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REVIEW ARTICLE

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Endometrial Cancer

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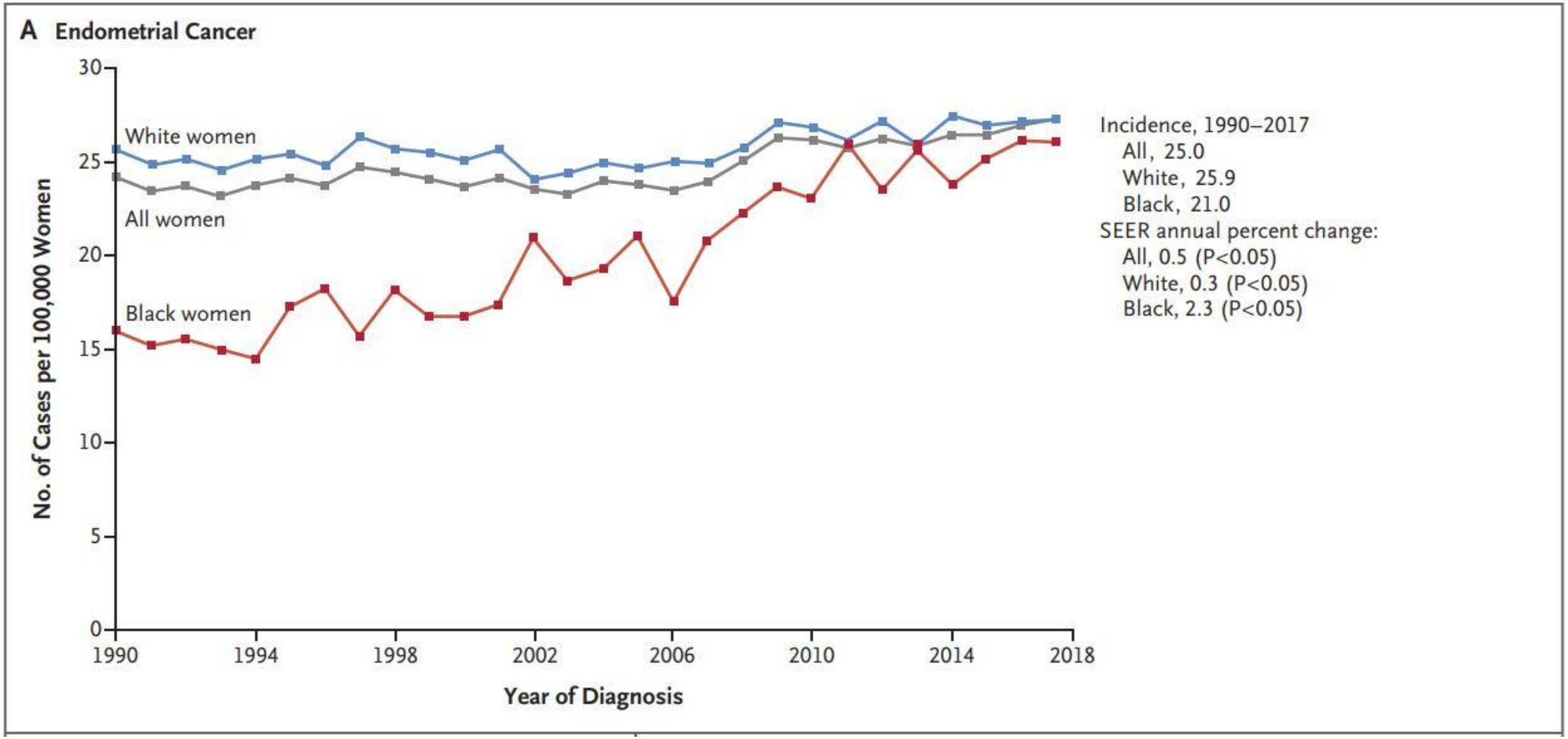
Outline

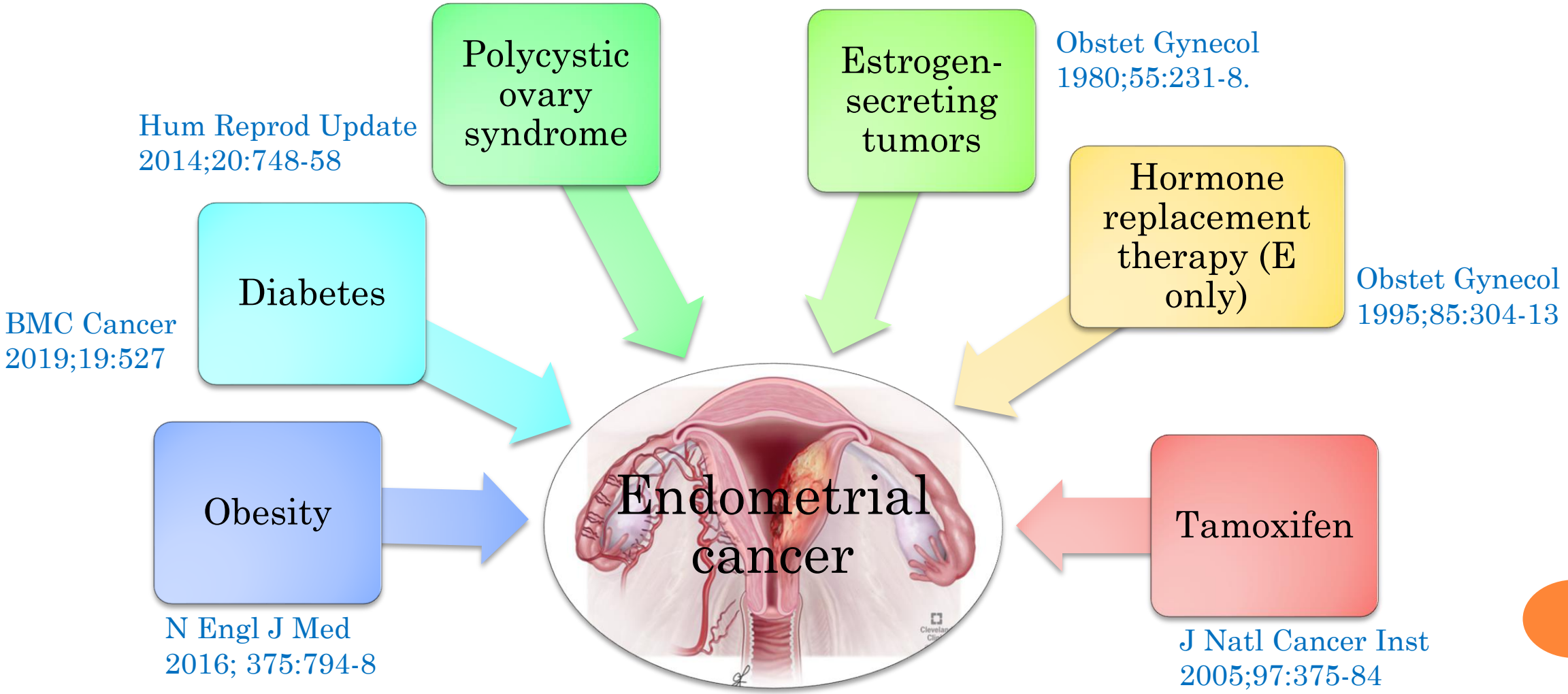
- Epidemiology and Preventive Options
- Pathological Features
- Molecular Characterization
- Surgical Management and Staging
- Adjuvant Therapy for Early-stage Disease
- Adjuvant Therapy for Node-positive Disease
- Therapeutics for Advanced and Recurrent Disease
- Future Directions

Epidemiology and Preventive Options

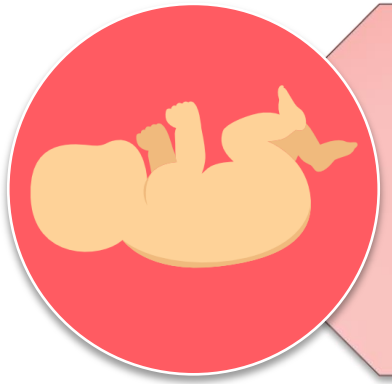
UNLIKE MOST CANCERS, **ENDOMETRIAL CANCER** IS **RISING** IN BOTH INCIDENCE AND MORTALITY.



