TUMORS OF THE VULVA, VAGINA, CERVIX, AND UTERUS

Kenneth Alonso, MD, FACP

VULVA

Vulva

- Squamous cell carcinoma is the most common histologic type of vulvar cancer.
- Basaloid and warty carcinomas related to infection with high risk HPVs (30% of cases), most commonly HPV-16.
- Arise from classic vulvar intraepithelial neoplasia
- Classic VIN presents either as a discrete white (hyperkeratotic) or a slightly raised, pigmented lesion.
- Epidermal thickening, nuclear atypia, increased mitoses, and lack of cellular maturation
- Occur at younger ages.

Vulva

- Keratinizing squamous cell carcinomas unrelated to HPV infection (70% of cases).
- These are more common in older women.
- Leukoplakia as precursor lesion
- Arise from differentiated vulvar intraepithelial neoplasia
- Marked atypia of the basal layer of the squamous epithelium and normal-appearing differentiation of the more superficial layers

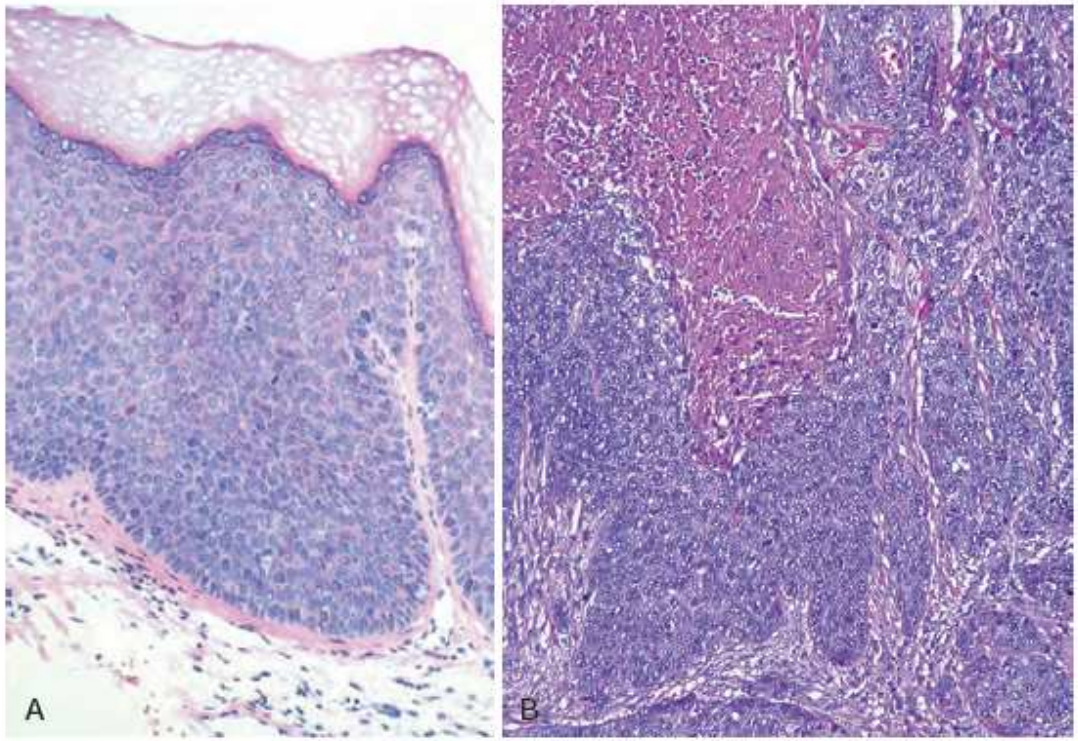


Figure 22-7 Variants of vulvar intraepithelial neoplasia. **A,** Classic vulvar intraepithelial neoplasia (HPV positive), showing nuclear enlargement, hyperchromasia, and small immature basaloid cells extending up to the epithelial surface. **B,** Basaloid vulvar carcinoma (HPV positive), composed of small, immature (basaloid) cells. This invasive tumor has an area of central necrosis.

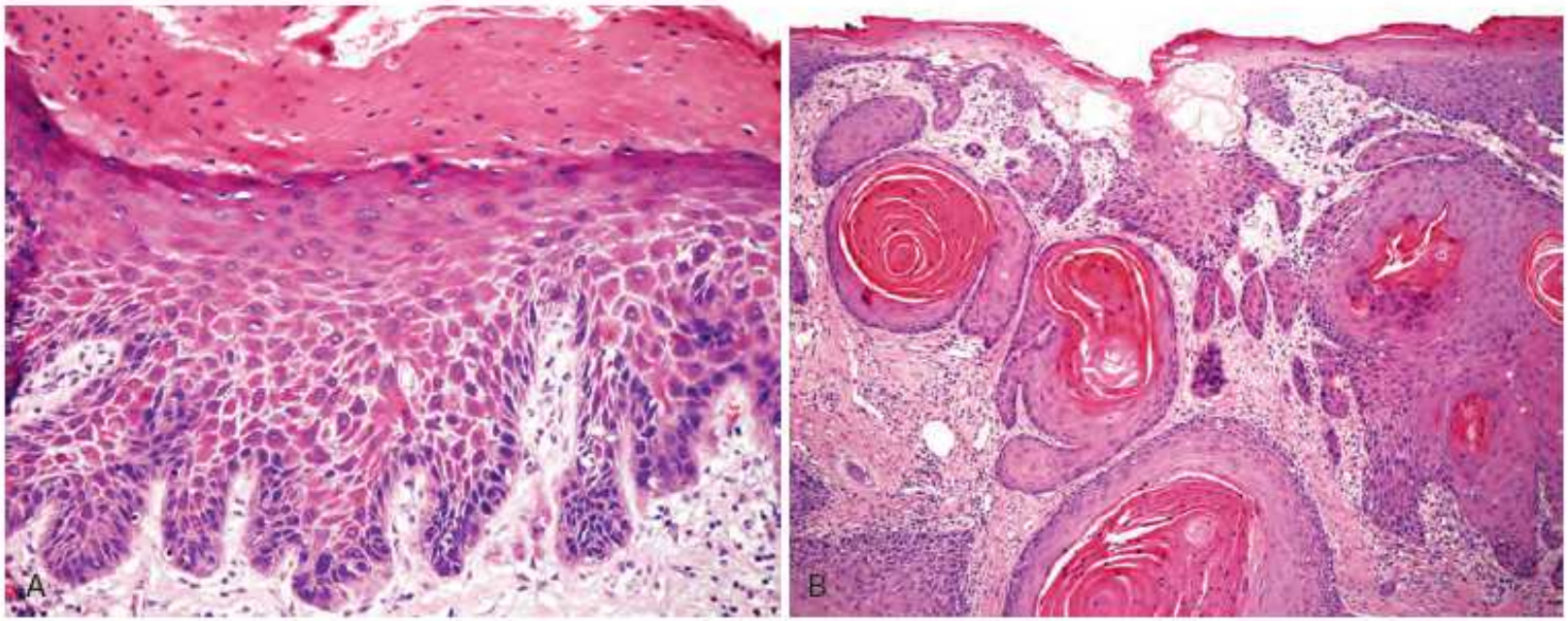


Figure 22-8 **A,** Differentiated vulvar intraepithelial neoplasia (HPV negative), showing maturation of the superficial layers, hyperkeratosis, and basal cell atypia. This is in-situ lesion; no invasion is present. **B,** Well-differentiated, keratinizing squamous cell carcinoma of the vulva (HPV negative).

Papillary hidradenoma

- Presents as a sharply circumscribed nodule, most commonly on the labia majora or interlabial folds
- May ulcerate.
- Consists of papillary projections covered with two layers of cells:
- An upper layer of columnar secretory cells covering a deeper layer of flattened myoepithelial cells.

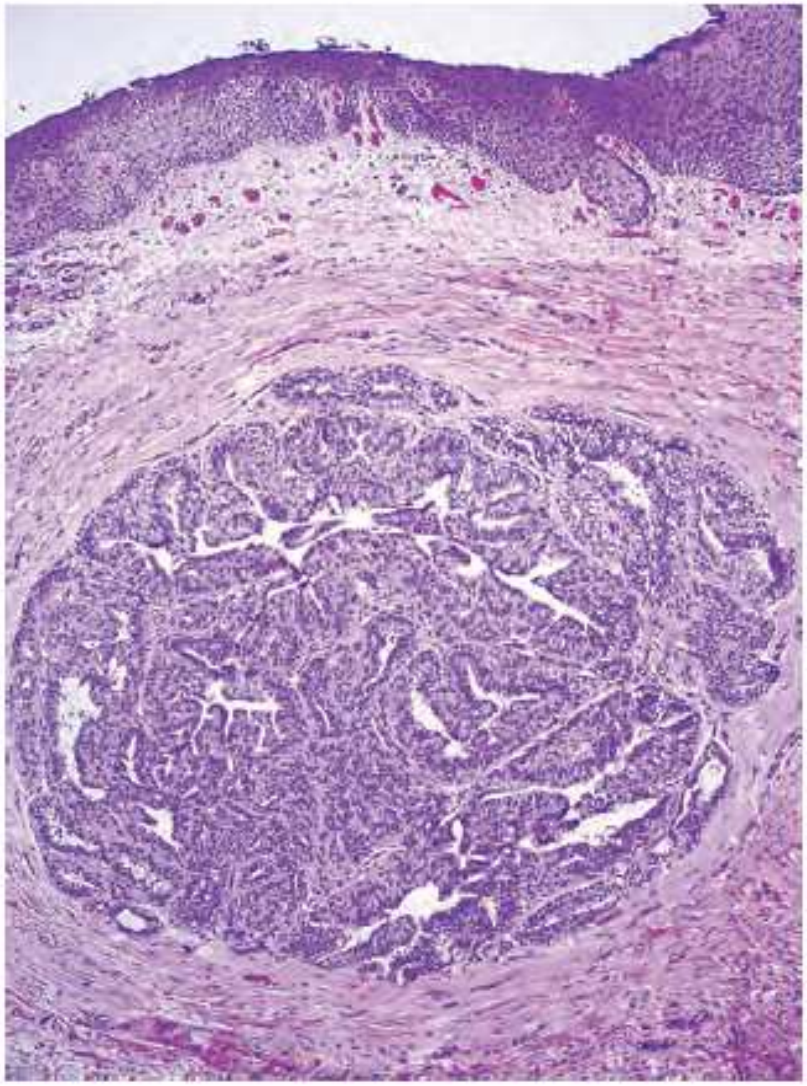


Figure 22-9 Papillary hidradenoma of the vulva, a well-circumscribed tumor composed of benign papillary projections covered with columnar secretory epithelium and underlying myoepithelial cells.

