بسم الله الرحمن الرحيم

Pathologic Challenges IN ENDOMETRIAL CARCINOMA

Narges Izadi-Mood, M.D
Professor of pathology ,
Department of Pathology,
Yas Hospital,
Tehran University of Medical Sciences

Pathologic Challenges IN ENDOMETRIAL CARCINOMA

- Endometrial carcinomas (EC) comprise a ***variety of neoplasms*** with ***variable patient outcomes/prognosis***
- ***Advanced-stage disease,*** identifying a ***need for additional therapy is simple***
- ***Early-stage disease,*** identifying whether ***an individual is "low," "intermediate," or "high risk"*** depends on **multiple pathologic features*, some of which are poorly reproducible.***
- Between women who may be cured by ***surgery alone*** and those at significant risk of both ***local and distant recurrence*** and therefore in need of adjuvant therapy, remains ***a tremendous challenge for clinicians caring for patients with EC***
- **Pathology** will continue to **play a central role in: diagnosis, prognostic assessment and treatment planning**.

Pathologic Challenges IN ENDOMETRIAL CANCER

- Multiple risk stratification systems for EC have been developed
- Assessment and comparison of the most commonly utilized risk stratification systems have shown that ***none reliably predict the risk of lymph node involvement or disease recurrence in early-stage ECs***, presumably due to the ***challenges noted previously***.

Pathologic Challenges IN ENDOMETRIAL CARCINOMA

- Histologic type
- Histologic grade
- Pathologic parameters related to staging
- Those independent of stage/LVSI

Traditional histomorphologic classification systems

Type 1 ECs

- 65 percent of Ecs
- Estrogen-driven
- Mostly endometrioid histology
- Lower grade
- Typically have less myometrial invasion than type 2 EC
- Patients have a favorable prognosis (>85 percent five-year survival rate)

Type 2 ECs:

- Diverse mix of high-grade tumors
- Nonestrogen-driven
- Clinically aggressive histologies (serous, clear cell, endometrioid G3, carcinosarcoma, rare variant).
- They have a poor response rate to progestogens,
- Patients tend to have poor outcomes

Traditional histomorphologic classification systems

- Typical examples of these histotypes are not difficult to diagnose based on careful examination of their morphologic features, allied with confirmatory immunohistochemistry if required.
- The most useful immunohistochemical studies to make the distinction between these 2 histotypes are P53, P16, DNA mismatch repair proteins, PTEN, ARID1A, ER, PR, Napsin A
- When evaluating immunomarker studies, it is important to bear in mind that reported studies vary in the cut-off points used to assess positive and negative staining, making it difficult to compare the results of different studies.

Pathologic Challenges IN ENDOMETRIAL CANCER

- ***In some cases***, the histopathologic and immunohistochemical characteristics are ***less clear-cut and overlap significantly***, which makes accurate classification difficult.

- ***Interobserver agreement of histologic type*** diagnosis is also limited and is ***only moderately reproducible in high-grade ECs*** (kappa value approximately 0.50 to 0.65).

- Diagnostic consensus***, even among expert pathologists,*** is ***observed in less than two-thirds of such cases***