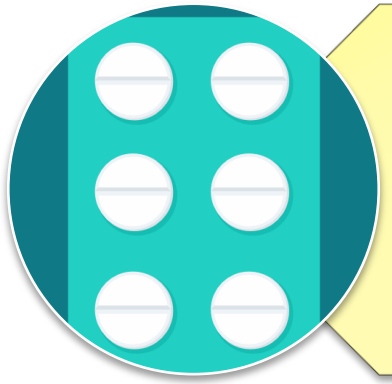
Risk factors



Protective factors



↑Parity ↓Risk

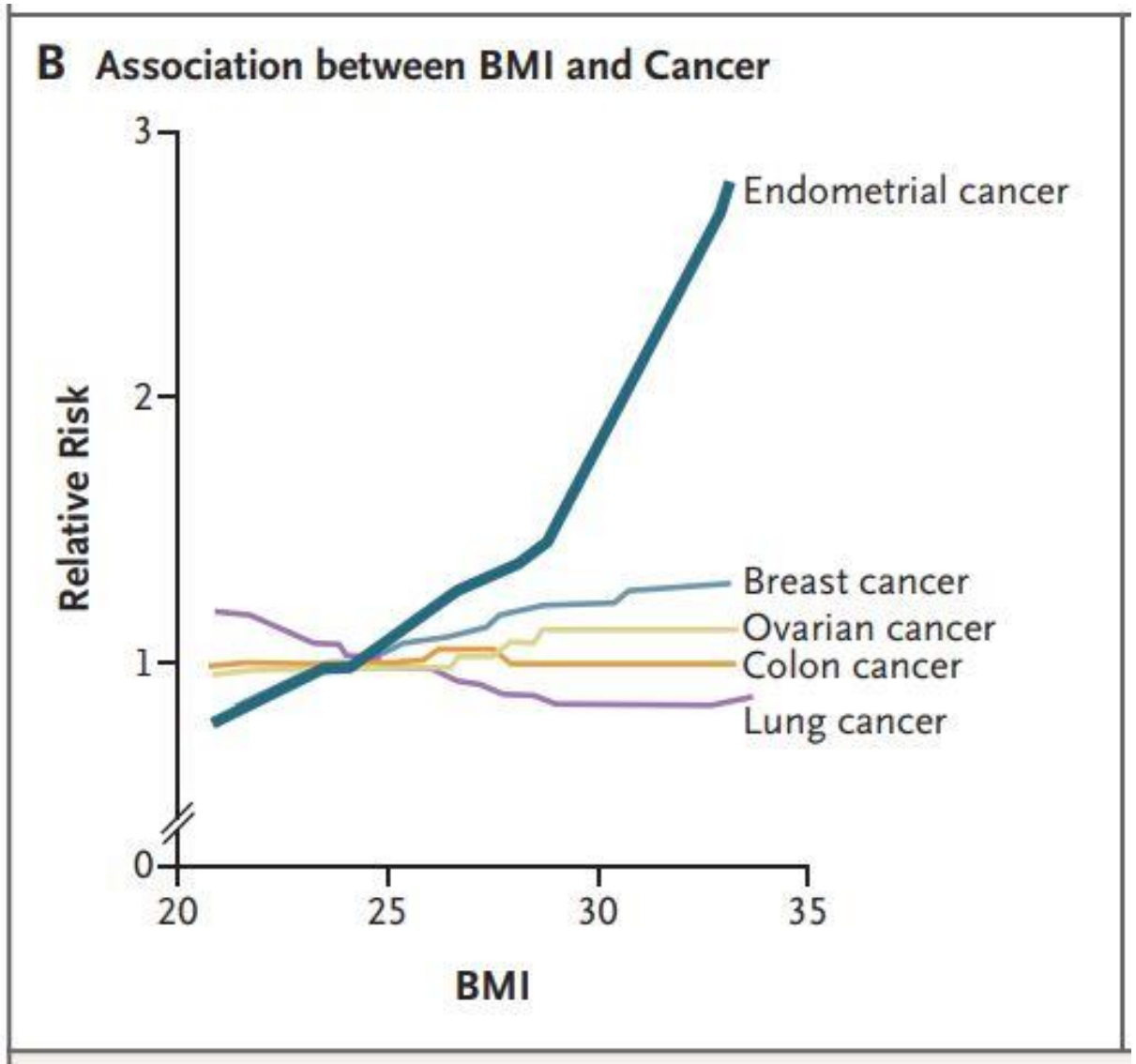


Oral contraceptives ↓Risk by 30~40%

↑Use ↑ Protection (decades after cessation)

Lancet Oncol 2015;16:1061-70

ENDOMETRIAL CANCER HAS THE STRONGEST ASSOCIATION WITH **OBESITY**.



- 57 % of EM cancer in the US → Obesity
- Women with normal BMI: 3% lifetime risk
- **BMI ↑ 5 →** EM cancer **risk ↑ > 50%**

Lancet 2014;384:755-65
Lancet 2008;371:569-78

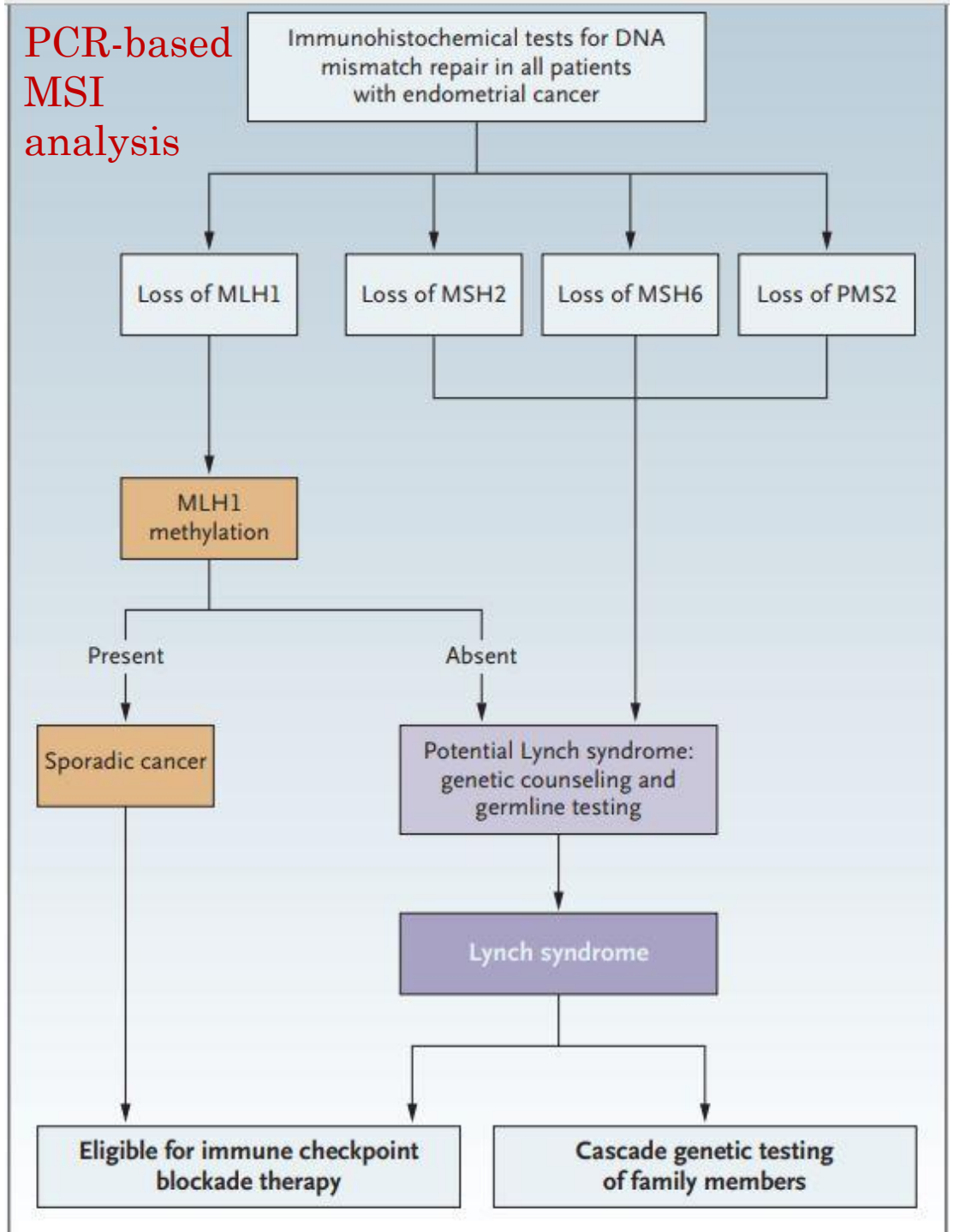
Fertility-sparing options in young obese patients with endometrial cancer