Extramammary Paget's disease

- Vulvar Paget's disease is typically not associated with underlying cancer and is confined to the epidermis of vulvar skin.
- Pruritic, crusted, usually on labia majora
- Paget's disease is a distinctive intraepithelial proliferation of malignant cells.
- Paget cells are larger than surrounding keratinocytes and are seen singly or in small clusters within the epidermis
- The cells have pale cytoplasm containing mucopolysaccharide (stain with Alcian blue or mucin)

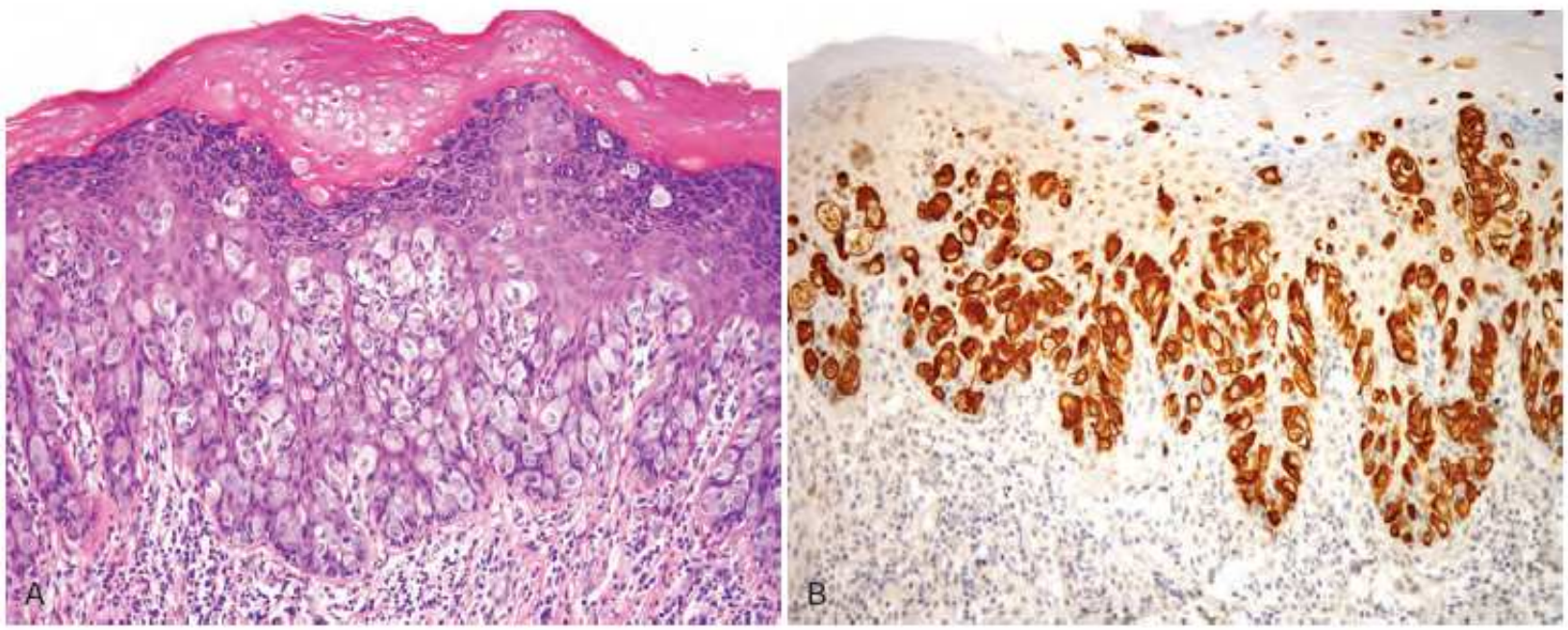


Figure 22-10 Paget disease of the vulva. **A,** The epidermis is infiltrated by large cells with pale-pink cytoplasm that are spreading along the basal portion of the squamous epithelium. There is inflammation in the underlying dermis. **B,** Immunostaining for cytokeratin 7 highlights the intraepidermal Paget cells.

VAGINA

Squamous carcinoma

- Squamous carcinoma of the vagina is usually from extension from the cervix (upper posterior vagina)
- Virtually all primary carcinomas of the vagina are squamous cell carcinomas associated with high risk HPVs
- Arise from vaginal intraepithelial neoplasia
- Lesions in the upper-third spreas to iliac nodes while those in the lower two-thirds spread to inguinal nodes

Embryonal rhabdomyosarcoma

- Sarcoma botyroides
- <5 years of age
- Polypoid, rounded, bulky masses that have the appearance and consistency of grapelike clusters
- The tumor cells are small and have oval nuclei, with small protrusions of cytoplasm from one end, resembling a tennis racket.
- Beneath the vaginal epithelium, the tumor cells are crowded in a cambium layer, but in the deep regions they lie within a loose fibromyxomatous stroma that is edematous and may contain many inflammatory cells

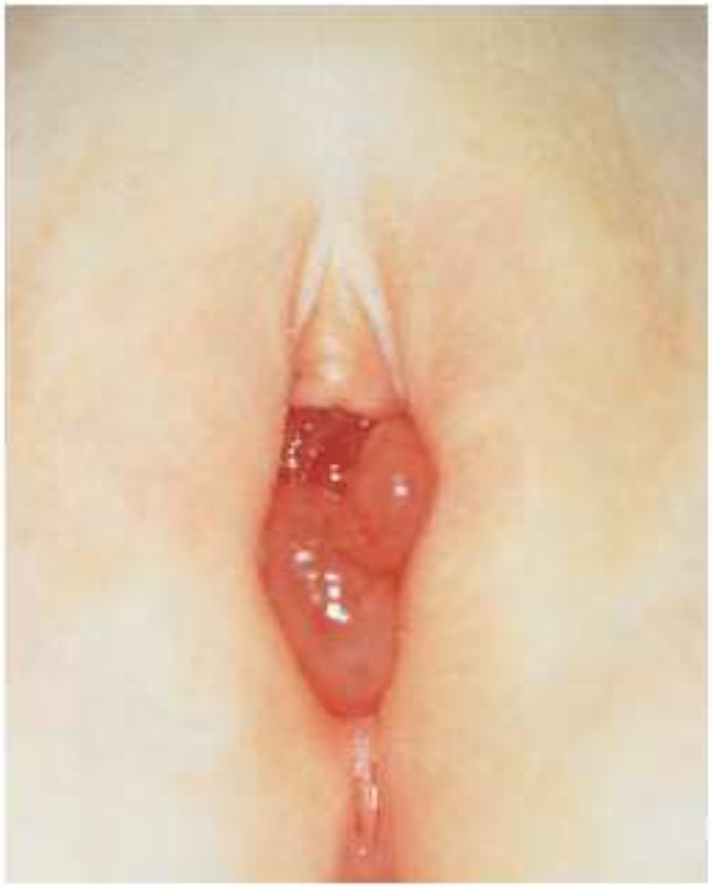


Figure 22-11 Sarcoma botryoides (embryonal rhabdomyosarcoma) of the vagina appearing as a polypoid mass protruding from the vagina. (Courtesy Dr. Michael Donovan, Children's Hospital, Boston, Mass.)

CERVIX

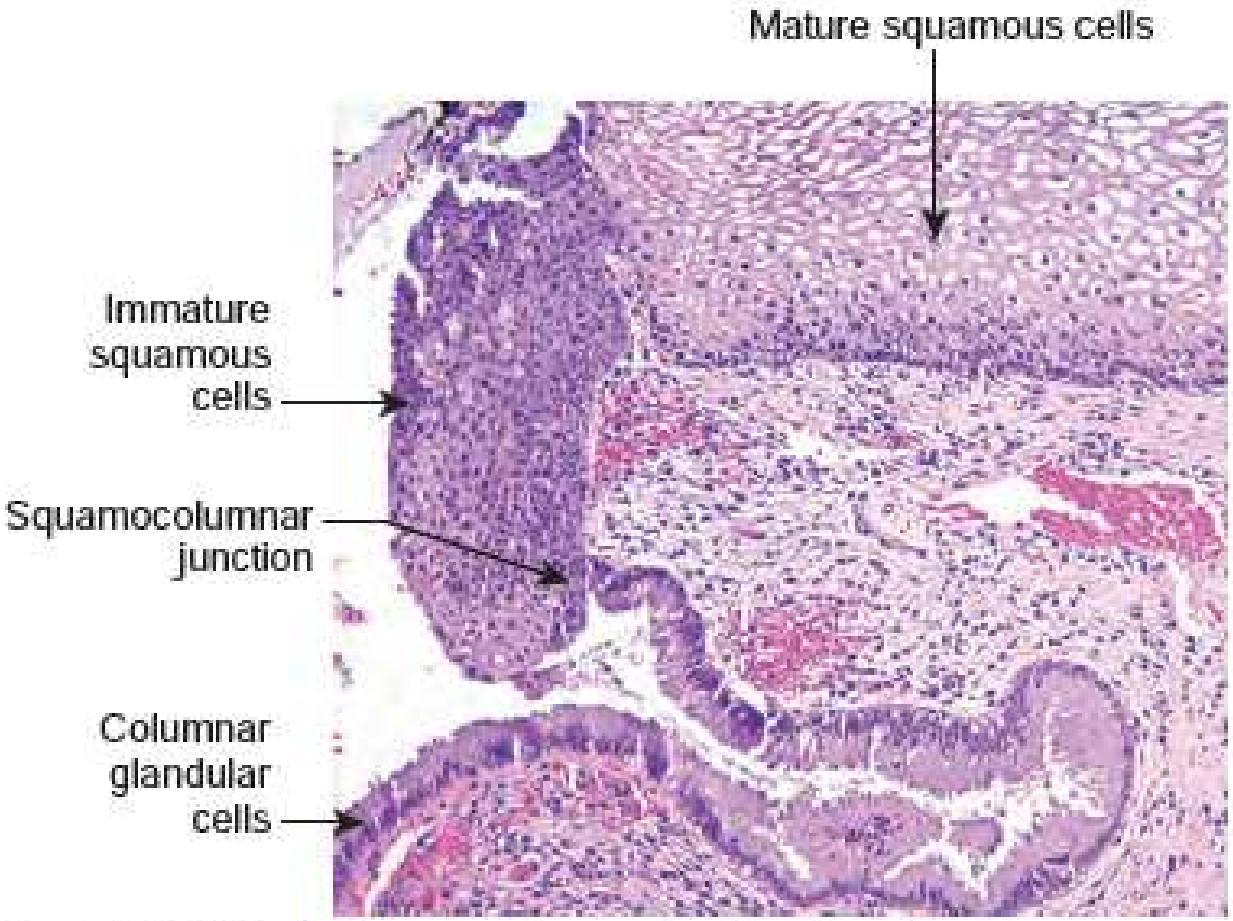


Figure 22-12 Cervical squamocolumnar junction showing mature, glycogenized squamous epithelium, immature squamous metaplastic cells, and columnar endocervical glandular epithelium.

