμβόλων (LVSI>5) **IIB**

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Επιθετικός ιστολογικός τύπος

Ενδοβλεννογονική ανάπτυξη **IC**

Διήθηση σε μυομήτριο/στρώμα τραχήλου **IIC**

Τα στάδια III και IV δεν επηρεάζονται από τη μοριακή ταξινόμηση ή τον ιστολογικό τύπο

Στάδιο III

- Διήθηση εξαρτημάτων **IIIA1**
- Ορογόνου/υποορογόνιου **IIIA2**
- Κόλπου/παραμητρίων **IIIB1**
- Πυελικού περιτοναίου **IIIB2**
- Λεμφαδένων πυελικών **IIIC1(i/ii)**
- Λεμφαδένων παραορτικών **IIIC2(i/ii)**

Στάδιο IV

- Διήθηση ουροδόχου/βλεννογόνου εντέρου **IVA**
- Εξωπυελικό περιτόναιο/επίπλουν **IVB**
- Απομακρυσμένη **IVC**

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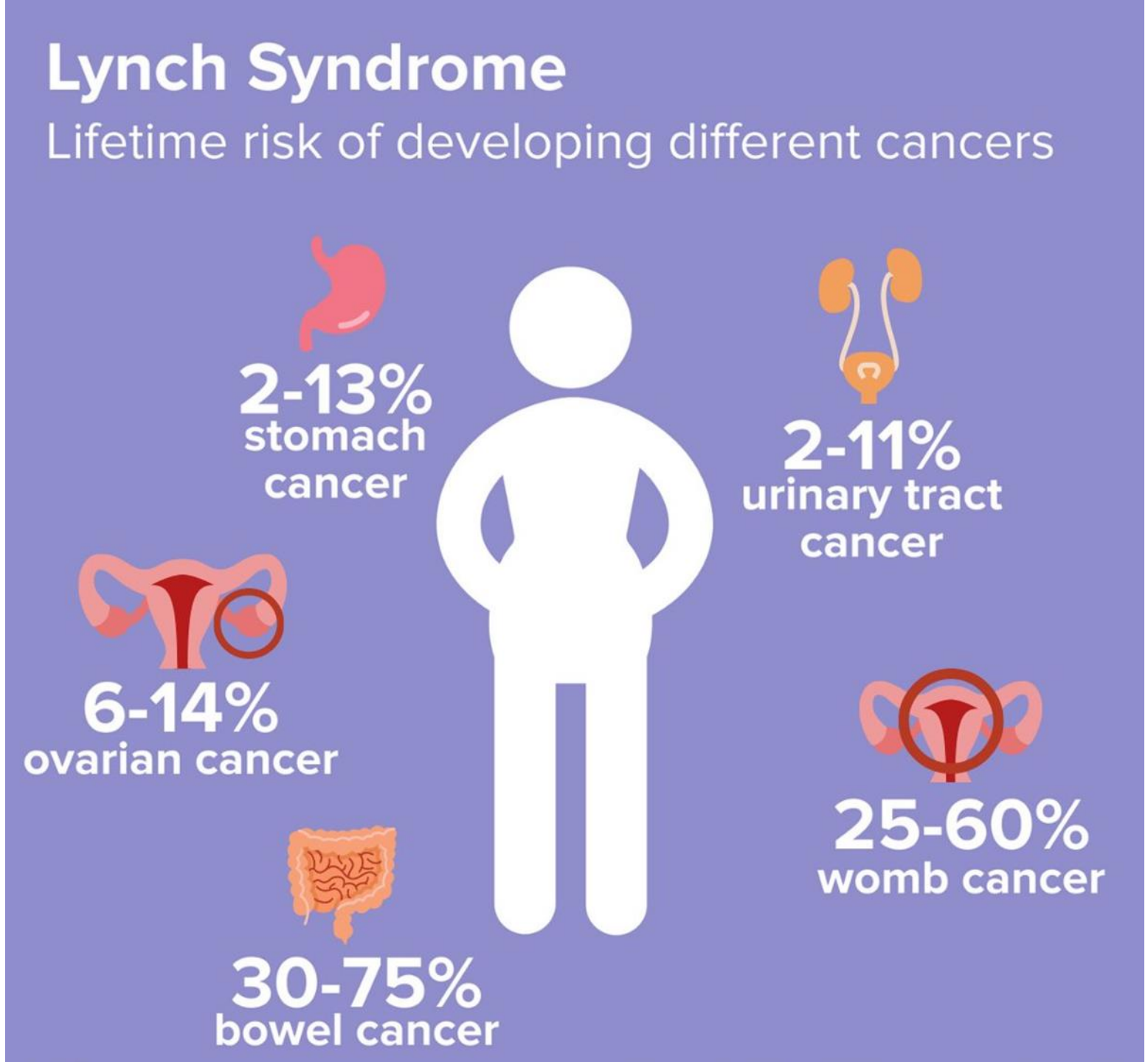
Για τα στάδια I και II