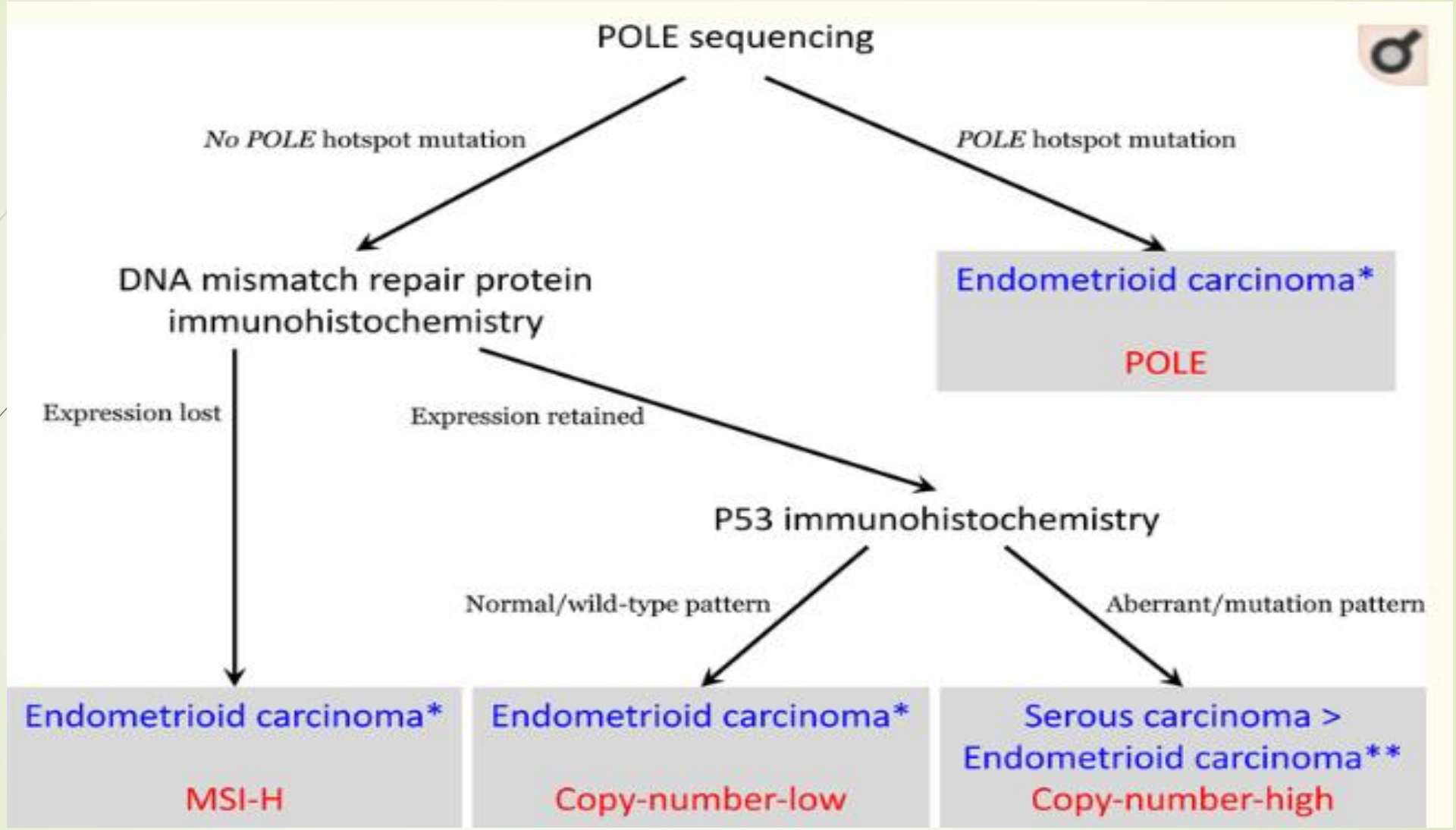
Pathologic Challenges IN ENDOMETRIAL CANCER

- For example, ***significant variation in grade assignment*** has been demonstrated among pathologists (kappa value approximately 0.65 or ***moderate level of interobserver agreement***).

- A further challenge is that ***grade assigned from diagnostic biopsies has also been shown to differ from that assigned based on the hysterectomy specimen***, ***with 15 to 30 percent of ECs upgraded on final pathology***

Traditional histomorphologic classification systems

- This classification does not adequately capture the ***complexity of these neoplasms.***
- In 2013, The Cancer Genome Atlas (TCGA) used ***genomic, transcriptomic, and proteomic analyses*** to characterize over 370 ECs, identifying ***four molecular subtypes based on tumor cell genomic architecture with distinct prognostic outcomes and clinicopathologic features***
- ***Novel classification system*** provides ***objective reproducible categorization and prognostic information*** and a framework for subclassification of ECs for interpretation of research endeavors and clinical trials ***but have not been fully integrated into routine clinical practice***