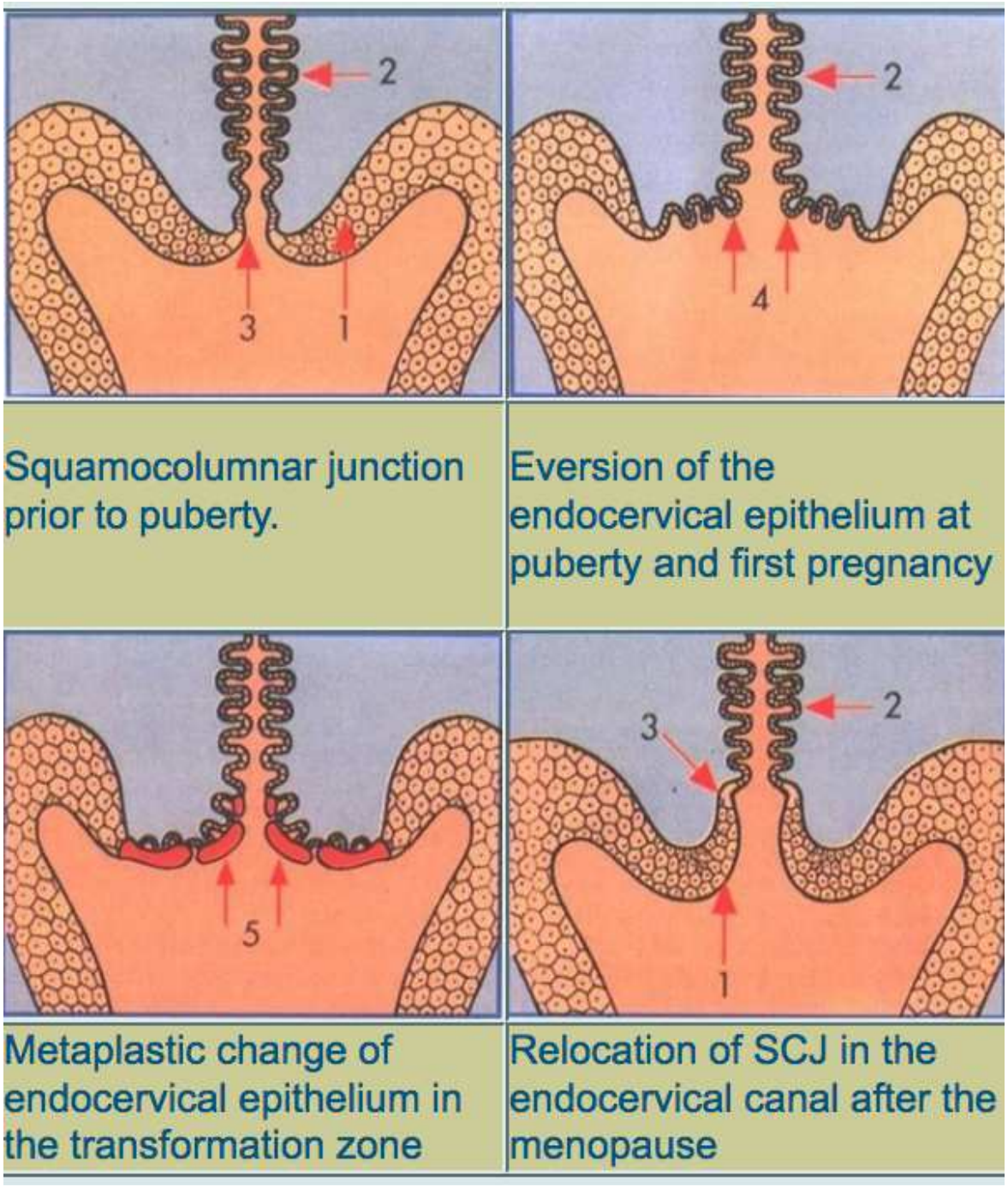
Figure 22-13 Endocervical polyp composed of a dense fibrous stroma covered with endocervical columnar epithelium.

Carcinoma of the cervix

- The major risk is infection by HPV.
- HPV16, 60% of cases
- HPV18,10% of cases
- The cervix, with its relatively large areas of immature squamous metaplastic epithelium, is particularly vulnerable to HPV infection
- Viral proteins E6 and E7 deregulate reparative proteins, p53 and Rb, at cell cycle check points that regulate cell growth and, thus, impair DNA repair as well
- Viral DNA integrated into chromosome

Carcinoma of the cervix

- E7 binds to the activated form of RB and promotes its degradation by proteasomes
- E7 interferes with p21 and p27 (cyclin dependent kinase inhibitors)
- E6 binds to p53 and promotes its degradation by proteasomes
- E6 of low risk HPV (e.g., 6 and 11) does not bind p53
- Interferes with Notch signaling
- Low risk HPV DNA remains epichromosomal



Carcinoma of the cervix begins at the endocervical junction.

The routine Pap smear

- Screen throughout active sexual life
- False negative rate is up to 20% and largely represents error sampling of cervix.
- Risk factors for cervical cancer include:
- First intercourse earlier than 18 years of age
- More than six sexual partners
- Oral contraceptive use for more than 10 years
- Screen no more frequently than every 2-3 years if significant dysplasia is not found.

The routine Pap smear

- A negative liquid based Pap smear every 2 years until the age of 30 may then yield to less frequent screening (every 3 years) with concomitant HPV testing in patients at risk for HPV infection, not simply with condylomata.
- Terminate screening at age 70 or following hysterectomy if not performed for cancer.

The routine Pap smear

- History of genital warts is not an indication for HPV testing as the HPV strains are not associated with cervical cancer.
- Screen only if dysplasia found.
- Partner with penile cancer or whose previous partner has had cervical cancer
- Cis-gender sexual activity transmits HPV
- Chlamydia screens are only for those less than 24 years of age or pregnant and at high risk

Pap smear

- Atypical squamous cells of uncertain significance [ASUS] may represent HPV infection if no other abnormality present. HPV determination is indicated.
- Absence of cells from transformation zone may reflect inadequate scraping of endocervical canal.
- Presence of endometrial cells in the Pap smear of a woman older than 40 not on hormone therapy requires further investigation.

Bethesda grading system

Mild dysplasia CIN-I	Moderate dysplasia CIN-II	Severe dysplasia or carcinoma in situ CIN-III	Invasive
Atypical squamous cells of undetermined significance (ASC-US)	Low-grade squamous intraepithelial lesion (LGSIL or LSIL)	Atypical squamous cells – cannot exclude HSIL (ASC-H) High grade squamous intraepithelial lesion (HGSIL or HSIL)	Squamous cell carcinoma
Occupies lower third of mucosal thickness	Occupies at least 50% of mucosal thickness	Occupies entire mucosal thickness; basement membrane intact	Invades basement membrane

Pap smear

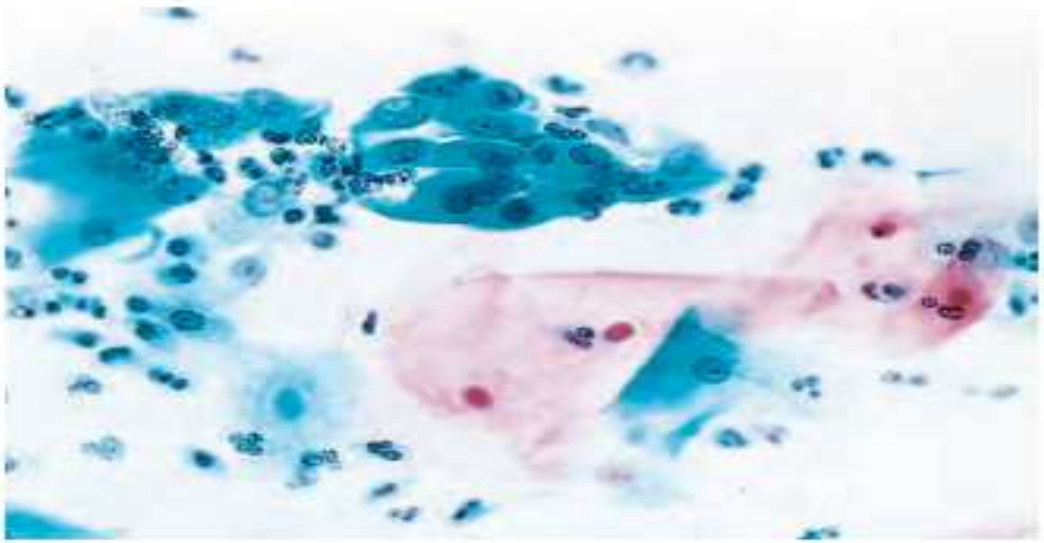
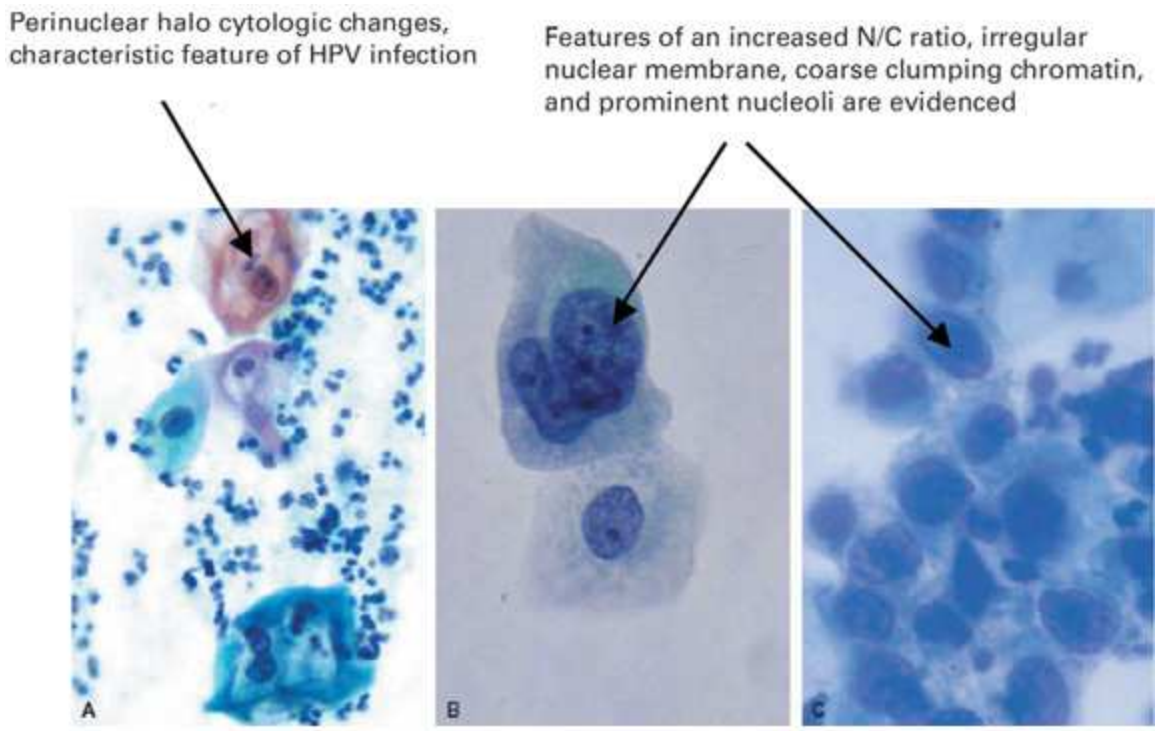


