HPV RELATED CERVICAL ADENOCARCINOMA

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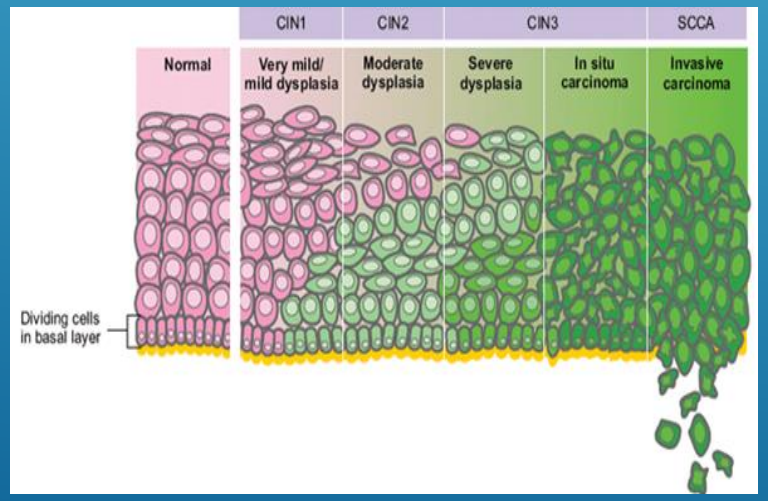
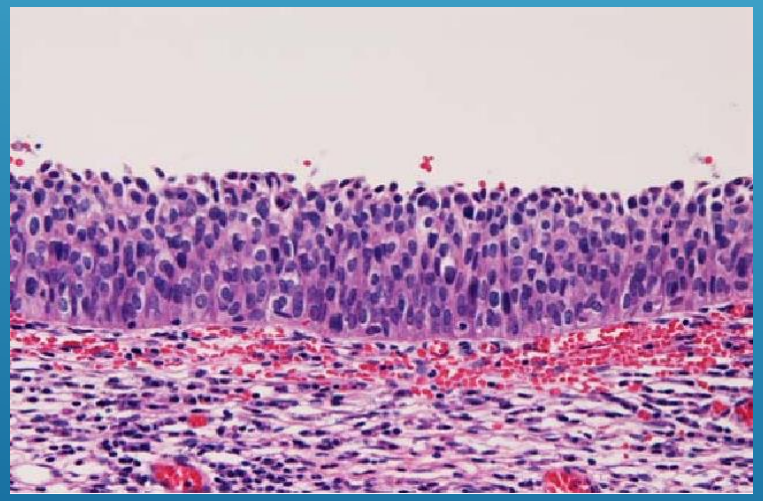
- Decreased incidence of ICC is mainly attributable to the early detection of squamous cell carcinoma (SCC) precursors through cytological screening and subsequent early treatment.





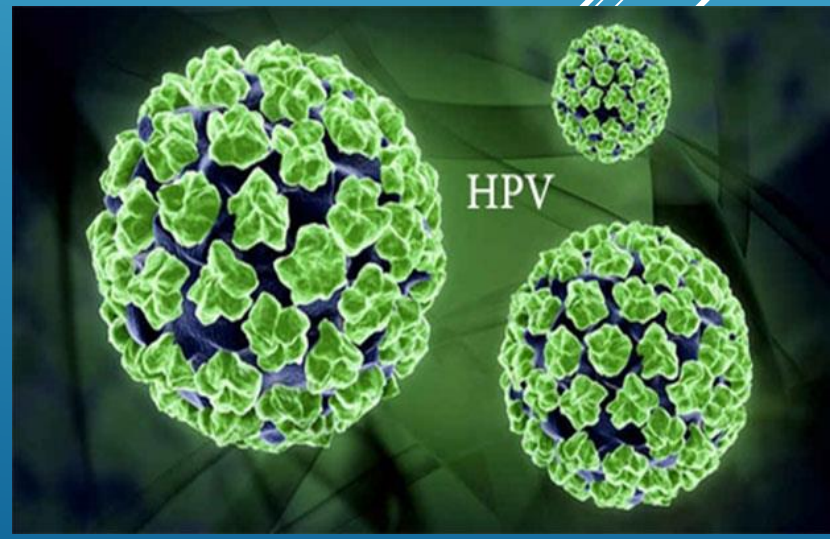
BUT, UNFORTUNATELY THIS IS NOT TRUE ABOUT CERVICAL ADENOCARCINOMA

- In a retrospective cohort including 74 patients with AIS, More than one half of the cases of AIS were not detected from screening Pap tests but were diagnosed during histologic examination of cervical biopsy or endocervical curettage, LEEP, or cone biopsy specimens (~66%).