- Anovulation →↑ estrogen ↓progestin → overstimulation of the endometrium → Development of precancer: Complex Atypical Hyperplasia or early EM cancer

Complete response rate	CAH	Endometrial cancer
Oral progestin	65.8% (Recurrence: 23.2%)	48.2% (Recurrence: 35.4%)
Progestin-containing IUD	91%	54%

- If higher-grade tumors or with myometrium invasion → Hysterectomy

PCR-based MSI analysis



Lynch syndrome: germline mutation in an MLH1 or MSH2 mismatch-repair gene

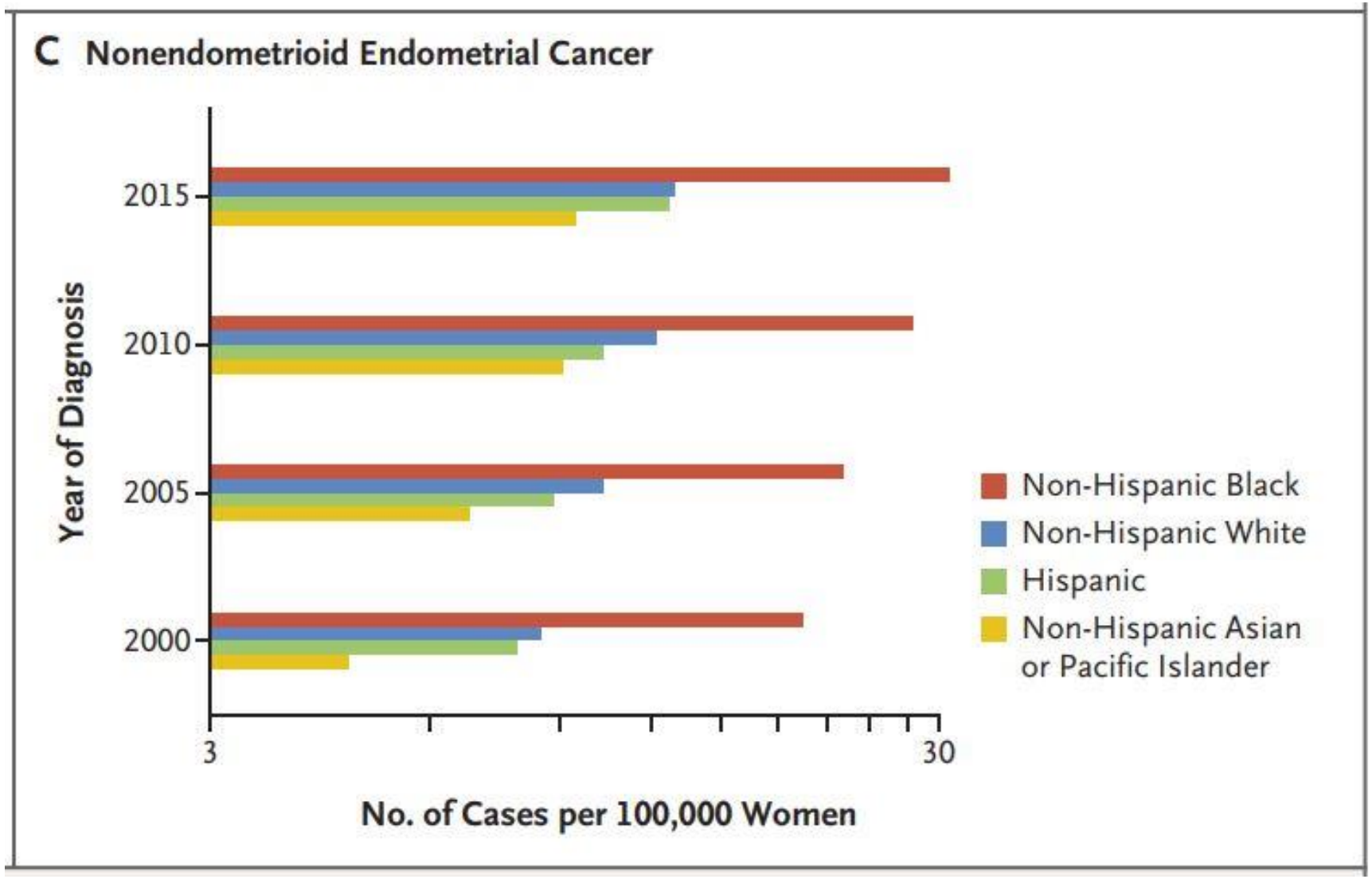
→ Lifetime EM cancer risk: 40~60%

(Median onset age: 48, younger than onset age of general population: 63)

- 3% in all EM cancer patients
- 9% in EM cancer patients under age 50
- **Immune checkpoint blockade** → advanced disease with high MSI (microsatellite instability)
- Colon cancer ↑
- Genetic counseling for family members → hysterectomy as a preventive option

MSH6 germline mutations: (Median onset age: 53)

Higher rate of increase among **Black women** of tumors with **higher grade, nonendometrioid** type, and **later stage**

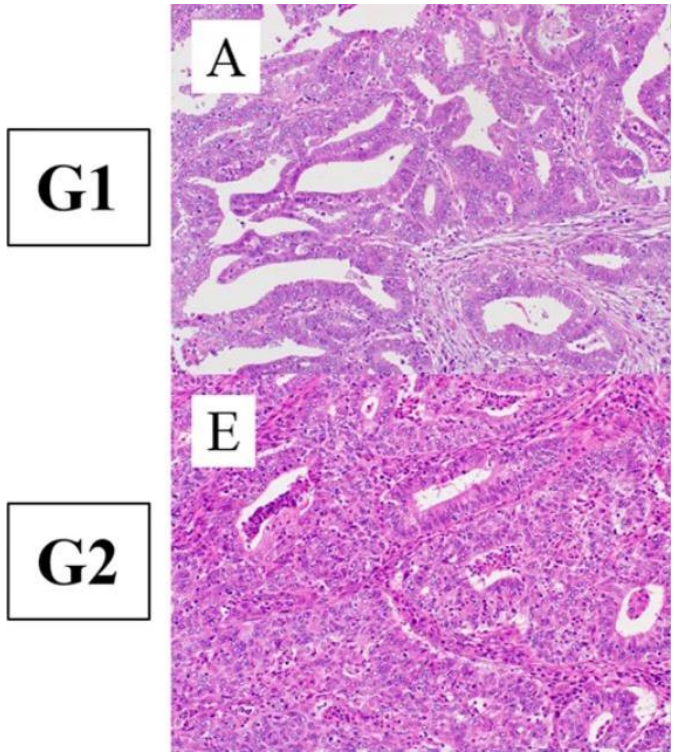


Pathological Features

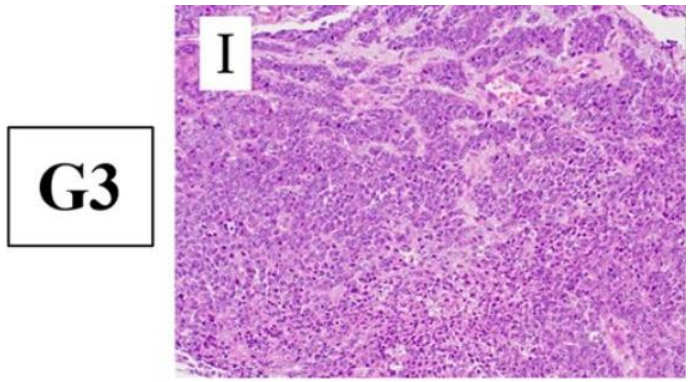
	Endometrioid	Nonendometrioid
Prevalence in EM cancer patients	80%	20% (older, postmenopausal women)
Precursor	Endometrial CAH with epithelial atypia	No known precursor lesions
Risk factors	Relative estrogen excess: obesity, unopposed E in HRT, estrogen-secreting tumor (ovarian granulosa-cell tumor)	Hormone-independent

Endometrioid carcinoma FIGO Grading

- Relative proportions of the glandular and solid-tumor components



Solid-tumor component:
Grade 1: < 6%
Grade 2: 6~ 50%
Low grade → good prognosis

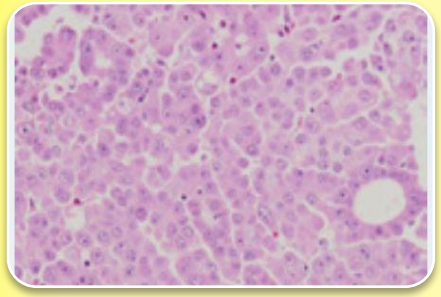


Grade 3: > 50%
High grade → Intermediate-to-poor prognosis

Mod Pathol 32, 1023–1031 (2019).