Figure 7-47 A normal cervicovaginal smear shows large, flattened squamous cells and groups of metaplastic cells; interspersed are neutrophils. There are no malignant cells. (Courtesy Dr. P. K. Gupta, University of Pennsylvania, Philadelphia, Pa.)

Pap smear



Source: Kantarjian HM, Wolff RA, Koller CA: *MD Anderson Manual of Medical Oncology*: http://www.accessmedicine.com

Cytologic changes associated with cervical intraepithelial neoplasia (CIN), including CIN1 with koilocytotic feature of HPV infection A. x600 magnification, CIN2 B. x1000 magnification, and CIN3 C. x1000 magnification.

Fig. 24-10 Accessed 08/01/2010

Pap smear

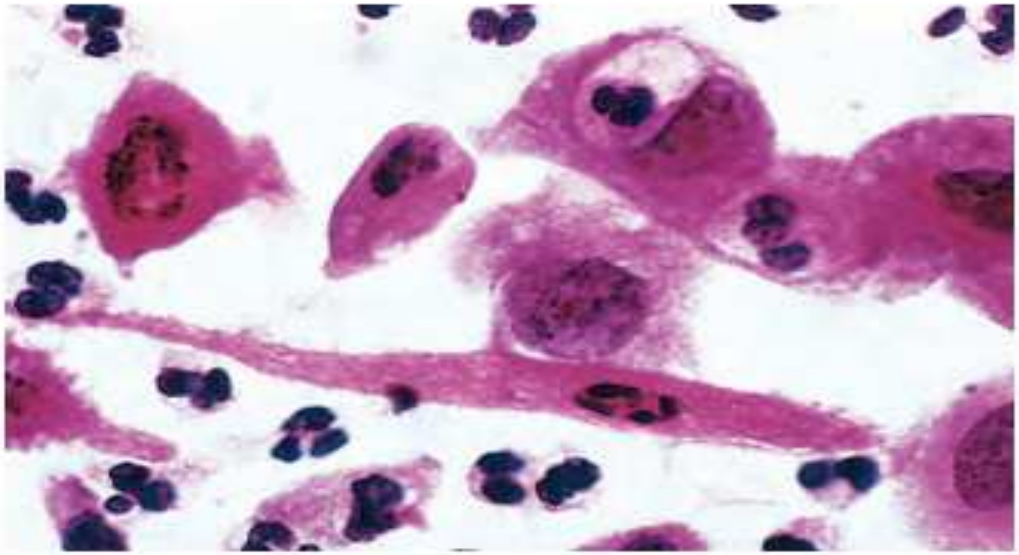
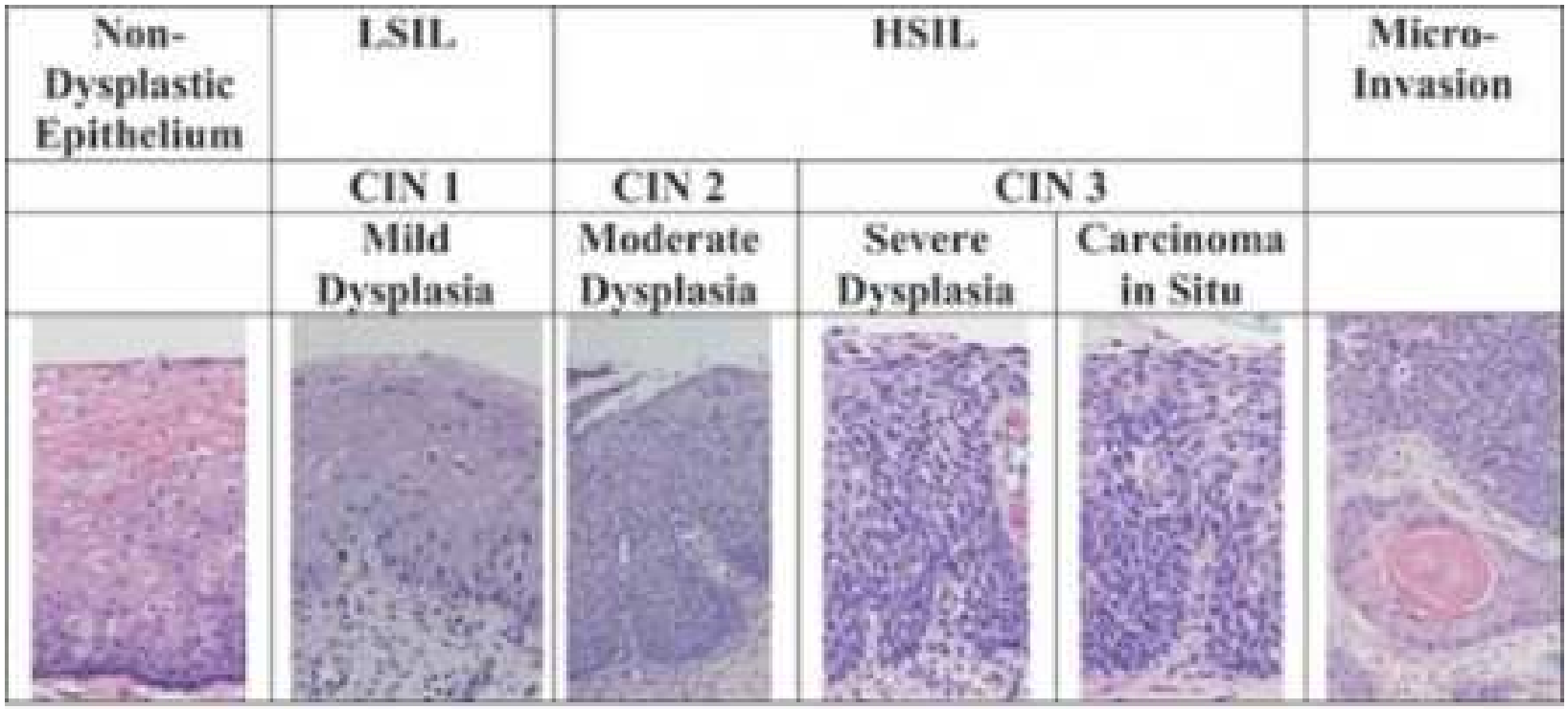


Figure 7-48 An abnormal cervicovaginal smear shows numerous malignant cells that have pleomorphic, hyperchromatic nuclei; interspersed are normal polymorphonuclear leukocytes. (Courtesy Dr. P. K. Gupta, University of Pennsylvania, Philadelphia, Pa.)

Carcinoma of the cervix

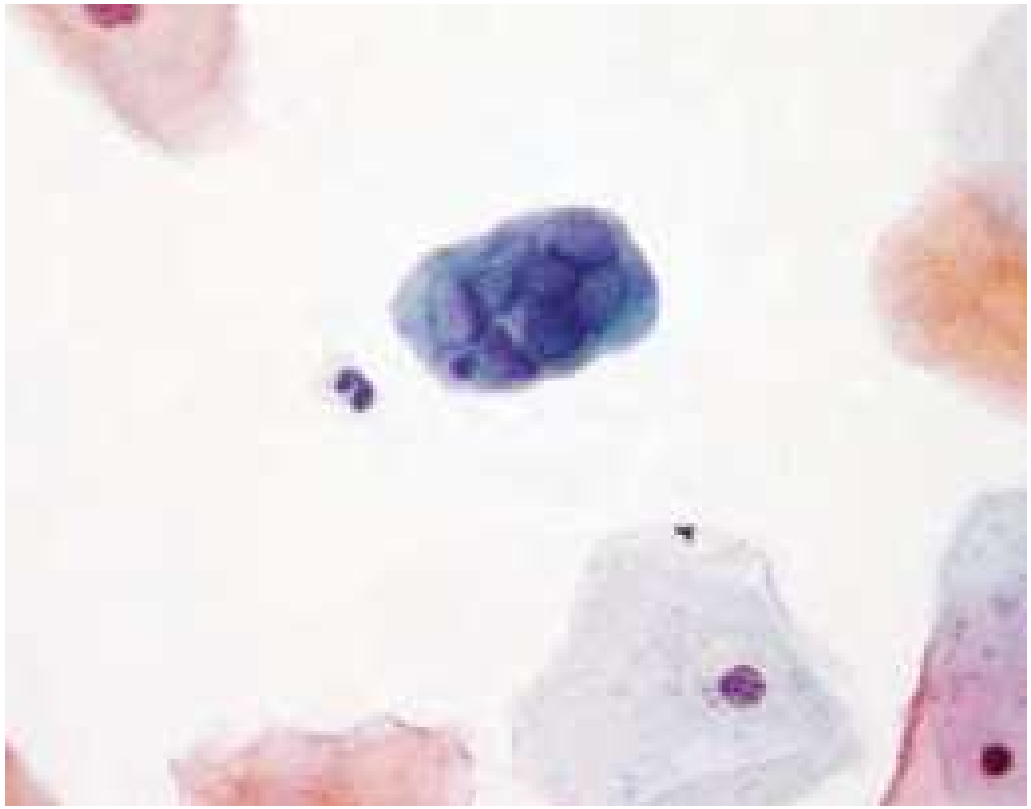
- The rate of progression from mild to moderate dysplasia is 1%/year, and can be followed on Pap smear.
- However, progression from moderate to severe dysplasia, the risk is 16% within 2 years and 25% within 5 years.
- Severe dysplasia if untreated leads to cancer in 12% of patients over a period of 20 years.
- Presents with abnormal vaginal bleeding (often postcoital). May complain of dyspareunia.