- J Am Soc Cytopathol. 2021 Aug 9:S2213-2945(21)00216-7. doi: 10.1016/j.jasc.2021.08.002

- *Approximately 41.5% of those undergoing LEEP had a previous diagnosis of AIS, and 54.7% of the cases were incidental findings.*

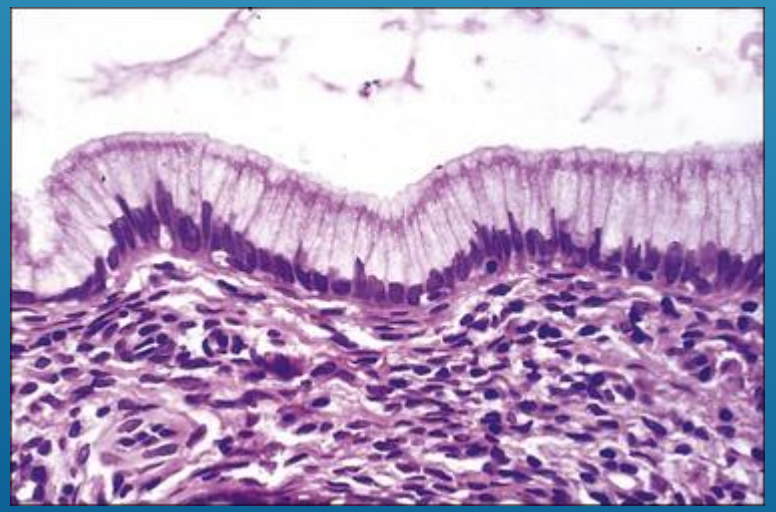
- In contrast, the incidence of cervical adenocarcinoma (ADC) has been steadily increasing, especially in younger women, with its rate approaching 20 to 25% of all ICC in some countries. Despite marked variation between regions in the incidence of ADC, **there is evidence for an absolute increase in ADC.**

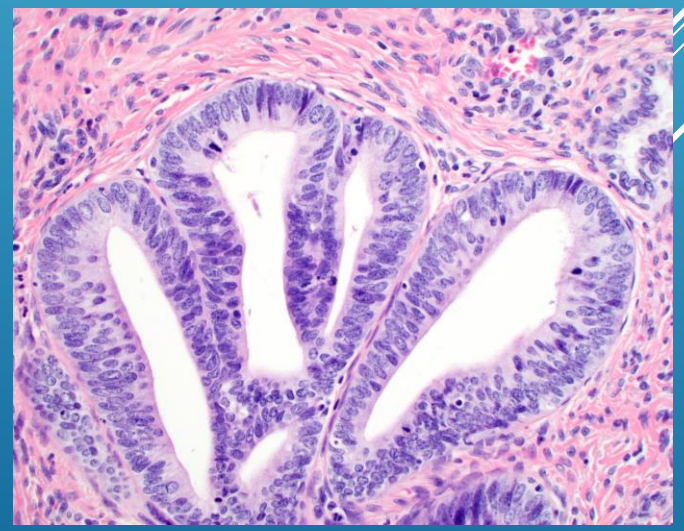


- Both Insitu adenocarcinoma (AIS) and invasive adenocarcinoma in the cervix may be HPV-related or HPV-unrelated(nearly 10%).

CERVICAL HPV- RELATED INSITU ADENOCARCIOMA

- ***Definition***
- ***Adenocarcinoma in situ (AIS), HPV-associated, is an HPV-associated glandular intraepithelial neoplasm.***
- ***Related terminology***
- ***Acceptable: high-grade cervical glandular intraepithelial neoplasia***
- ***Localization***
- ***Squamocolumnar junction and proximal endocervix (less common)***
- ***Clinical features***
- ***The most common presentation is abnormal cervical cytology that shows atypical endocervical glandular cells, often associated with high-grade squamous intraepithelial lesions (HSILs)***





- **Epidemiology**
- The mean patient age at presentation is in the fourth decade of life, 10–15 years younger than the mean age for invasive endocervical adenocarcinoma. Because of their location in the endocervical canal and difficulties in their cytological and colposcopic assessment, cervical AIS lesions are more likely to be missed in cytological cervical screening than their squamous cell counterparts. **As a result, they are diagnosed relatively rarely.**