- **Αν POLE μεταλλάξεις=>IAm**
- **Επί απουσίας POLE & MMRd αν p53 μετάλλαξη=>IICm**



Original research

ESGO/ESHRE/ESGE Guidelines for the fertility-sparing treatment of patients with endometrial carcinoma

Alexandros Rodolakis ,[1] Giovanni Scambia ,[2] François Planchamp ,[3] Maribel Acien ,[4] Attilio Di Spiezio Sardo,[5] Martin Farrugia,[6] Michael Grynberg,[7,8,9] Maja Pakiz ,[10] Kitty Pavlakis,[11,12] Nathalie Vermeulen,[13] Gianfranco Zannoni ,[14] Ignacio Zapardiel ,[15] Kirsten Louise Tryde Macklon[16]

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- Patients with a pregnancy wish should be referred to specialized care, especially those with genetic syndrome (Level of evidence V, grade A).
- Joint care and counseling with a multidisciplinary team of at least gynecologic oncologists, fertility specialists, pathologists, and radiologists should be proposed to all patients with a pregnancy wish (Level of evidence V, grade A).

Review of Initial Pathology by an Experienced Histopathologist

- A request for a second opinion by an experienced histopathologist is recommended if fertility-sparing treatment is considered (Level of evidence III, grade A).
- The G1, G2, G3 grading system is recommended. The binary grading system for endometrial carcinoma should not be used for these patients (Level of evidence III, grade A).
- The use of immunohistochemistry (PTEN, ARID1A, etc) for the evaluation of several biomarkers is not recommended for diagnostic purposes (Level of evidence IV, grade D).

Differentiation of the Tumor

- Fertility-sparing treatment is considered for endometrioid patients with endometrial carcinoma with grade 1, stage IA without myometrial invasion and without risk factors (Level of evidence V, grade A).
- Evidence for grade 2 endometrioid endometrial carcinoma is limited. Therefore fertility-sparing treatment should be discussed on a case-by-case basis (Level of evidence IV, grade C).

Establishing a Reliable Histopathology

- Hysteroscopic guided endometrial biopsy is preferred over blind biopsy for confirming diagnosis of endometrial carcinoma (Level of evidence III, grade A).