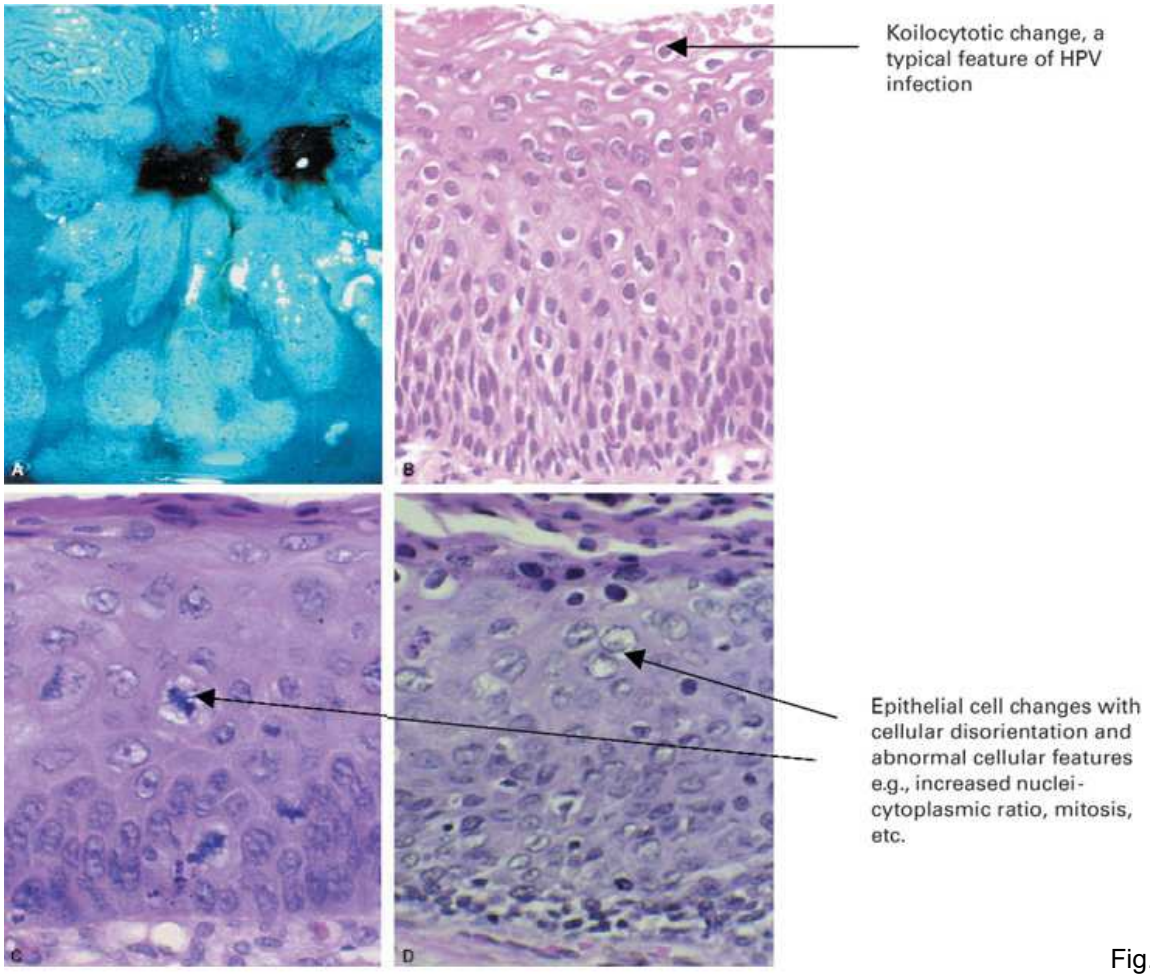
Images courtesy of Chisa Aoyama, MD, David Geffen School of Medicine at UCLA.

https://hackteria.org/wiki/images/thumb/0/0e/CIN-4.jpg/447px-CIN-4.jpg
Accessed 05/05/2020

HSV cytopathic effect



Grading



A. Colpophotograph illustrating a low-grade cervical intraepithelial neoplasia (CIN) in the transformation zone. B, C, and D. Histopathology of cervical intraepithelial neoplasia (CIN I, II, and III respectively) (H&E stain; x400 magnification).

Fig. 24-4 Accessed 08/01/2010

Grading

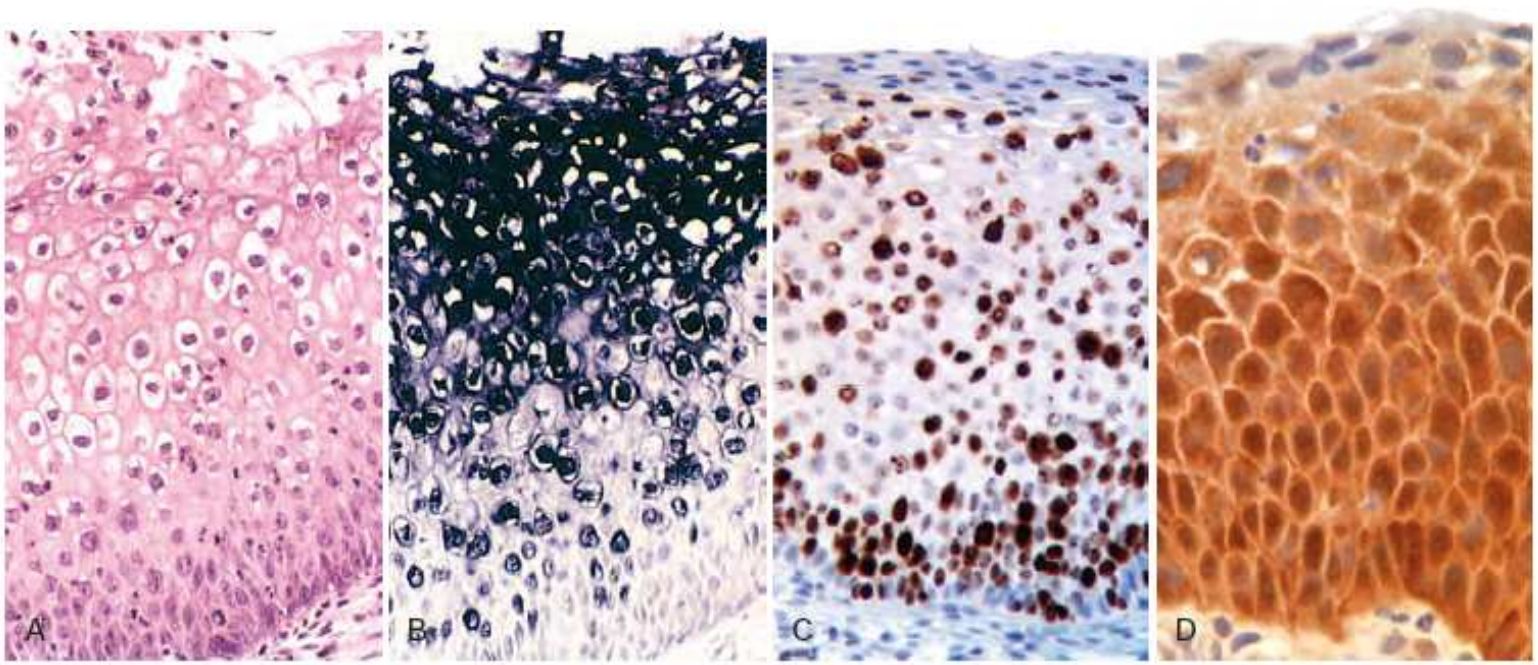


Figure 22-15 **A,** Low-grade squamous intraepithelial lesion (LSIL)—Routine hematoxylin and eosin staining shows marked koilocytic change, seen as perinuclear "halos" in suprabasilar cells. **B,** In situ hybridization test for HPV DNA. The dark granular staining denotes HPV DNA, which is typically most abundant in the koilocytes. **C,** Diffuse positivity for the proliferation marker Ki-67 (seen as brown nuclear staining), illustrates abnormal expansion of the proliferating cells from the normal basal location to the superficial layers of the epithelium. **D,** Upregulation of the cyclin-dependent kinase inhibitor p16 (seen here as brown staining) characterizes high-risk HPV infections.