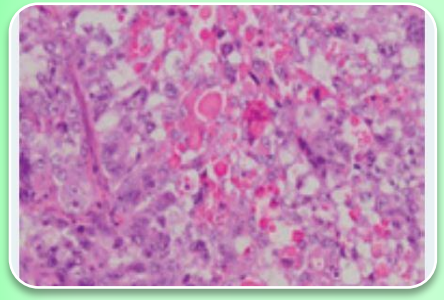
NONENDOMETRIOID CARCINOMAS

High grade



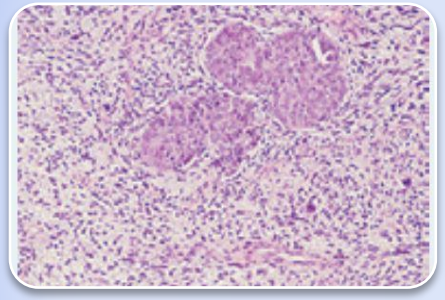
Serous carcinoma

- Most common nonendometrioid
- Poor prognosis
- Extrauterine disease in 37% of patients with no EM stromal or myometrial invasion



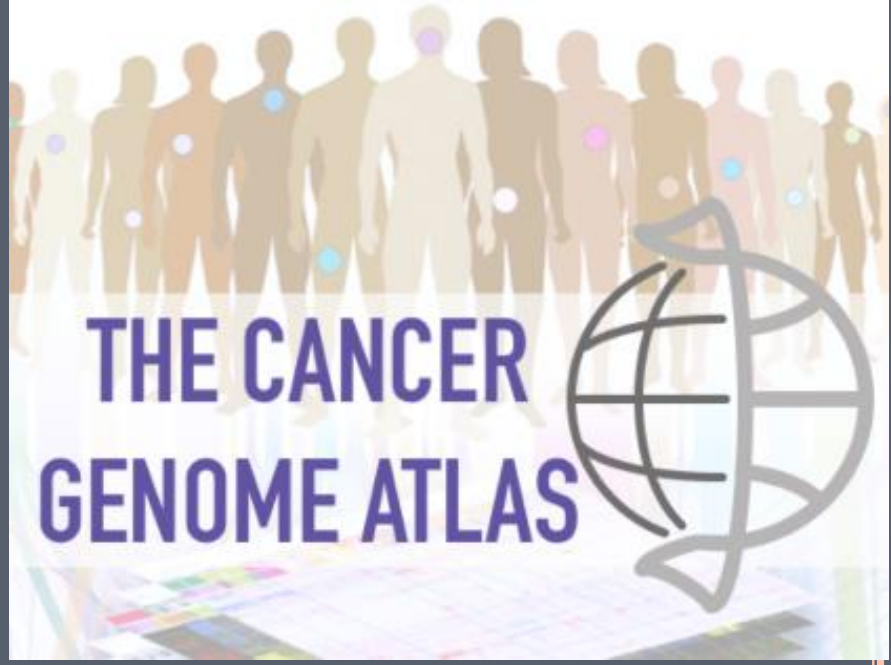
Clear cell carcinoma

- Worse prognosis than serous



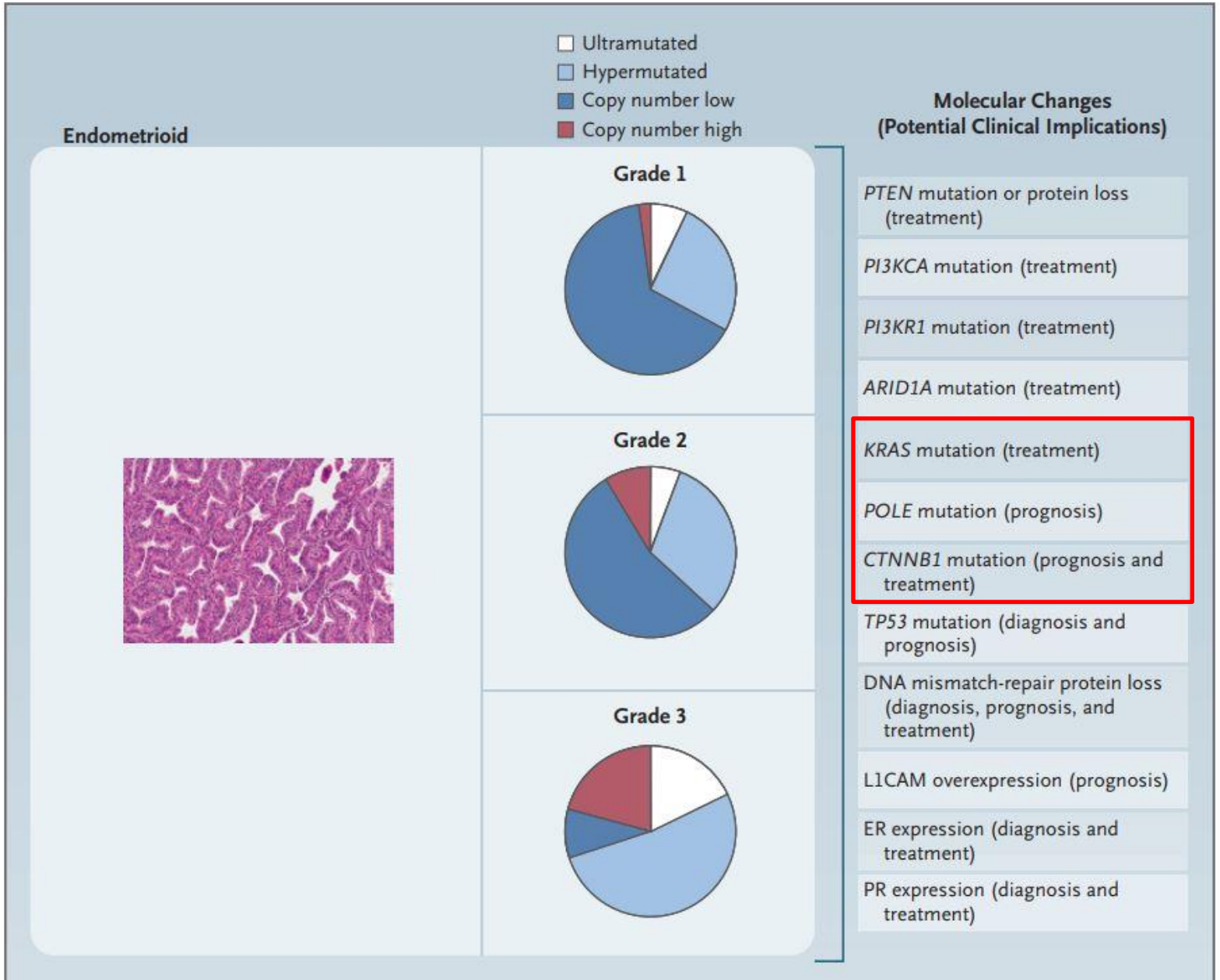
Carcinosarcoma (Malignant Mixed Müllerian Tumors)

- The worst prognosis
- Pathology: high-grade metaplastic carcinoma
- Recurrence and metastasis pattern: carcinoma