- **Etiology**
- These neoplasms are associated with infection with high-risk HPV (HR-HPV), most notably HPV16 and HPV18, or HPV45. Of the AIS cases that are diagnosed by cytology and/or biopsied by a colposcopist, 99% are HPV-associated { 22323075 }. Of these, > 90% are positive for HPV16 and/or HPV18, a proportion similar to that seen with invasive cervical adenocarcinoma { 22323075 }. The established greater importance of HPV18 in invasive adenocarcinoma versus in invasive squamous cell carcinoma { 20473886 } is also seen for AIS (~50%) versus its squamous preinvasive equivalent (CIN 2/3; ~20%) { 22323075 }. Rare cases of HPV-independent AIS also exist { 23552379 }.

- **Macroscopic appearance**
- Colposcopically, AIS may be subtle. Lesions can be difficult to appreciate high in the endocervical canal { 25950554 }. HSIL may also be present.

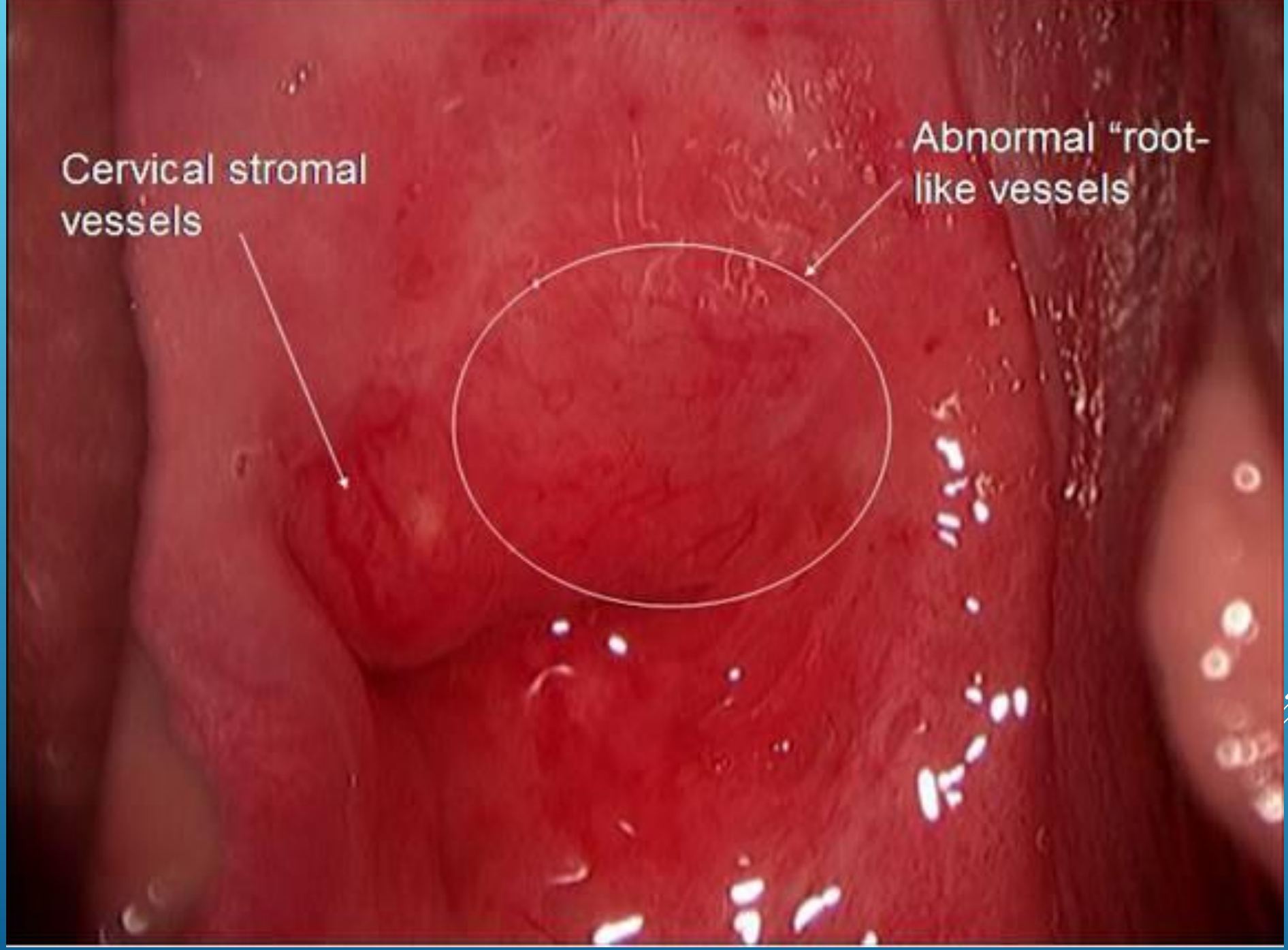
COLPOSCOPIC FINDINGS OF ADENOCARCINOMA IN SITU

- The colposcopic findings of glandular lesions are often difficult to identify. The current American Society of Coloscopy and Cervical Pathology (ASCCP) guidelines for atypical glandular cells (AGC) require colposcopic evaluation and directed biopsies, endocervical curettage, and D&C for women over 35 years of age. The two primary findings are (1) a wide area of eversion and (2) ginger root–like vessels.