Carcinoma of the cervix

- May be exophytic or invasive
- Spread by direct extension
- Squamous cell carcinoma (70%)
- Composed of nests and tongues of malignant squamous epithelium, either keratinizing or non-keratinizing, which invade the underlying cervical stroma
- Invasive carcinoma is usually non-keratinizing.
- Almost all are PD-L1 positive

Carcinoma of the cervix

- Adenocarcinoma (20-25%)
- Characterized by proliferation of glandular epithelium composed of malignant endocervical cells with large, hyperchromatic nuclei and relatively mucin-depleted cytoplasm
- HPV related
- HPV18 common
- Generally, ER+, PD-L1 negative

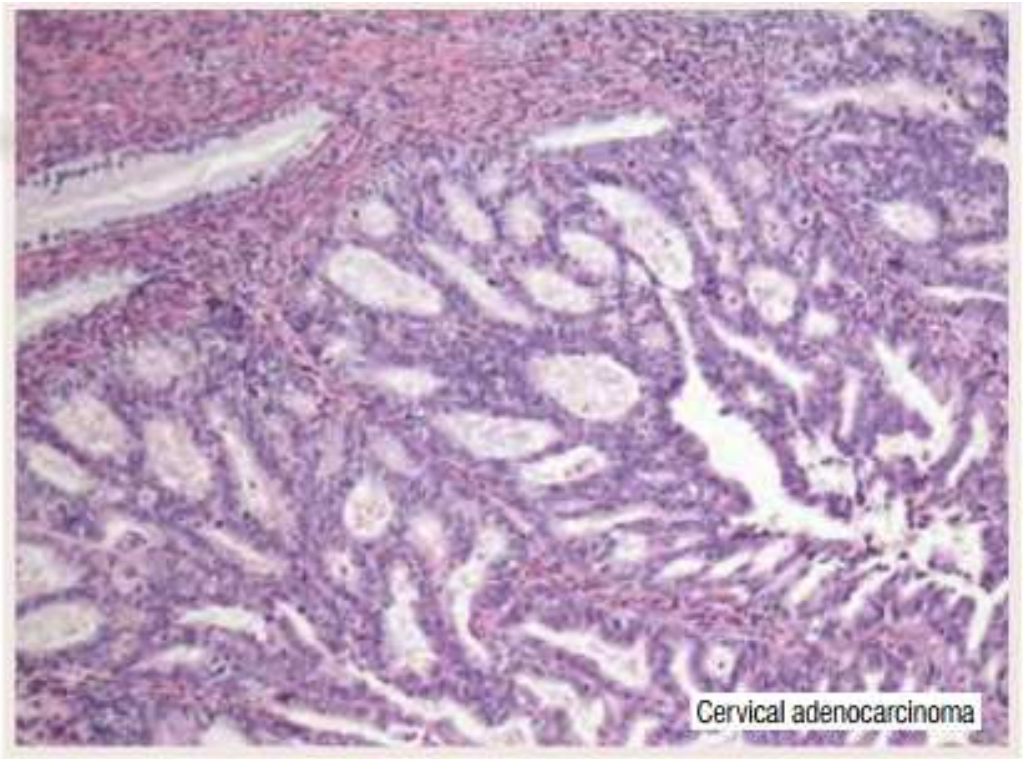
Carcinoma of the cervix

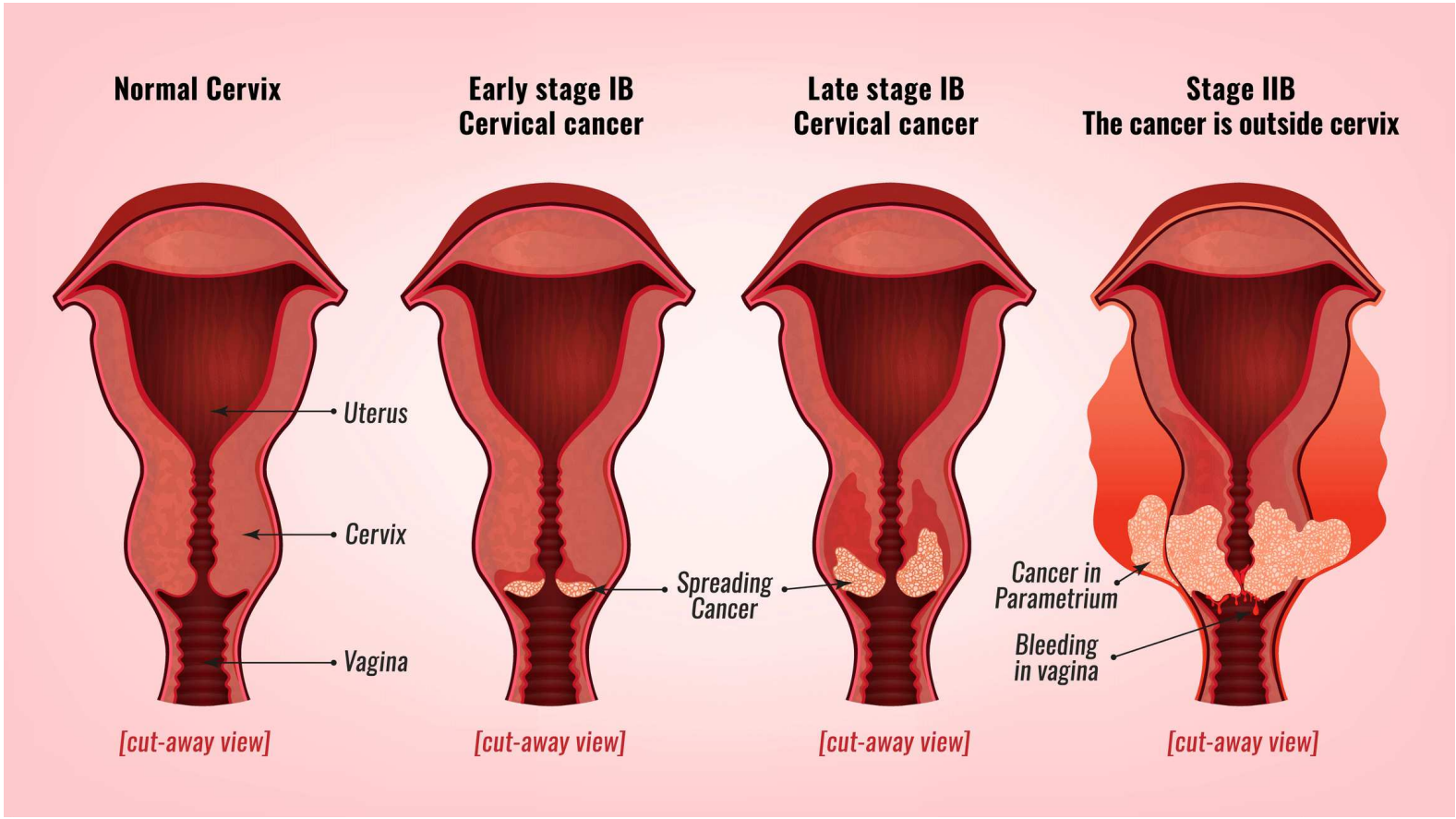
- Histological types include endocervical and mucinous; mixed adenosquamous carcinomas may occur.
- Gastric type mucinous and clear cell adenocarcinoma and adenocarcinoma arising from mesonephric remnants are not HPV related

- Neurodenocrine carcinoma (5%)
- 80%, small cell variant
- HPV related
- PIK3CA, KRAS, and TP53 usual mutations
- Highly aggressive

Carcinoma of the cervix

- Serious reactions have been reported with the general administration of HPV vaccine (infertility, loss of bladder function)
- Vaccination regimens in advanced and precancerous lesions are associated with >50% clinical response rates and evidence of induction of HPV-specific immunity.


Cervical adenocarcinoma



https://physicianreviews.org/wp-content/uploads/2018/12/Stages-of-Cervical-Cancer.gif

Stage	Extent of disease	5-year survival
0	Carcinoma in situ (CIN)	~100%
I	Limited to cervix	
Ia1	Microscopic disease: stromal invasion <3mm, lateral spread <7mm	>95%
Ia2	Microscopic disease: stromal invasion <3mm and >5mm, lateral spread <7mm	
Ib1	Macroscopic lesion <4cm in greatest dimension	~90%
Ib2	Macroscopic lesion >4cm in greatest dimension	80-85%
II	Extension to uterus/parametria/vagina	~75-78%
IIa1	Involvement of upper two thirds of vagina *without* parametrial invasion, <4cm greatest diameter	
IIa2	Involvement of upper two thirds of vagina *without* parametrial invasion, >4cm greatest diameter	
IIb1	Involvement of upper two thirds of vagina *with* parametrial invasion	
III	Extension to pelvic side wall and/or lower third of vagina	~47-50%
IIIa	Involvement of lower third of vagina	
IIIb	Extension to pelvic side wall and/or hydronephrosis	
IV	Extension to adjacent organs or beyond true pelvis	~20-30%
IVa	Extension to adjacent organs e.g. bladder, bowel	
IVb	Distant metastases	

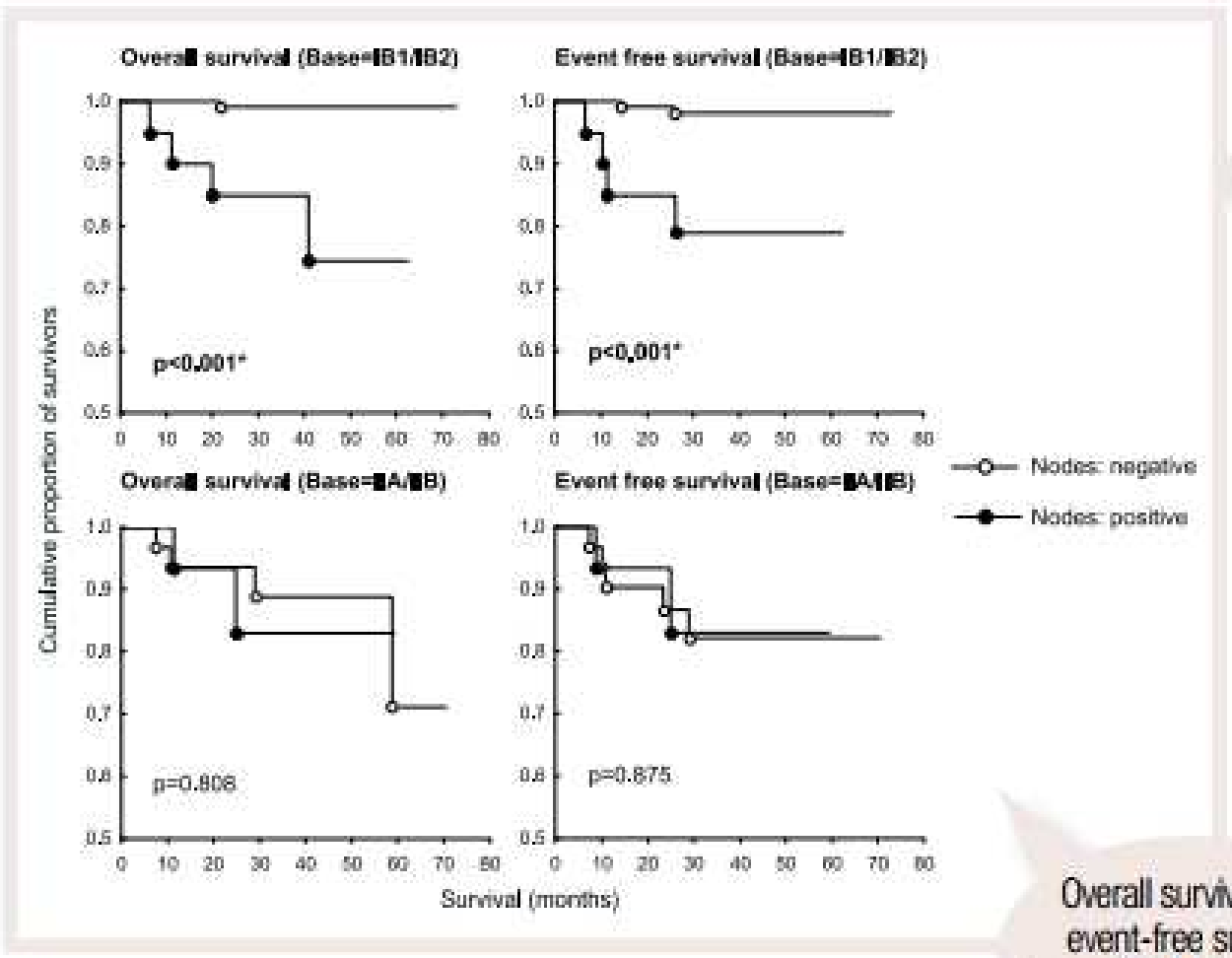
https://www.bing.com/images/search?view=detailV2&ccid=kuUo8sHH&id=589F93720A53C9B67CAEDA66A518C6D744008DBE&thid=OIP.kuUo8sHHPPeF2EVCJe9chwHaGh&mediaurl=http%3A%2F%2Fgeekymedics.com%2Fwp-content%2Fuploads%2F2014%2F01%2Fcervical-cancer-staging-FIGO.jpg&exph=611&expw=693&q=staging+cervical+cancer&simid=608019725107987627&ck=73EB5120E100286