Molecular Characterization

Endometrioid carcinoma



PI3K-AKT pathway
High incidence: CTNNB1, KRAS, POLE mutations

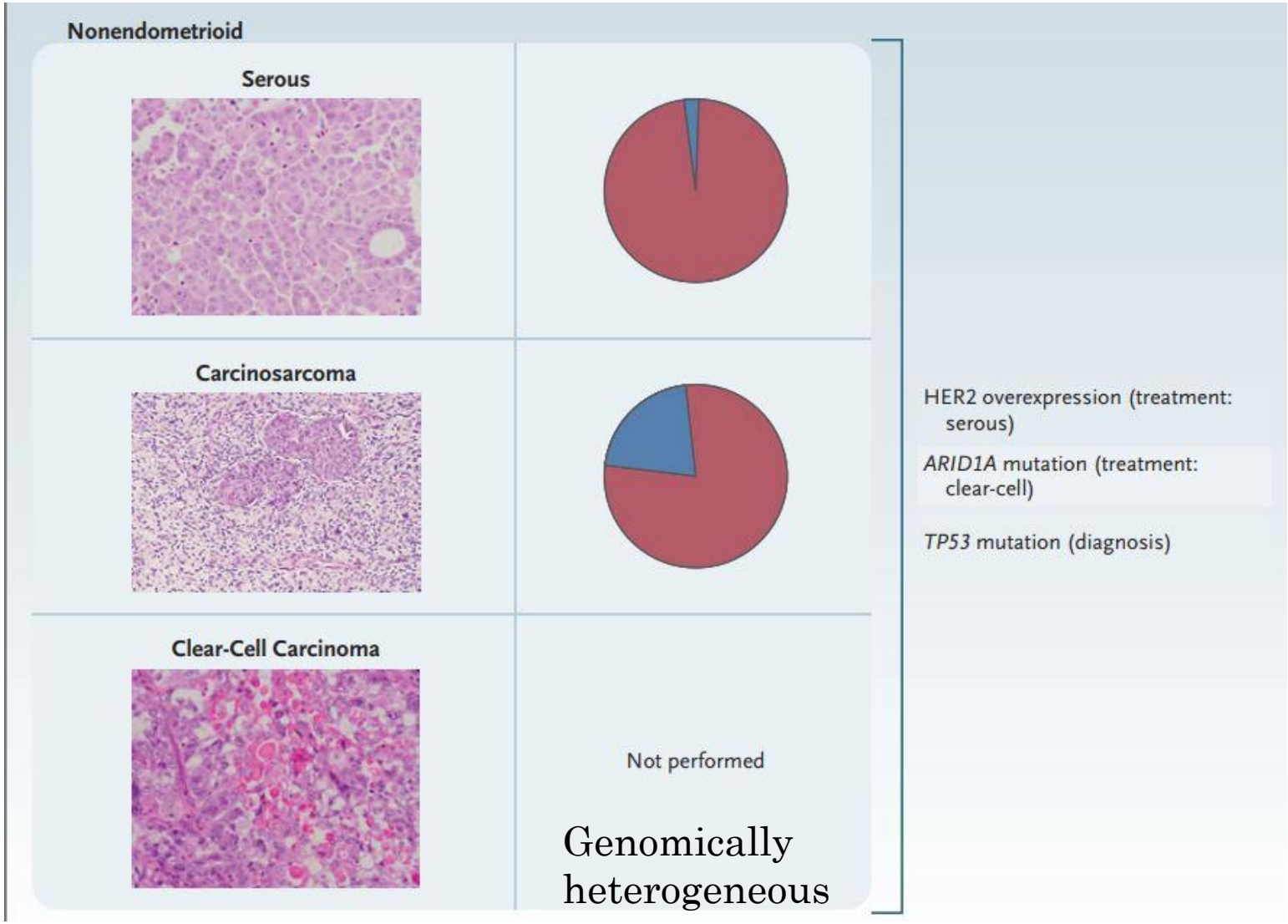
Ultamutated → significantly longer survival (***POLE*** mutations)

Nature 2013;497:67-73

Hypermutated → high levels of MSI and a high mutation rate

"Copy-number-low" →microsatellite-stable endometrioid carcinomas

NONENDOMETRIOID CARCINOMA



TP53 mutations, low mutation rate, and frequent copy-number alterations ("copy-number–high" group)

Nature 2013;497:67-73

TCGA: Diversity of endometrioid histotype

- Young, obese women have hormone-driven disease with a good prognosis ?
- Endometrioid carcinoma driven by activation of the WNT–β-catenin signaling pathway (not always hormone-dependent)

J Natl Cancer Inst 2014;106(9):dju245

- Higher-grade and advanced-stage endometrioid cancers: similarly heterogeneous
- Grade 3 endometrioid tumors with "immune driven" genotype → better outcomes

- It is not possible to perform full, TCGA-scale genomic analyses for individual endometrial cancers in the clinical laboratory for patient care.

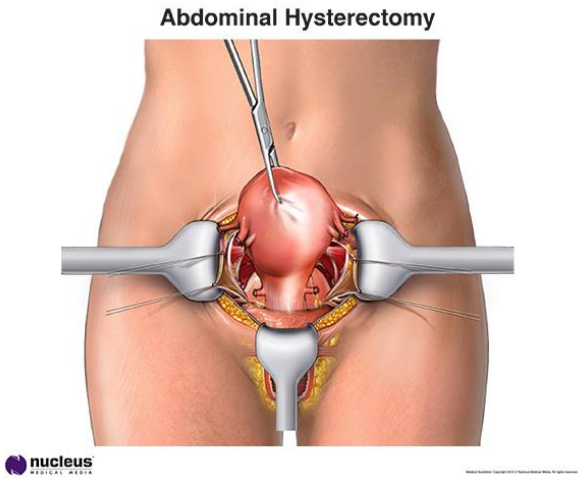
- DNA mismatch-repair deficiency
- CTNNB1 exon 3 mutation
- TP53 mutation: more common in grade 3 tumor, worse prognosis
- p53 overexpression and null expression patterns on immunohistochemical analysis

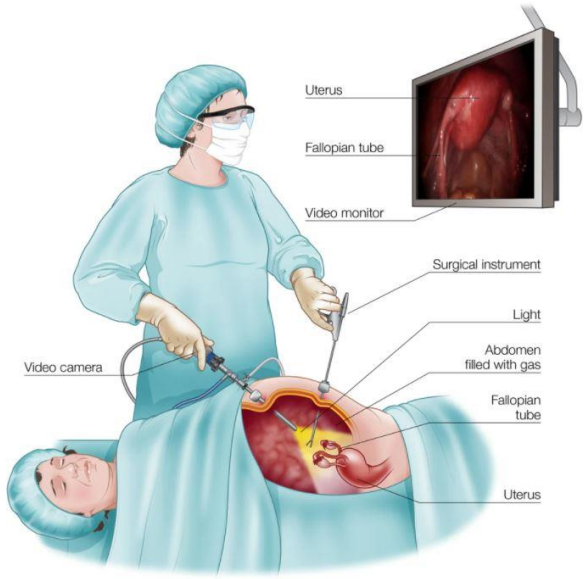
→ Poor survival in endometrioid carcinoma

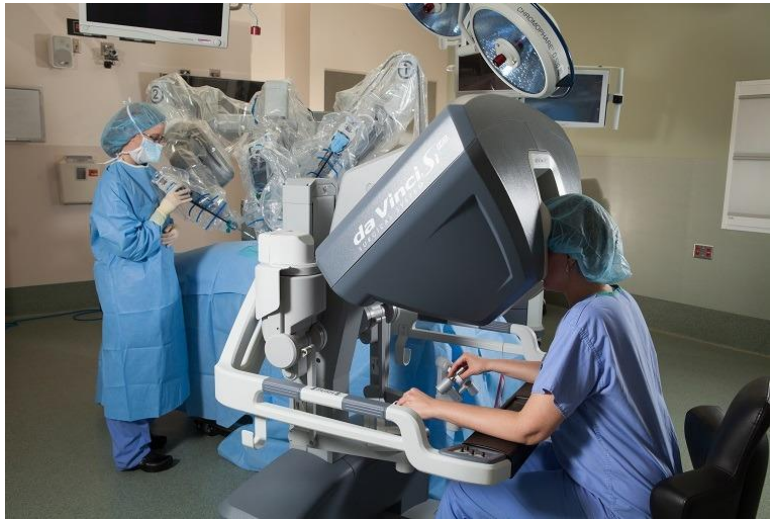
- **PORTEC-4a**: randomly assigns women with early-stage disease (high-intermediate risk) to vaginal brachytherapy or treatment based on a molecular risk profile

Surgical Management and Staging

SURGERY IS THE MAINSTAY OF THE INITIAL MANAGEMENT OF ENDOMETRIAL CANCER.