Rodolakis et al., Int J Gynecol Cancer 2023;33:208-222

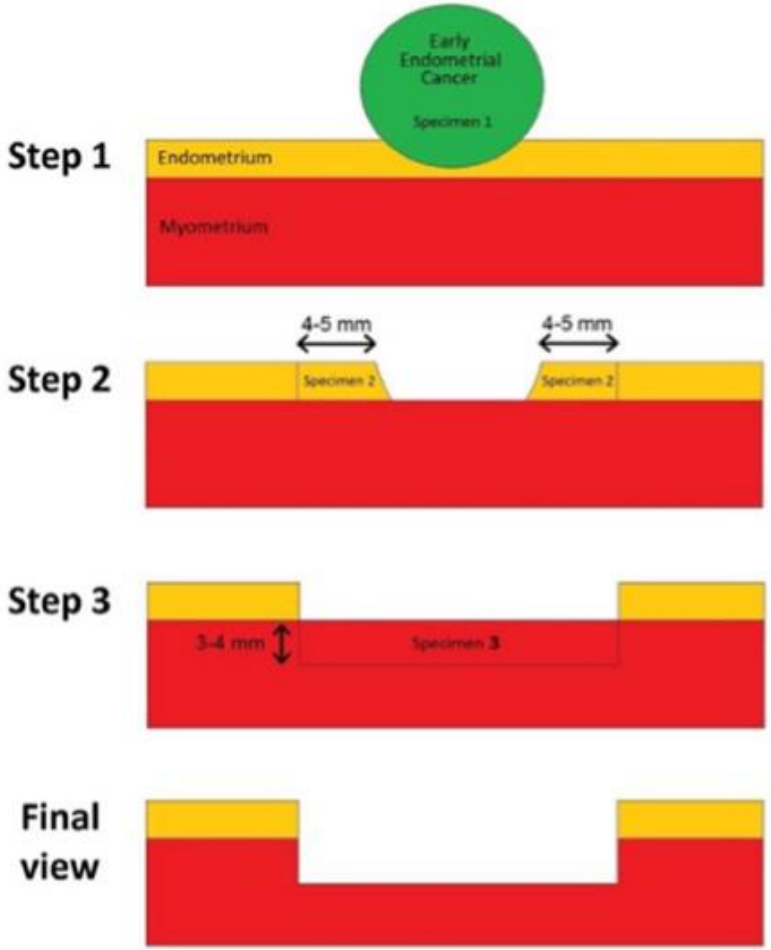

Figure 4 Schematic representation of hysteroscopic resection of focal endometrial endometrioid carcinoma following the 'three steps' technique.

Myometrial Invasion

- Pre-operative assessment of myometrial invasion in patients with endometrial carcinoma should be performed using MRI or transvaginal ultrasound by a specialized radiologist/sonographer. Standardized high-quality protocols for MRI should be used to reach the highest possible accuracy (Level of evidence III, grade A).

Exclude Extra-Uterine Disease/Synchronous or metastatic

- MRI or CT scan is recommended for detecting pelvic or para-aortic lymph nodes and distant metastases (Level of evidence II, grade B).
- Adnexal involvement should be ruled out by pelvic MRI or transvaginal ultrasound (Level of evidence II, B).
- CT should not be used for pre-operative assessment of myometrial invasion in patients with endometrial carcinoma (Level of evidence III, grade A).

Rodolakis et al., Int J Gynecol Cancer 2023;33:208-222

Selection of Medication

- A combined approach consisting of hysteroscopic tumor resection, followed by oral progestins and/or levonorgestrel-intra-uterine device, is the most effective fertility-sparing treatment both for complete response rate and live birth rate compared with other treatment options (Level of evidence II, grade B).
- Gonadotropin-releasing hormone analogs should not be considered as a first-line treatment (Level of evidence II, grade B).

The Role of Hysteroscopic Resection

- If an early and focal myometrial invasion (1–2 mm) is suspected from the resection material, a fertility-sparing approach may be discussed on a case-by-case basis. In this circumstance, complete hysteroscopic lesion resection, followed by oral progestins and/or levonorgestrel-intra-uterine device, can be proposed as fertility-sparing treatment (Level of evidence IV, grade C).

Dose of Progestins

- Orally administered megestrol acetate at a dose of 160–320 mg/day or medroxyprogesterone acetate at a dose of 400–600 mg/day is recommended (Level of evidence III, grade B).
- A levonorgestrel-intra-uterine device at a dose of 52 mg, alone or in combination with oral progestins, is a safe and effective approach (Level of evidence III, grade B).