FIGO stages	TNM categories		
Stage IIIB	T1, T2, T3	N1	M0
Stage IVA	T4	Any N	M0
Stage IVB	Any T	Any N	M1

FIGO, International Federation of Gynecology and Obstetrics; TNM, tumour node metastasis.

Regional lymph nodes (LNs) for cervical cancer are pelvic nodes including the: paracervical, parametrial, internal iliac (II), obturator (OB), common iliac (CI), external iliac (EI) and presacral (PS).

Involvement of para-aortic (PA) or inguinal LNs is considered distant metastasis.



Overall survival and event-free survival according to FIGO stag and LN status

Involvement of para-aortic LNs significantly worsens prognosis.

Additional prognostic parameters include: parametrial involvement, lymphovascular space invasion (LVSI) and histological type (a better prognosis for squamous cell cancer).

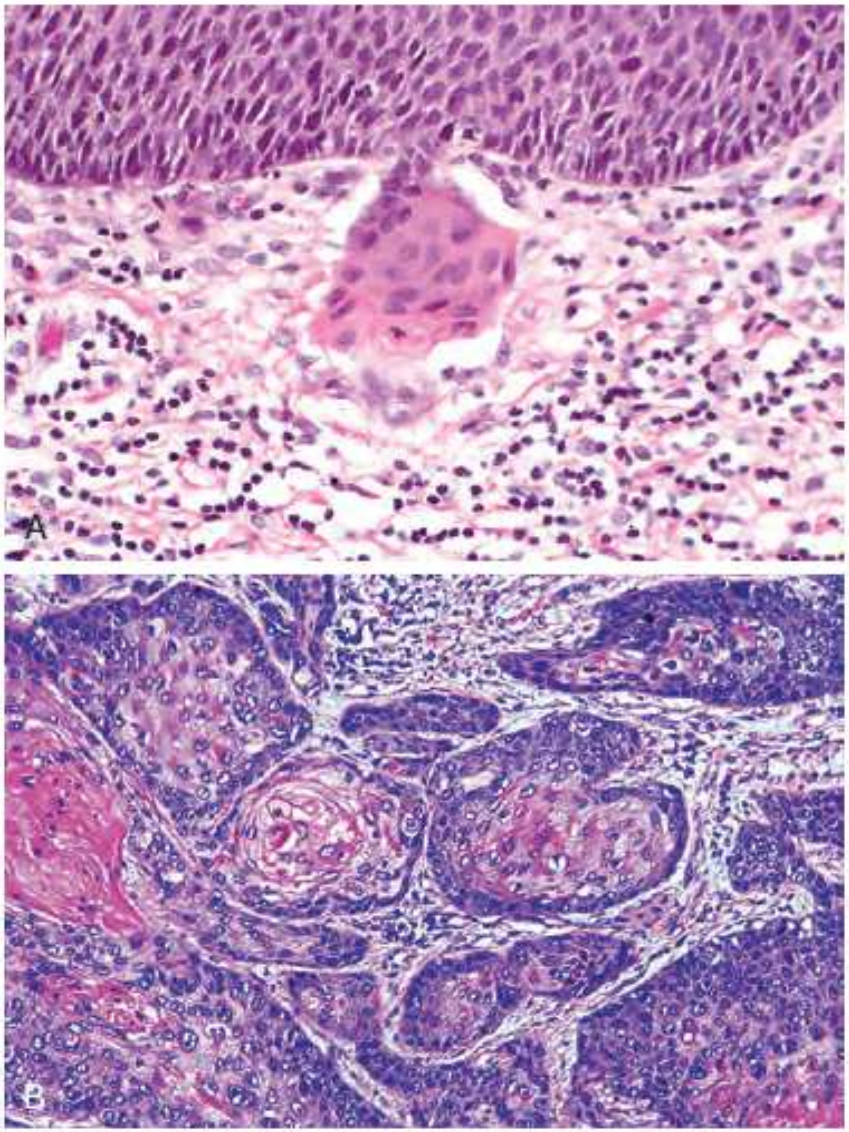


Figure 22-16 Squamous cell carcinoma of the cervix. **A,** Microinvasive squamous cell carcinoma with invasive nest breaking through the basement membrane of high-grade squamous intraepithelial lesion. **B,** Invasive squamous cell carcinoma.