POLE sequencing
No POLE hotspot mutation
POLE hotspot mutation
DNA mismatch repair protein immunohistochemistry
Endometrioid carcinoma*
POLE
Expression lost
Expression retained
P53 immunohistochemistry
Normal/wild-type pattern
Aberrant/mutation pattern
Endometrioid carcinoma*
MSI-H
Endometrioid carcinoma*
Copy-number-low
Serous carcinoma >
Endometrioid carcinoma**
Copy-number-high

Endometrioid carcinoma

- Most common EC histology, ***75 to 80%*** of cases
- Most endometrioid ECs are ***low grade (grade 1 or 2),*** diagnosed at an ***early stage***, and have a ***good prognosis***
- Can be of ***all four molecular subtypes***, which indicates the ***genetic heterogeneity*** within this histologic type.
- ***Many grade 3 endometrioid ECs*** have a ***genomic profile similar to serous Ecs, behave more aggressively and have a poorer prognosis than other molecular subtypes of grade 3 endometrioid EC***
- ***Approximately 5 percent of low-grade endometrioid carcinomas*** are ***p53abn with worse outcomes***

Serous endometrial carcinoma

- 10% percent of cases
- A very large majority of SECs are of the p53abn molecular subtype.
- Clinically occult extrauterine disease is often present at diagnosis
- SEC often diffusely infiltrates the myometrium and may have extensive lymphovascular space invasion and peritoneal spread, similar to ovarian carcinoma.
- However, SEC confined to the endometrium (or a polyp) with minimal myometrial invasion and no distant disease after surgical staging has a good prognosis.

Clear cell carcinoma

- An uncommon subtype, comprising <5***% of EC***, and patients are usually older, postmenopausal women
- Clear cell ECs ***can be of any of the four molecular subtypes***; *POLE*mut clear cell carcinomas have the most favorable prognosis while p53abn clear cell carcinomas are associated with aggressive behavior
- The mismatch repair (MMR) deficient cases often show ***mixed morphology, with clear cell and endometrioid components***
- Clear cell ECs are typically negative for estrogen receptor protein and positive for Napsin A, which can aid in distinguishing this form of high-grade carcinoma from its mimics: SEC and the secretory variant of endometrioid EC.

Mixed carcinoma

- Mixed carcinomas have at least two distinct histologic components
- Typically endometrioid and a high grade nonendometrioid pattern (usually serous, sometimes clear cell).
- These neoplasms are ***almost all clonal*** rather than being a collision between two synchronous but independent primary neoplasms and ***are usually the same molecular subtypes throughout*** (ie, they are an example of morphologic variability within a molecular subtype).

Undiferentiated/dediferentiated carcinoma

- ***Undiferentiated carcinoma*** **:**These neoplasms have no glandular or squamous differentiation. Most express epithelial antigens (eg, cytokeratin), but this is typically focal.
- ***Dediferentiated carcinomas***: are composed of FIGO grade 1 or 2 endometrioid EC adjacent to areas of undifferentiated carcinoma.
- Undifferentiated/dedifferentiated carcinomas are frequently MMR deficient, often have mutations in genes encoding proteins of the switch/sucrose nonfermentable (SWI/SNF) complex, and, in most cases, do not have mutations in *TP53*.
- This category of neoplasms is ***the least well understood of the major histologic types of EC as it was only recently described***

Carcinosarcoma

- Carcinosarcoma (previously known as malignant mixed müllerian tumor) is an uncommon, aggressive, biphasic carcinoma (not sarcoma) that accounts for <5% of ECs.
- A large majority of carcinosarcomas are of the p53abn molecular subtype (90 percent of carcinosarcomas characterized by The Cancer Genome Atlas had *TP53* mutations),
- They can also be of the other three molecular subtypes of EC

Pathologic Challenges IN ENDOMETRIAL CANCER

- ***Staging remains the most powerful prognostic indicator in EC and depends on accurate assessment of a range of pathologic factors***
- The 2009 FIGO staging formulation for endometrial carcinoma and carcinosarcoma , which is simplified from the 1988 classification.
- Pathologists no longer need :
  - To distinguish less than 50% myometrial invasion from no myometrial invasion
  - Differentiate between endocervical epithelium and endometrial involvement by tumor.
  - Use peritoneal washing status to inform stage
- **Despite these simplifications, many complexities and unanswered questions remain.**