Duration of Treatment

- The recommended duration of therapy is 6–12 months, within which a complete response should be achieved (Level of evidence III, grade B).
- The maximum time to achieve complete response should not exceed 15 months (Level of evidence IV, grade C).
- In the absence of any kind of response at 6 months, multidisciplinary counseling is recommended for adapting the management on a case-by-case basis (Level of evidence IV, grade B).

Response (Partial vs Complete vs No Response)

- Hysteroscopic resection followed by progestins either by oral and/or intra-uterine device administration is recommended to achieve both the highest complete response rate and the highest live birth rate (Level of evidence II, grade B).
- Weight control during fertility-sparing treatment is highly recommended to increase the chance of response (Level of evidence II, grade A).

Follow-up with Maintenance Treatment for Patients Willing or Not Willing to Conceive Immediately

- Two consecutive endometrial biopsies showing complete response with a minimal interval of 3 months are necessary to consider the success of the fertility-sparing treatment (Level of evidence IV, grade C).
- The complete response is mandatory to consider follow-up with maintenance treatment until pregnancy is planned (Level of evidence II, grade A).
- Clinical pelvic examination and ultrasound scan are recommended at every 3-month follow-up visit (Level of evidence IV, grade B).

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- Endometrial histological assessment should be performed every 3–6 months by hysteroscopy according to the results of imaging (Level of evidence IV, grade B).
- MRI could be considered on a case-by-case basis (Level of evidence IV, grade C).

Recurrence Rate After Fertility-sparing Treatment

- The risk of recurrence after fertility-sparing treatment for endometrial carcinoma may be equal for progestins or a levonorgestrel-intra-uterine device (Level of evidence II, grade B).

Pregnancy

- Women undergoing fertility-sparing treatment for endometrial hyperplasia or endometrial carcinoma should be encouraged to actively aim to conceive as soon as the complete response is achieved (Level of evidence V, grade B).
- Assisted reproductive technology should be considered in order to improve success rate and reduce the interval to conception without a higher risk of recurrence (Level of evidence III, grade B). However, natural conception may be considered in women with good reproductive potential within a defined time (6–9 months) (Level of evidence V, grade C).
- Close surveillance by a multidisciplinary team should be continued and maintenance therapy with a levonorgestrel-intra-uterine device should be recommended to women who decline surgery after delivery and who do not plan their second pregnancy immediately after the first one (Level of evidence III, grade B).

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Definitive and Completion Surgeries

- Definitive surgery is recommended in cases of non-responders, inability to conceive, recurrence or disease progression (Level of evidence II, grade A).
- For patients with a strong desire to preserve fertility, a second conservative approach can be considered on a case-by-case basis (Level of evidence IV, grade B).
- Completion surgery is recommended after completing child-bearing (Level of evidence II, grade A).
- Removal of ovaries should be considered on a case-by-case basis (Level of evidence III, grade B).

Molecular Profiling of Early-onset Endometrial Carcinoma and Correlation with Response to Treatment

- Performing the ProMisE molecular classifier in all young patients with grade 1, low-stage endometrial carcinoma who wish to preserve fertility is encouraged, although available data do not allow clinical applicability (Level of evidence IV, grade B).
- Immunohistochemistry for the identification of mismatch repair-deficient tumors is mandatory in order to identify patients at high risk for Lynch syndrome (Level of evidence III, grade A).
- If a Lynch syndrome is identified, patients should have an appropriate counseling on the risk of developing additional cancers (Level of evidence III, grade A).
- In a tumor with p53abn phenotype, testing for MSH-H and *POLE* mutation should be considered in order to define whether the tumor belongs to the multiple classifiers or to the copy number high molecular subgroup (Level of evidence III, grade A).
- In women harboring copy number high (p53abn) tumors, conservative therapy would be inappropriate (Level of evidence IV, grade D).