- Unlike squamous intraepithelial lesions (SIL), the glandular lesions do not produce the typical acetowhite lesion. The reason is that the glandular lesions do not produce a surface epithelium with dense nuclei like the squamous lesions. Instead, the surface is composed of glandular cells and blood vessels.

- Approximately 40% of adenocarcinoma in situ (ACIS) will have an associated SIL. The colposcopist usually identifies the SIL with a directed biopsy and then proceeds to a loop electrosurgical excision (LEEP). The LEEP will find the ACIS, or in some cases, an early adenocarcinoma.


Abnormal vessels still
prominent after acetic acid


Cervical stromal vessels
Abnormal "root-like vessels

CERVICAL HPV RELATED INVASIVE ADENOCARCINOOMA

- The mean patient age at presentation is 40–42 years, significantly younger than for HPV-independent adenocarcinomas.

- Invasive cervical adenocarcinoma- Facts

•When grossly visible (by definition, FIGO stage IB or greater), lesion can be exophytic, ulcerated or flat On cut section

•There is variable growth into cervical wall

•Barrel shaped cervix with diffuse enlargement can be seen, if lesion is widely invasive

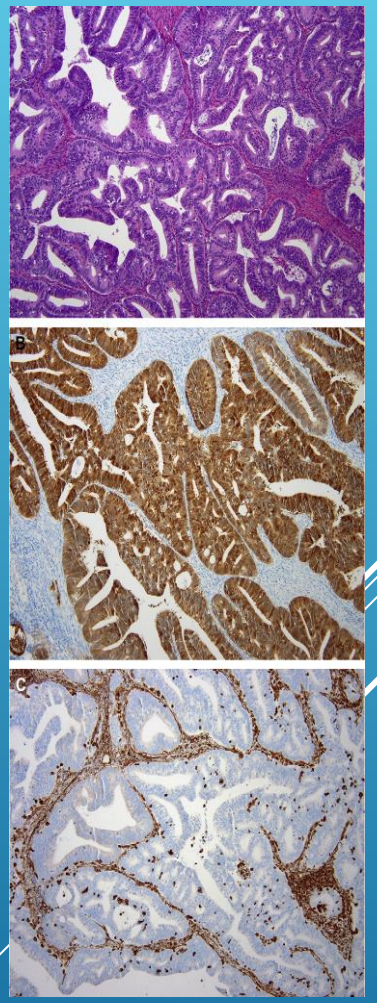
▸ HPV types 18 and 16 are the most common etiologic factors.

•Silva pattern classification has important prognostic impact.