- Standard procedure: Total hysterectomy + Bilateral salpingo-oophorectomy + Sentinel lymph-node evaluation
- Obese and multiple comorbidities: **Minimal invasive approaches** (↓Postoperative complications ↑short-term quality of life)
- Long-term follow-up: no significant difference in overall survival regarding the initial surgical approach

J Clin Oncol 2009;27:5331-6
Lancet Oncol 2010;11:772-80

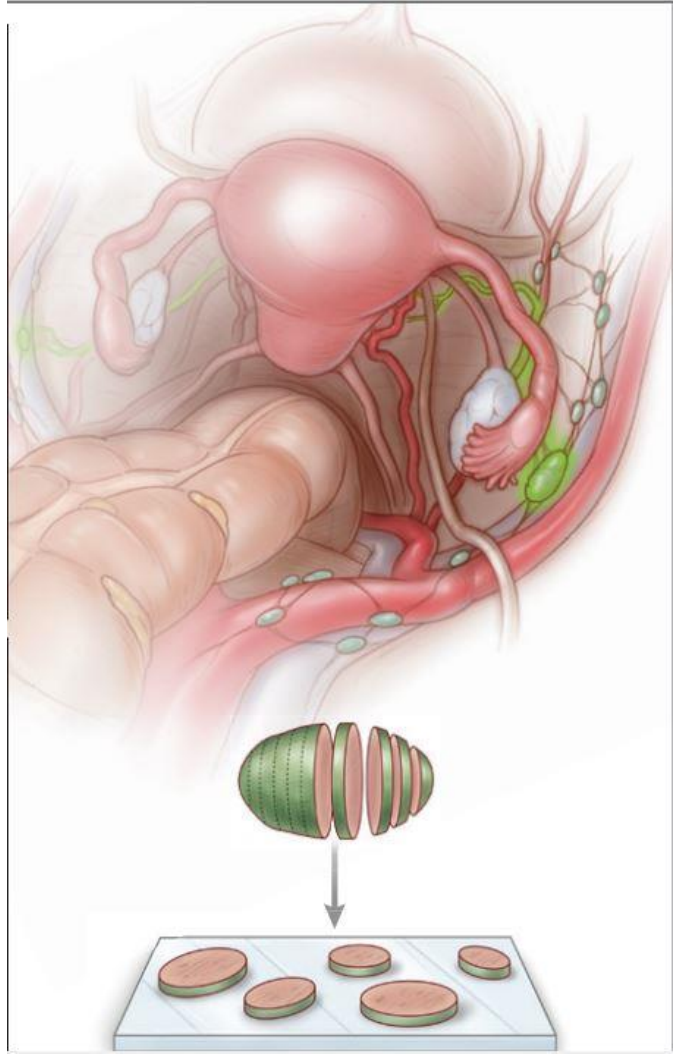
SENTINEL LYMPH NODE STRATEGY

- Standard lymphadenectomy of the pelvic and paraaortic nodes (BPLND+PALNS):
- > 30% patients developed lymphedema
- Short-term risks: ↑surgical times and ↑ blood loss

Gynecol Oncol 2020;156:467-74

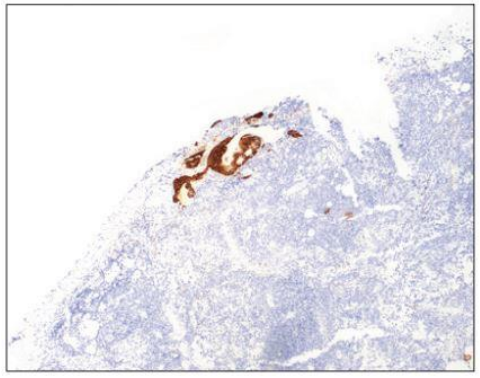
- Sentinel-lymph-node strategy: Injection of indocyanine green dye into the cervix → Identification and removal of bilateral sentinel LNs (or side-specific lymphadenectomy if the sentinel node is not identified) → Pathological ultrastaging

Lancet Oncol 2018;19:1394-403



- ✓ FIRES trial: 385 women, 86% successful mapping of at least one sentinel node (false negative rate: 2.8%) *Lancet Oncol 2017;18:384-92*
- ✓ Study on higher-risk disease, including grade 3 tumors and serous histologic features: 89% successful mapping (false negative rate: 4.3%)