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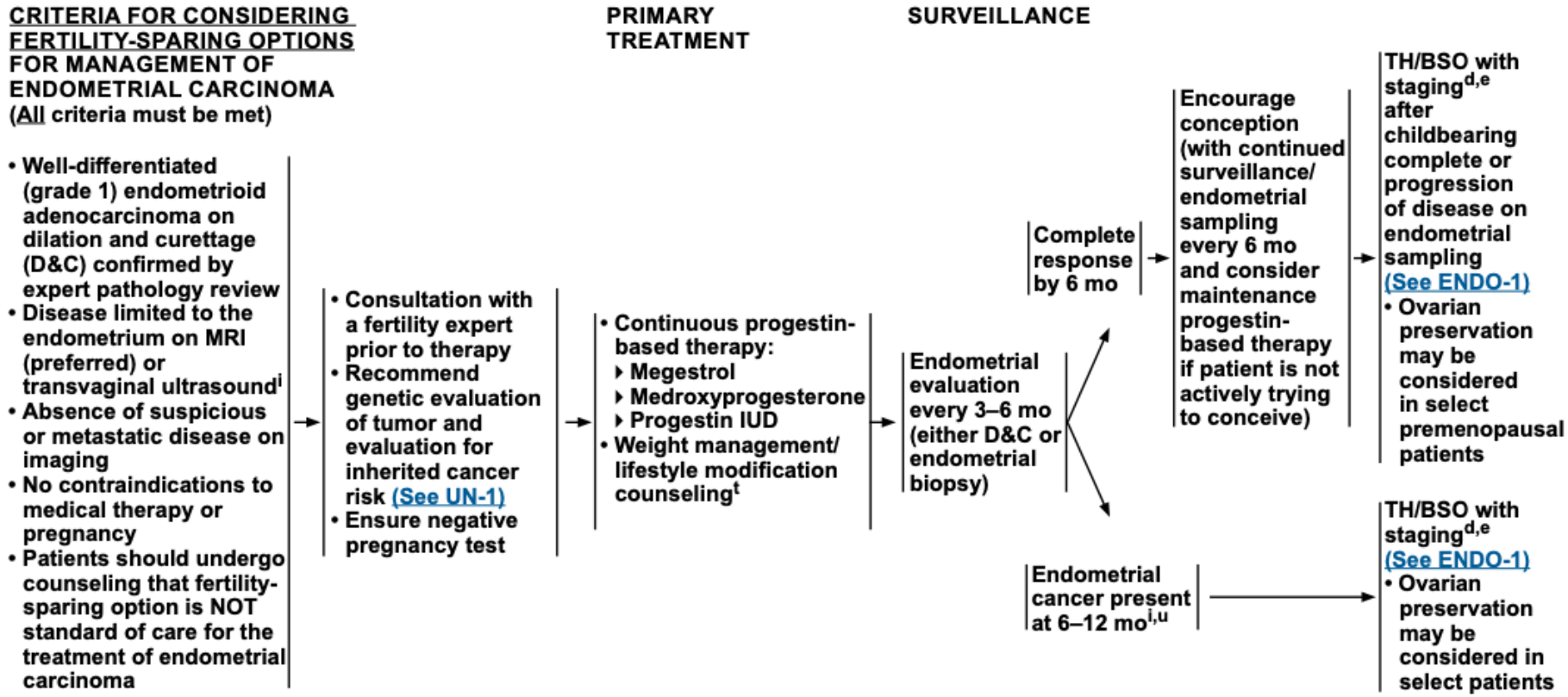

[d] MIS is the preferred approach when technically feasible. See Principles of Evaluation and Surgical Staging (ENDO-C).
[e] The degree of surgical staging to assess disease status depends on intraoperative findings. Multidisciplinary expertise is recommended. See Principles of Evaluation and Surgical Staging (ENDO-C).
[i] See Principles of Imaging (ENDO-B).
[t] See Healthy Lifestyles (HL-1) and Nutrition and Weight Management (SNWM-1) in the NCCN Guidelines for Survivorship.
[u] Gunderson CC, et al. Gynecol Oncol 2012;125:477-482 and Hubbs JL, et al. Obstet Gynecol 2013;121:1172-1180.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

„The talk and the relationship with the patient is the most relevant drug in medicine!“

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