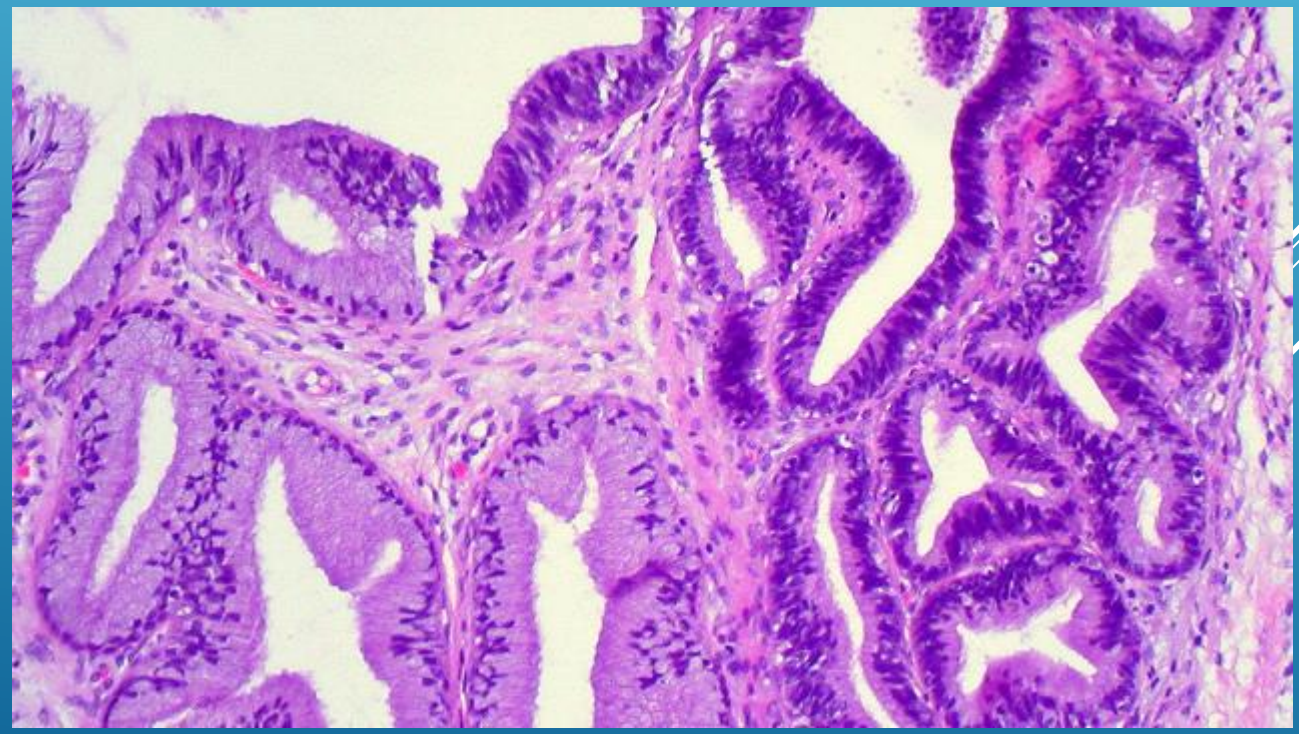
•Differentiation between insitu and invasive adenocarcinoma may be very difficult in some cases.

•Ovaries and fallopian tubes are the most common sites of distant metastasis.

- **P16 immunostaining** is the best surrogate marker for HPV detection in cervical adenocarcinoma.



- Endocervical adenocarcinoma in situ (AIS) is not always identified on cervical Papanicolaou (Pap) test cytology because the Pap test has relatively low sensitivity for the diagnosis endocervical glandular lesions.



- Our results have demonstrated that the ability to detect AIS with routine screening Pap testing or biopsy/curettage has variable efficacy depending on the screening methods. Given the relatively low combined sensitivity of Pap testing and biopsy/endocervical curettage in the diagnosis of AIS, all LEEPs and cervical cone biopsies performed for squamous cell abnormalities should be thoroughly evaluated for glandular lesions.

- Invasive ECAs are classified based on descriptive morphological characteristics, particularly
  cytoplasmic features, as assessed on hematoxylin-eosin (H&E) stained slides. Categorizing
  ECAs using the WHO 2014 classification has important limitations, as subjective definitions
  are derived empirically, rather than being linked to clinical or biological features.

HPV ASSOCIATED CERVICAL ADENOCARCINOMA (HPVA)-90%

- Based on **International Endocervical Adenocarcinoma Criteria and Classification (IECC)**, HPVA ECAs were further subcategorized, mostly based on cytoplasmic features, to provide continuity with pre-existing classification schemes, as follows:
-
  - **Usual-type (The most common type)**
  - **Villoglandular:**
  - **Mucinous, not otherwise specified (NOS)**
  - **Mucinous, intestinal type**
  - **Mucinous, signet ring cell type**
- • **Invasive stratified mucin-producing carcinoma (iSMILE)**

- **However**, unlike cervical squamous cell carcinoma (SCC) where nearly all cases are etiologically associated with HPV infection, approximately 10% of ECAs in Western countries are unrelated to HPV.