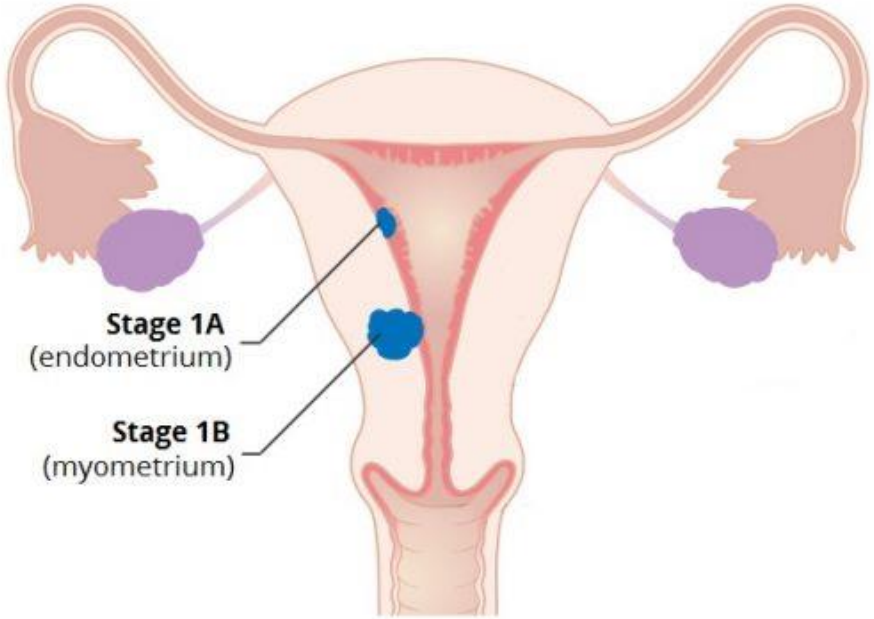
Gynecol Oncol 2017;146:234-9

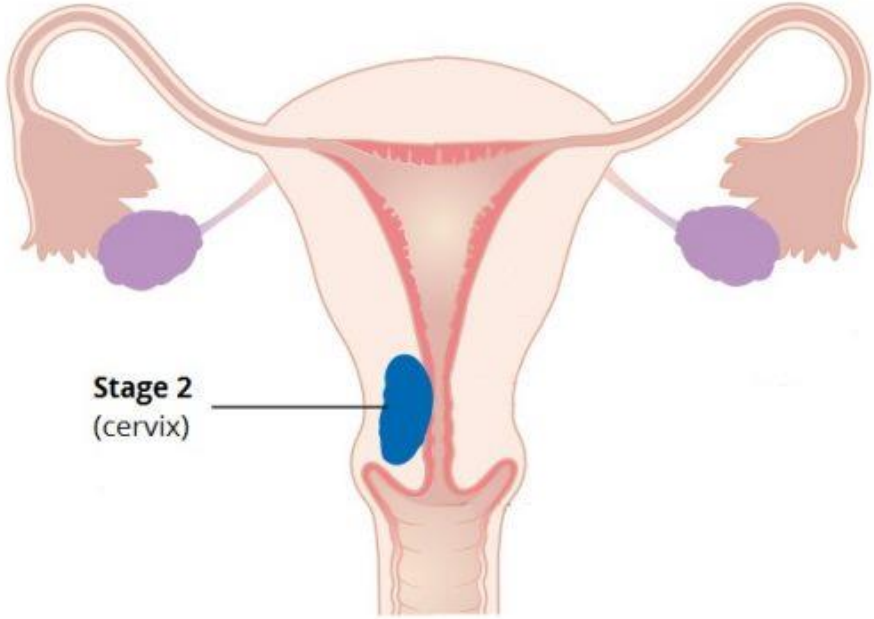


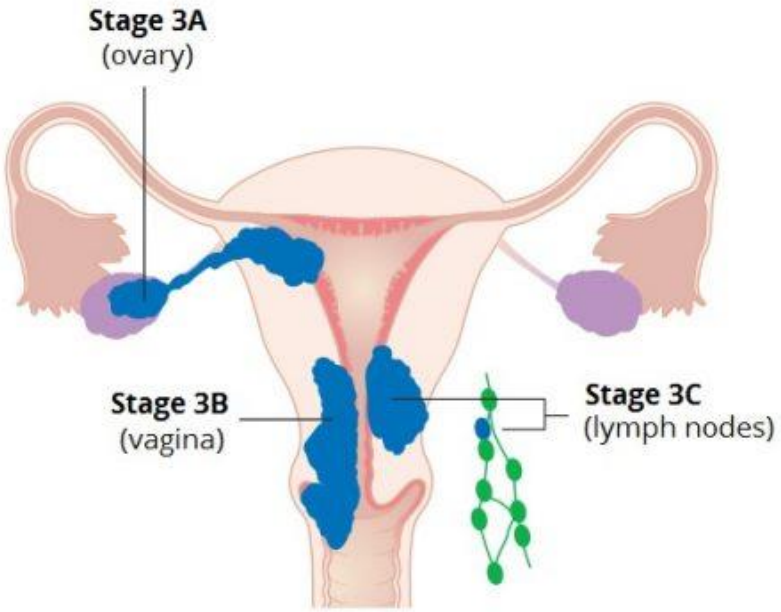
Primary Tumor (T)		
TNM system, T category	FIGO system	T criteria
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
T1	I	Tumor confined to corpus uteri, including endocervical glandular involvement
T1a	IA	Tumor limited to the endometrium or invading less than half of the myometrium
T1b	IB	Tumor invading one half or more of the myometrium
T2	II	Tumor invading the stromal connective tissue of the cervix but not extending beyond the uterus Does not include endocervical glandular involvement
T3	III	Tumor involving serosa, adnexa, vagina, or parametrium
T3a	IIIA	Tumor involving the serosa, adnexa, or both (direct extension or metastasis)
T3b	IIIB	Vaginal involvement (direct extension or metastasis) or parametrial involvement
T4	IVA	Tumor invading the bladder mucosa, bowel mucosa, or both Bullous edema is not sufficient to classify a tumor as T4

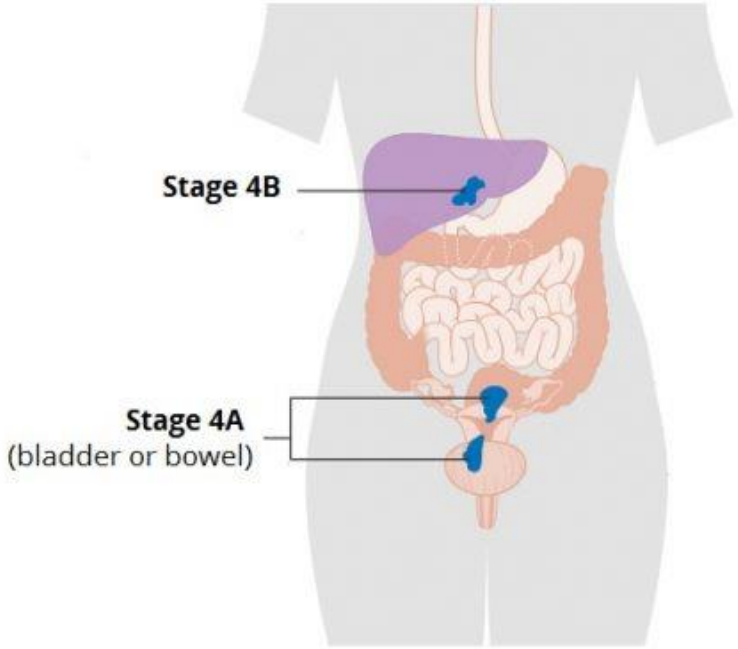
Regional Lymph Nodes (N)		
TNM system, N category	FIGO system	N criteria
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N0(i+)		Isolated tumor cells in regional lymph node, ≤0.2 mm in diameter
N1mi	IIIC1	Regional lymph node micrometastasis (>0.2 mm to 2.0 mm in diameter) to pelvic lymph nodes
N1	IIIC1	Regional lymph node macrometastasis (>2.0 mm in diameter) to pelvic lymph nodes
N2mi	IIIC2	Regional lymph node micrometastasis (>0.2 mm to 2.0 mm in diameter) to paraaortic lymph nodes, with or without positive pelvic lymph nodes
N2	IIIC2	Regional lymph node macrometastasis (>2.0 mm in diameter) to paraaortic lymph nodes, with or without positive pelvic lymph nodes

Distant Metastasis (M)		
TNM system, M category	FIGO system	M criteria
cM0		No distant metastasis on clinical (c) assessment
cM1	IVB	Distant metastasis (includes metastasis to inguinal lymph nodes, lung, liver, or bone or intraperitoneal disease) Also includes metastasis to pelvic or paraaortic lymph nodes, vagina, uterine serosa, or adnexa
pM1	IVB	Distant metastasis (includes metastasis to inguinal lymph nodes, liver, or bone or intraperitoneal disease) microscopically confirmed on pathological (p) assessment Excludes metastasis to pelvic or paraaortic lymph nodes, vagina, uterine serosa, or adnexa









https://teachmeobgyn.com/gynaecology/uterine/endometrial-cancer

Adjuvant Therapy for Early-stage Disease

- ≈ 75% of patients with endometrial cancer: FIGO stage I disease with 5-year overall survival rates > 90%

Stage I endometrioid EM cancer	The remaining
Grade 1 or 2, < 50% myometrial invasion	Age, tumor grade, histologic features, extent of myometrial invasion, lymphovascular invasion
97% survival rate	LIR (low-intermediate-risk) HIR (high-intermediate-risk) High-risk
No adjuvant therapy required *National Comprehensive Cancer Network. Uterine neoplasms, version 1. 2020*	No survival benefit from adjuvant therapy in the **HIR** subgroup • De-escalation: whole-pelvis radiotherapy→ vaginal brachytherapy or surveillance *Lancet 2010; 375:816-23.*

Patients with early-stage but **high-risk** disease

- Grade 3 tumors, > 50% myometrial invasion, +/- lymphovascular invasion
- ↑ Risk of recurrence → Pelvic radiation therapy (traditionally)

- **(GOG)–249** trial and **PORTEC-3**: No survival advantage for any strategy over pelvic irradiation in this subgroup

J Clin Oncol 2019;37:1810-8

- Vaginal cuff brachytherapy: under study

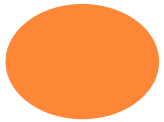
Patients with early-stage endometrial **serous** carcinoma or **carcinosarcoma**

- High risk of distant spread, even when the disease is confined to the endometrium

  Gynecol Oncol 2009;115:244-8
- ↑ Risk of extrapelvic recurrence

- Adjuvant therapy is generally recommended, although no prospective, randomized trials have shown a survival benefit.
- **Systemic chemotherapy** (carboplatin + paclitaxel) and **vaginal brachytherapy**

  Gynecol Oncol 2005;98:353-9
  Gynecol Oncol 2005;99:557-63



Adjuvant Therapy for Node-positive Disease

Stage III disease: High risk of both local and distant recurrence

THE BEST ADJUVANT TREATMENT FOR THESE PATIENTS REMAINS **CONTROVERSIAL.**

PORTEC-3

Lancet Oncol 2019;20:1273-85

- Overall and 5-year recurrence-free survival rates: Chemoradiation therapy + 4 cycles of carboplatin and paclitaxel chemotherapy **>** RT alone
- **Molecular subtyping:** Patients with ***p53*** abnormalities benefit from the addition of chemotherapy; ***POLE*** mutations → highly favorable outcomes in both groups → De-escalation of adjuvant therapy