Pathologic Challenges IN ENDOMETRIAL CANCER

- ***FIGO staging ignores significant clinical heterogeneity within each substage.***
- The 2009 FIGO classification system also does not take into account the ***mode of dissemination, suggesting that lymphovascular and peritoneal spread, direct extension, and implantation without invasion are clinically equivalent.***

Myometrial Invasion

- Depth of myometrial invasion has consistently been found to be **an independent predictor of both lymph node (LN) metastasis and overall prognosis in EC**.
- **Absence or presence**
- **Depth of myometrial invasion** should be reported in all EC as "none or less than half" OR "half or more."
- For this reason, **depth of invasion has been a component of the FIGO staging system for EC for over 2 decades**.

Myometrial invasion

- **Assessment for the presence and depth of myometrial invasion can be difficult.**
- Several studies have reported **interpathologist discrepancy rates of approximately 30%**,
- Irregular endomyometrial junction
- Inapparent and metaplastic endometrial stroma
- Measuring tumor thickness rather than depth.

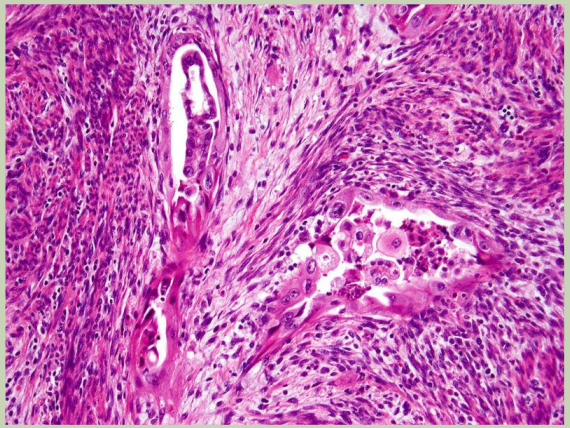
Myometrial Invasion

- Even if the tumor is massive and protrudes into the endometrial cavity, this does not justify measuring its thickness and reporting that measurement as the depth of myometrial invasion
- The less commonly encountered undercalls are related to unfamiliarity with less common invasion patterns: "***microcystic elongated and fragmented" (MELF) and "adenoma malignum-like."***
- "**MELF" and "adenoma malignum-like" invasion patterns** are not difficult to recognize once a few basic guidelines are considered

Myoinvasive endometrioid carcinoma with a Microcystic, ELongated and Fragmented pattern (MELF)

- "MELF pattern invasion is usually first detected at scanning magnification because of its tendency to elicit an **obvious myxoinflammatory myometrial response to invasion.**
- The **neoplastic epithelial cells may be difficult to distinguish** at first, because they tend to be **obscured by the stromal response**
- The ***cells that constitute the invasive foci also differ in appearance when compared with adenocarcinoma in the endometrial compartment***.
- They are frequently:

squamous metaplastic, **elongated with attenuated cytoplasm** and, paradoxically, may also have a **histiocyte-like appearance** with a **low nuclear-to-cytoplasmic ratio**.



MELF

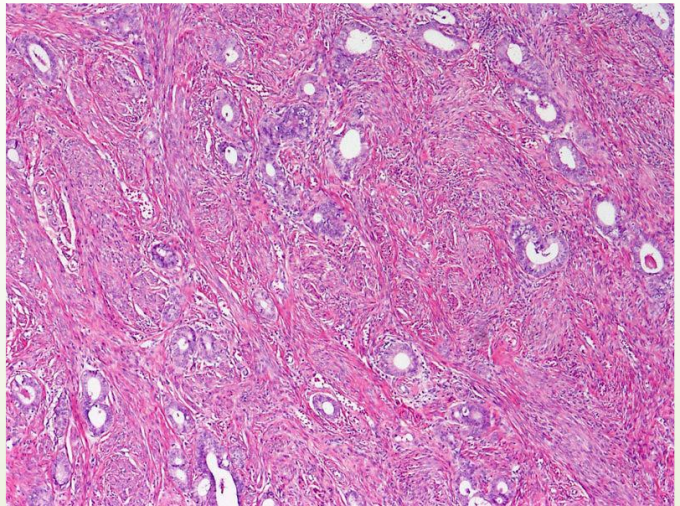
- The **cytoplasmic attenuation may mimic the appearance of endothelial cells**, such that **distinction between myometrial invasion and lymphovascular invasion becomes difficult.**
- Furthermore, when there is **true lymphovascular invasion**, a frequent finding in MELF invasion, the **intravascular tumor cells may retain a histiocytoid appearance**, **unlike most of the overlying tumor**