- **Eur J Cancer. 2001; 37:246–50.**
- **Gynecol Oncol. 2009; 114:390–4.**

NON-HPV ASSOCIATED CERVICAL ADENOCARCINOMA(NHPVA)-10%

- *Endometriod type adenocarcinoma*
- *Gastric type adenocarcinoma*
- *Serous carcinoma*
- *Clear cell carcinoma*
- *Mesonephric adenocarcinoma*
- *Invasive adenocarcinoma-NOS*

- According to the latest World Health Organization (WHO) Classification
  of Tumours of Female Reproductive Organs, **the most frequent type of ECA is usual-type, which is HPV-related.**

- In the past decade, there has been growing awareness of HPV-unassociated endocervical adenocarcinomas.6,7 The gastric-type adenocarcinoma, for example, was recognized in the latest WHO classification (2014) as the second most frequent subtype of ECA.

- Gastric type cervical sdenocarcinoma is HPV-unrelated, despite being categorized as a subtype of "mucinous ECA," which is itself a combination of HPV-positive and HPV–negative adenocarcinomas.

- Comparison of usual-type HPV-associated ECA with gastric-type HPV-
  unassociated ECA reveals important differences in tumor behavior and patient survival,
  with significantly worse clinical outcomes for patients with gastric-type adenocarcinoma,
  even when matched for stage.

- Gastric-type adenocarcinomas more frequently metastasize to distant sites, including viscera and peritoneum. This, as well as data from studies of the vulva and oropharynx, suggest that a classification based on pathogenesis is most likely more clinically informative and reproducible than the current WHO scheme.

- HPV-associated adenocarcinoma (HPVA)—Apical mitotic figures and apoptotic
  bodies appreciable at scanning magnification. If those features were not seen at scanning
  magnification, a cursory exam at 200x was performed to detect additional cases. Those with
  easily-identified apical mitotic figures and apoptotic bodies were considered HPVA.

- Cervical cancer is staged according to the Fédération Internationale de Gynécologie et d´Óbstétrique (FIGO) system using a combination of **clinical, imaging, and pathology** findings.

- The experience with this staging system, however, is based primarily on studies of squamous cell carcinoma, which is by far more common, and has been extrapolated to adenocarcinoma.

- As a result, both adenocarcinomas and squamous carcinomas are staged and treated similarly, although there is increasing evidence to suggest that adenocarcinomas show different epidemiology, prognostic factors, patterns of spread and failure after treatment compared with squamous cell carcinomas

- Curr Oncol Rep 2015;17:17–26.
- Int J Gynecol Cancer 2014;24:S96–101.

- Staging of FIGO IA1, IA2, and IB1 invasive endocervical adenocarcinomas (EACs) is currently based on the depth of invasion.

- Int J Gynaecol Obstet 2019;145:129–35.
- Int J Gynaecol Obstet 2019;147:279–80.

- **However**, an accurate assessment of this parameter can be challenging in a variety of scenarios such as:

- 1.well-differentiated invasive adenocarcinomas without architectural complexity and no stromal reaction that are difficult to distinguish from insitu adenocarcinoma.

- 2.Tumors where it is not possible to separate the invasive from the in situ component.

- polypoid lesions, and specimens lacking proper orientation or integrity of the mucosal surface.

- **In spite** of these potential challenges, depth of invasion is a major determinant of treatment.

- According to the current National Comprehensive Cancer Network (NCCN) guidelines, patients with FIGO stage IA1 tumors that lack lymphovascular invasion (LVI) could undergo conservative treatment with conization and follow-up (if margins are negative) or simple hysterectomy when preservation of fertility is not required.

- Patients with FIGO stage IA2 tumors and those with IA1 tumors associated with LVI or with positive margins undergo radical surgery (radical hysterectomy, or alternatively large conization or radical trachelectomy as fertility preservation approaches); sentinel lymph node (SLN) mapping and/or pelvic lymph node (LN) dissection are also considered in this group of patients.

- Patients that undergo simple/radical hysterectomy or radical trachelectomy may experience surgical complications such as bladder dysfunction, vascular or ureteral injuries, and blood loss among others.

- Am J Obstet Gynecol 2020;222:249.e1–10.

- In addition, 10% to 41% of patients treated with LN dissection can experience lower extremity lymphedema as postoperative morbidity.