J Clin Oncol 2020;38:3388-97

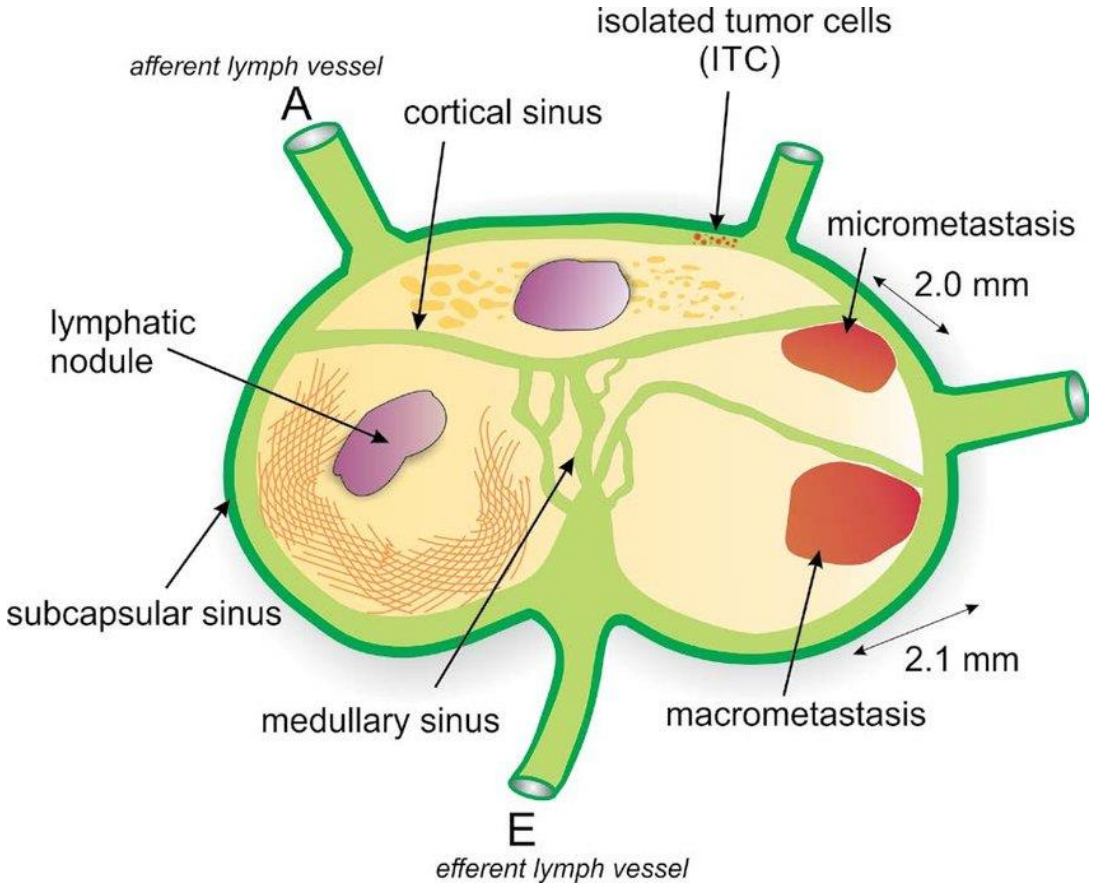
GOG-258

- Relapse-free survival: Chemoradiation therapy + 4 cycles of carboplatin and paclitaxel ≈ Chemotherapy alone (6 cycles of carboplatin and paclitaxel)

N Engl J Med 2019;380:2317-26

New questions with sentinel-node evaluation

- How to treat isolated tumor cells, micrometastases, and macrometastases?



Therapeutics for Advanced and Recurrent Disease

Molecular characterization of endometrial tumors is critical in directing treatment.

- Histologic analysis
- Estrogen receptor (**ER**) and progesterone receptor (**PR**) status
- **MSI** analysis
- Human epidermal growth factor receptor 2 (**HER2**) status for uterine serous cancers
- **Next generation sequencing** to identify somatic mutations → enrollment in a clinical trials

First-line treatment for most advanced and recurrent endometrial cancers

- Standard of care: Combination chemotherapy with **carboplatin + paclitaxel**
- Median progression-free survival: 13 months
- Overall survival: 37 months
- No benefit of adding bevacizumab and biologic agents

J Clin Oncol 2020 September 29

Gynecol Oncol 2018;150:274-81
Gynecol Oncol 2019;155:406-12

HER2 OVEREXPRESSION IN UTERINE SEROUS CANCER

- **Trastuzumab** + carboplatin + paclitaxel
- Prolong progression-free survival
- Effect: Primary treatment > Recurrent disease

J Clin Oncol 2018; 36:2044-51

Advanced or recurrent **endometrioid** endometrial tumors, grade 1 or 2 & **ER/PR(+)**

- Kelley and Baker (1961): hormone therapy with progesterone
- First-line treatment: chemotherapy
- **Hormone therapy**: reserved for limited performance status or 2nd or 3rd line treatment
- Efficacy of single agent progestin (medroxyprogesterone acetate or megestrol acetate) < Combination therapies

- **Megestrol acetate + Tamoxifen**: 27% response rate; 53% of the women with response lasting > 20 months

Gynecol Oncol 2004;92:10-4

COMBINATIONS OF ANTIHORMONAL AND BIOLOGIC AGENTS FOR **ENDOMETRIOID** ENDOMETRIAL CANCERS

- **Everolimus + Letrozole**: 32% response rate, similar efficacy with Megestrol acetate + Tamoxifen but ↓ risk of blood clots

J Clin Oncol 2015;33:930-6
Gynecol Oncol 2018;149:2

- **Everolimus + Letrozole + metformin**: 28% response rate; 45% with PR(+) patients

Clin Cancer Res 2020;26:581-7

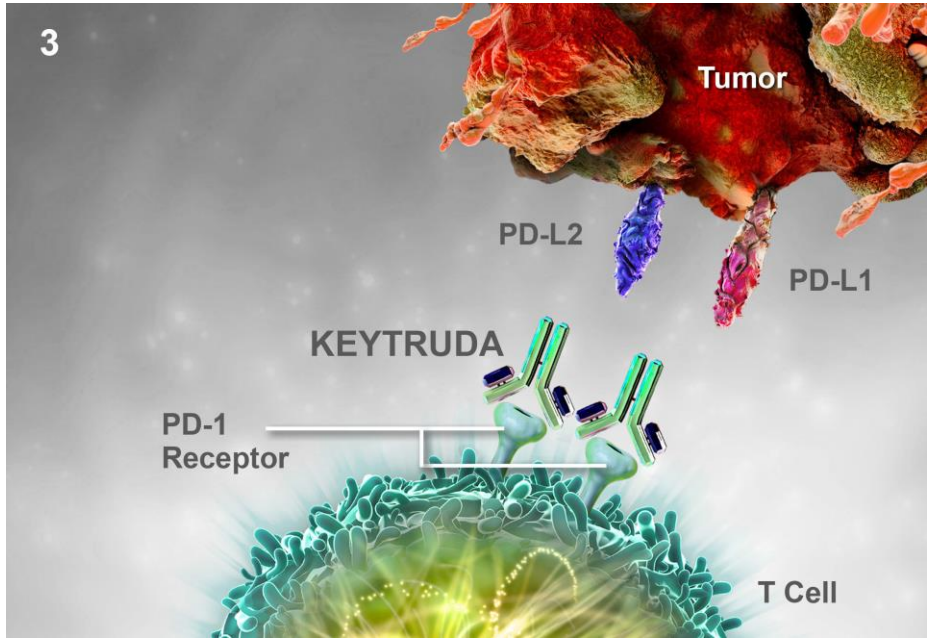
- **Fulvestrant**, aromatase inhibitor, and Tamoxifen, can be considered.

- Monotherapy < Combination

Second- and third-line treatment: **MSI** status → DNA mismatch repair function

- **Pembrolizumab**, immune checkpoint inhibitor
- **KEYNOTE-158**: Single-agent pembrolizumab, 49 patients with high-MSI, recurrent endometrial cancer → Overall response rate of 57% (16 % complete responses + 41% partial responses)

J Clin Oncol 2020;38:1-10



Patients with high-grade tumors that are NOT characterized by high MSI

- A new combination of an oral targeted therapy, **lenvatinib**, multi-tyrosine kinase inhibitor, and **pembrolizumab**

- Single-group, phase 2 trial (**KEYNOTE-146**): Response rate ≈ 40% at 24 months among unselected patients with recurrent endometrial cancer (no high MSI and uterine serous cancers) ; 64.5% had a response lasting for at least 12 months

Lancet Oncol 2019;20:711-8

- Side effects of lenvatinib can be clinically significant.

→ Close monitoring and dose reduction

Patients with good performance status in whom second- or third-line treatment fails

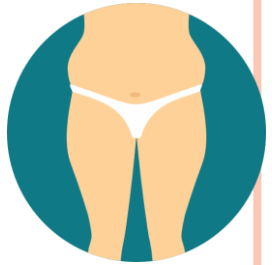
- Standard-of-care options: **bevacizumab**, **paclitaxel**, and **doxorubicin**

- **Next-generation sequencing**: somatic mutations for clinical trials
  - PI3K pathway: endometrioid tumors
  - Homologous recombination repair pathways: high-grade or serous tumors

Future Directions

Understanding
Prevention
Treatment

- **Obesity** and endometrial cancer: more complex than proestrogenic hormonal imbalance
- Identifying **additional risk factors**
- New preventive and fertility-sparing options
- **Health education** on women
- TCGA-type studies: development of **biologic understanding** of the disease
- **Molecular diagnostics**: histologic features and biomarkers
- **Targeted therapeutics**



Thank you for listening. May the healthy uterus be with you!