MELF

- MELF invasion is statistically associated **with lymphovascular invasion and metastasis to regional lymph nodes**, but it has **not yet been shown to be an independent prognostic indicator.**
- MELF has been shown to be a consequence of epithelial-to-mesenchymal transition present at the invasive front of endometrial carcinomas, with loss of epithelial cell adhesion molecules such as E-cadherin
- It is possible that this pattern is over-represented in tumors with defective MLH1 expression

Myoinvasive endometrioid adenocarcinoma with an “adenoma malignum-like” pattern

- The ***adenoma malignum-like invasion pattern displays variable numbers of well-formed endometrioid glands haphazardly distributed throughout the myometrium***, but a ***stromal response to invasion is either minimal or absent*** (14, 19).
- This can be distinguished from adenomyosis by virtue of the chaotic arrangement of neoplastic glands, rather than the focal or multifocal clustered neoplastic glands surrounded by endometrial stroma that is characteristic of adenomyosis.
- The **adenoma malignum-like pattern of invasion probably does not have prognostic significance when compared to tumors with conventional forms of myometrial invasion**. I



Myoinvasive endometrioid adenocarcinoma with an “adenoma malignum-like” pattern

- It should also be noted that despite this entity’s name, it bears ***no clinical or pathological relationship to minimal deviation adenocarcinoma of the endocervix.***

- The only feature that adenoma malignum-like invasion shares with minimal deviation adenocarcinoma of the endocervix is the ***presence of invasive well-differentiated glands without an accompanying stromal response***.

Lymphovascular invasion

- The recognition of lymphovascular invasion is usually straightforward.
- Both the **presence** of lymphovascular invasion and its **extent** are prognostically important.
- Foci of lymphovascular invasion should be sought **at the advancing edge of the tumor as it invades myometrium.**
- Occasionally, with **serous carcinomas**, one can confidently diagnose lymphovascular invasion within **an endometrial polyp** or **within endometrial stroma**.
- Otherwise, **foci suspicious for lymphovascular invasion** should not be interpreted as being "positive for lymphovascular invasion" when **intravascular tumor is found within the tumor itself.**

Lymphovascular invasion

- Distinction of the **pseudo-endothelial appearance of MELF from true lymphovascular invasion** can be accomplished with one of the endothelial immunohistochemical markers, such as FLI-1, podoplanin, and/or CD31.
- One of the most challenging differential diagnoses involves distinguishing lymphovascular invasion from **artifactual tissue displacement**
- It has been reported that artifactual tissue displacement into myometrial vessels, spaces not lined by endothelium, fallopian tube lumen and peritoneal washings is seen **more commonly in laparoscopic and robotic operative procedures** compared with open, or traditional, operative approaches

Lymphovascular invasion

- Although the phenomenon was originally considered solely a result of uterine **manipulation and tumor fragmentation**, it has also been reported that **both surgeons and pathologists are responsible for this artifactual phenomenon**
- **Uterine manipulation and tumor fragmentation** resulting from the operative procedure presents the **pathologist with friable tumor** that can be **dragged through the tissue during prosection**
- **Fixation for several hours in formalin before prosection** has been shown to **minimize the occurrence of these artifacts**
- Clues pointing to the presence of artifact include ***finding neoplastic and non-neoplastic endometrium, oftentimes crushed and distorted, as well as stroma in vessels and non-endothelial-lined spaces of varying sizes close to the tumor and in distant sections.***
- Occasionally, **it may be impossible** to confidently diagnose lymphovascular invasion in the presence of such artifact.

Thanks for attention


THANKS