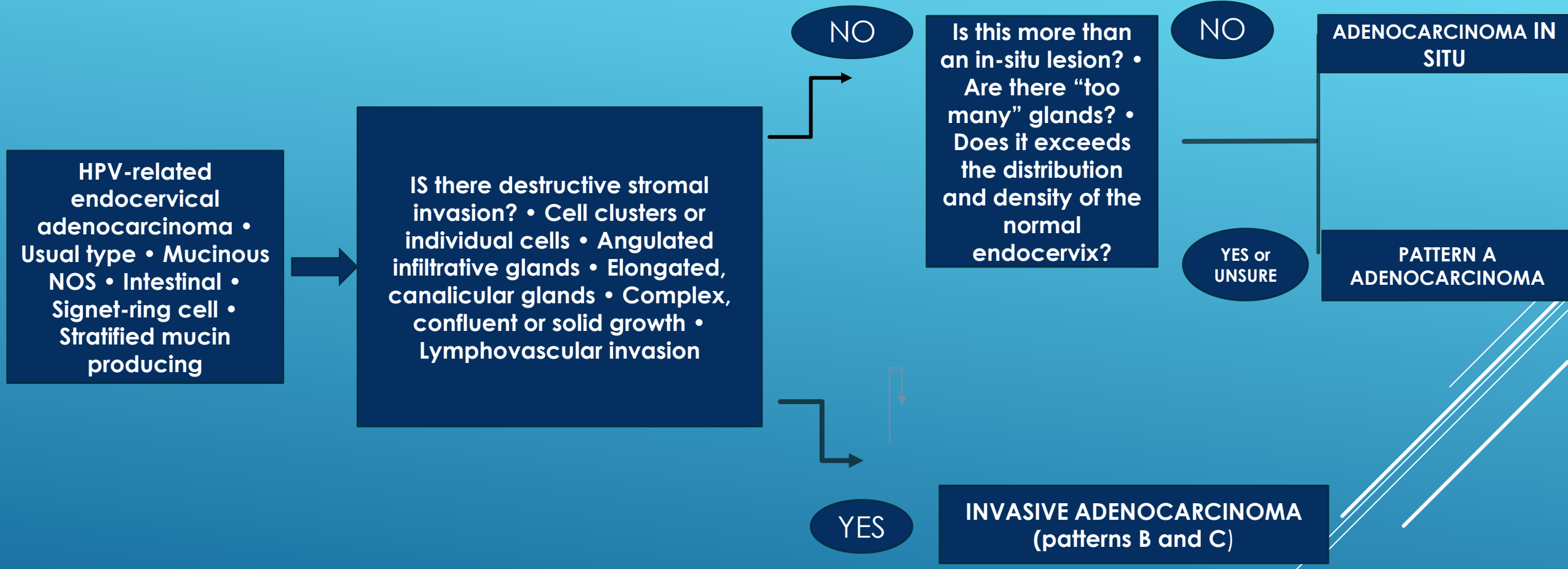
- Int J Gynecol Cancer 2020;30:252–60.
- Jpn J Clin Oncol 2018;48:1036–40.

- Importantly, the literature indicates that few patients with early FIGO stage tumors have evidence of LN metastasis, seen in less than 1% of stage 1A1 patients and near 2% of stage 1A2 patients.

- Gynecol Oncol 2016;141:36–42.

- In an attempt to improve the current risk stratification system for patients affected by HPV-associated invasive cervical adenocarcinoma, a group of pathologists led by Dr Elvio Silva have proposed the use of a system based on the following histologic features: tumor-stromal interface, presence or absence of LVI, architecture and grade of cytologic atypia.

- Int J Gynecol Pathol 2013;32: 592–601. 21.
- Am J Surg Pathol 2015;39:667–72.


HPV-related endocervical adenocarcinoma • Usual type • Mucinous NOS • Intestinal • Signet-ring cell • Stratified mucin producing
IS there destructive stromal invasion? • Cell clusters or individual cells • Angulated infiltrative glands • Elongated, canalicular glands • Complex, confluent or solid growth • Lymphovascular invasion
NO
Is this more than an in-situ lesion? • Are there "too many" glands? • Does it exceeds the distribution and density of the normal endocervix?
NO
ADENOCARCINOMA IN SITU
YES or UNSURE
PATTERN A ADENOCARCINOMA
YES
INVASIVE ADENOCARCINOMA (patterns B and C)