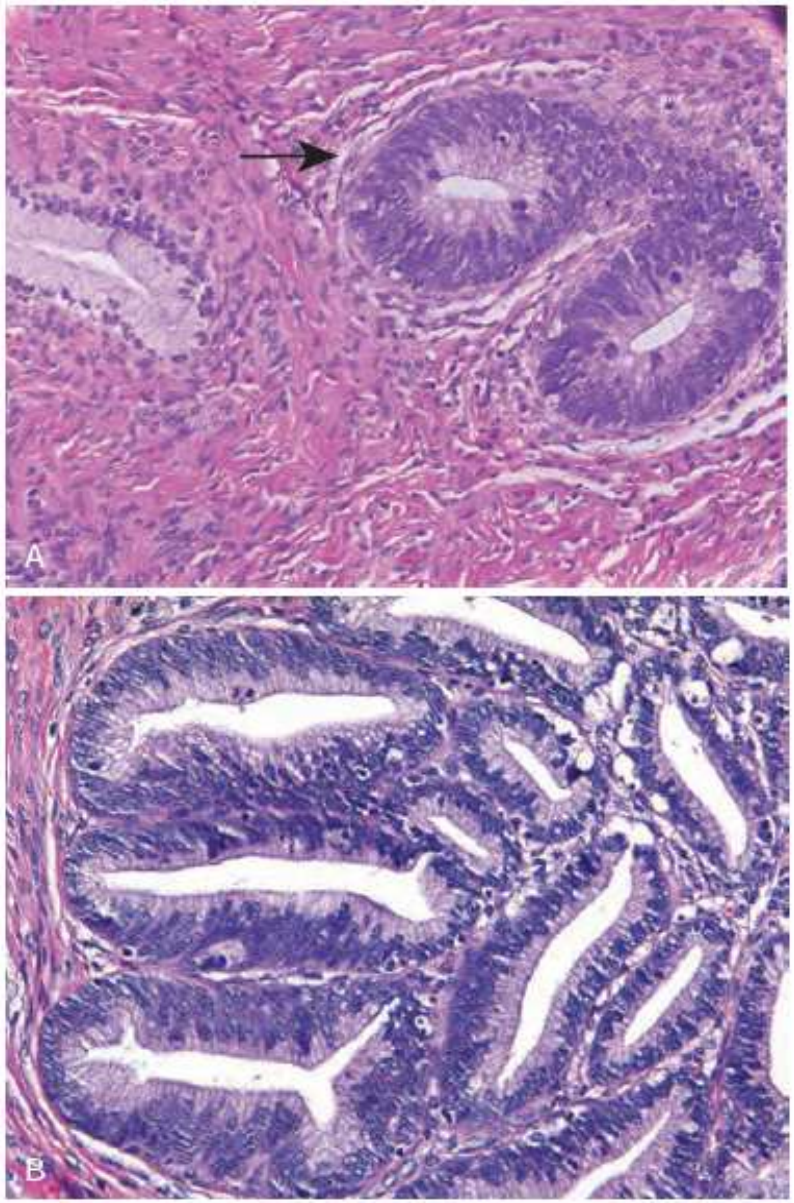


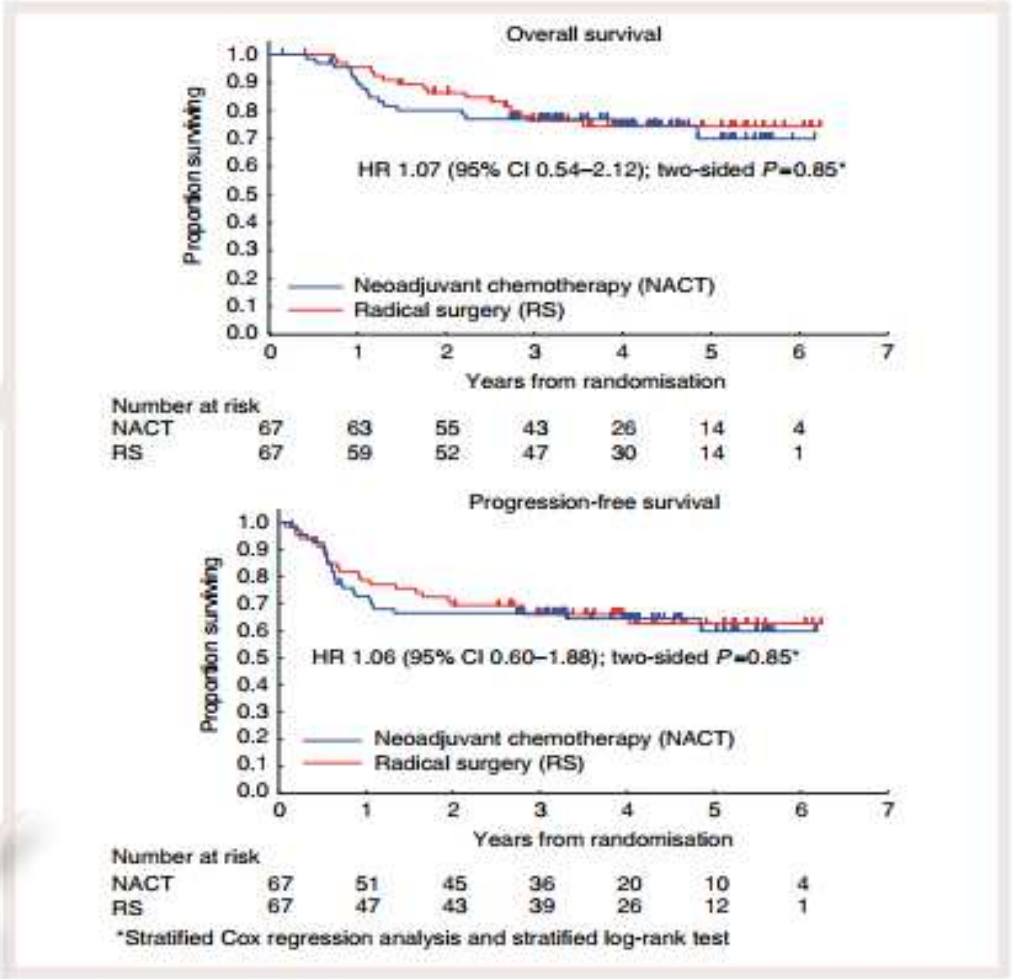
Figure 22-17 Adenocarcinoma of the cervix. **A,** Adenocarcinoma in situ *(arrow)* showing dark glands adjacent to normal pale endocervical glands. **B,** Invasive adenocarcinoma.

Therapy

- Simple hysterectomy or conization is considered a sufficient procedure for Stage IA cervical cancer, due to the very low risk of parametrial involvement and an excellent prognosis.
- No lymph node staging required
- LN staging is mostly recommended in Stage IA2, due to a higher risk of LN involvement. These cases are good candidates for SLN biopsy and ultrastaging (search for micrometastases).
- 15-30% with local disease have para-aortic disease

Therapy

- The principle of radical hysterectomy (RH) is removal of tissue surrounding the cervix (parametrium) and/or the upper part of the vagina in addition to the uterus with or without adnexa.
- If the aim is to preserve fertility, the distal part of the cervix, with the upper part of the vagina, is removed either with the parametrium (radical trachelectomy) or without it (simple trachelectomy).
- 2-3% recurrence
- Postoperative morbidity is caused mostly by the resection of the parametria and upper vagina.



CI, Confidence interval; HR, hazard ratio.

Therapy

- 10-50% have voiding dysfunction following surgery
- 10-30% have anorectal dysfunction following surgery
- 30% lymphedema or pelvic lymphocele as a consequence of pelvic lymphadenectomy
- Prognostic significance of para-aortic lymphadenectomy uncertain
- Micrometastases associated with worse prognosis
- Stage IB and IIA may be treated with radiation and chemotherapy (Cisplatin, 5FU) as alternative to radical hysterectomy and chemotherapy

Therapy

- Chemoradiation is the standard treatment option for ≥FIGO Stage IIB, III and IVA.
- Ovaries removed from field to preserve fertility.
- In pregnancy, chemotherapy in second or third trimester well tolerated (55% cisplatin to fetus)
- Cisplatin and paclitaxel chemotherapy with bevacizumab in Stage IVB, relapsed, and metastatic disease.
- If PD-L1 positive, addition of pembrolizumab (PD-L1)
- Radiotherapy is used to control bleeding from cervix
- Tisotumab vedotin-tftv (anti-Tissue Factor antibody conjugated with microtubule disruptor, MMAE) if PD-L1 negative. Blocks angiogenesis as well.
- Ocular toxicity

Therapy

- Pelvic exenteration (PE) is a treatment of choice in cases with central pelvic recurrence or tumor progression, with or without previous radiotherapy.
- PE can be performed as an anterior (preserving rectum), posterior (preserving urinary bladder and urethra) or total procedure, with consequent creation of a colostomy and/or urostomy (continent or incontinent).

Therapy

- PE is associated with high postoperative morbidity (50%–90%), mortality (up to 10%) and in some cases a long-term deterioration in quality of life, depending on the indication and stage of the disease.
- Overall survival 50%
- Para-aortic lymph nodes most important prognostic parameter

UTERUS

Adenomyosis

- The extension of endometrial glands and stroma into the uterine musculature.
- About 15% of patients with adenomyosis have associated endometriosis.
- Incidence peaks in women in their 40’s.
- Menorrhagia and dysmenorrhea.
- Gross appearance that of a diffusely enlarged myometrium with focal glandular abnormalities.
- Surgery only effective option.

Leiomyoma

- Uterine leiomyomas (fibroids) are perhaps the most common tumor in humans.
- Present in 75% of females of reproductive age.
- May be asymptomatic.
- Occur within the myometrium (intramural), just beneath the endometrium (submucosal) or beneath the serosa (subserosal)
- If submucosal or intramural, may compromise uterine cavity and interfere with pregnancy.
- Often multiple
- Malignant transformation rare.

Leiomyoma

- Whorled bundles of smooth muscle cells with rare mitotic figures characterizes leiomyoma.
- Each uterine leiomyoma is a unique clonal neoplasm.
- 40% have chromosomal abnormality:
- t(12;14)(q14-15;q23-24), del 7(q22-32), trisomy 12, and rearrangements of 6p, 3q, and 10q
- 12q14 and 6q involve HMGIC and HMGIY genes that encode closely related DNA-binding factors that regulate chromatin structure.

Leiomyoma

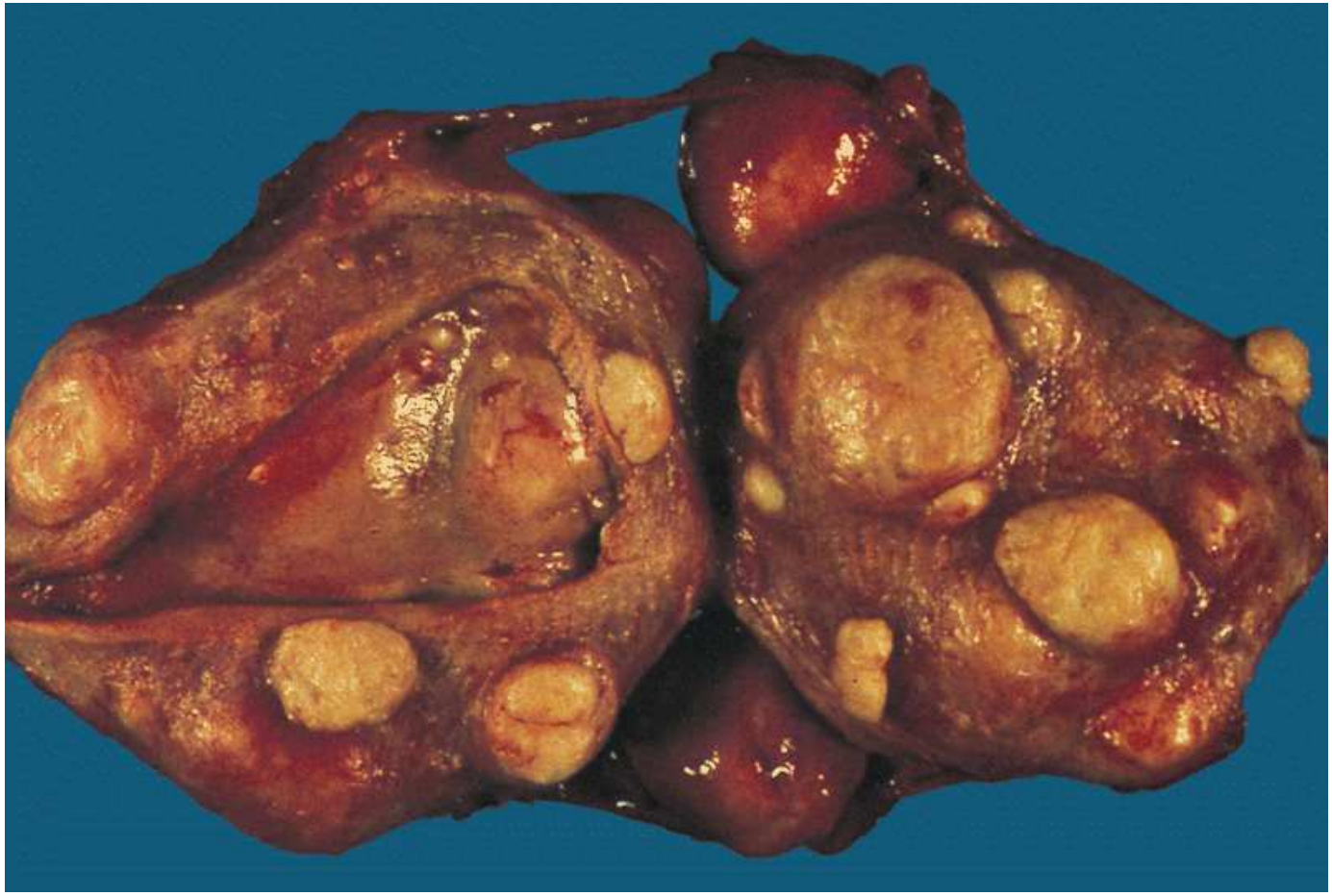


Plate 4A

Silverberg, Steven S, and Kurman, Robert J, “Tumors of the uterine corpus and gestational trophoblastic disease,” Atlas of Tumor Pathology. Third Series, Fascicle 3. Armed Forces Institute of Pathology. Washington, DC . 1991.

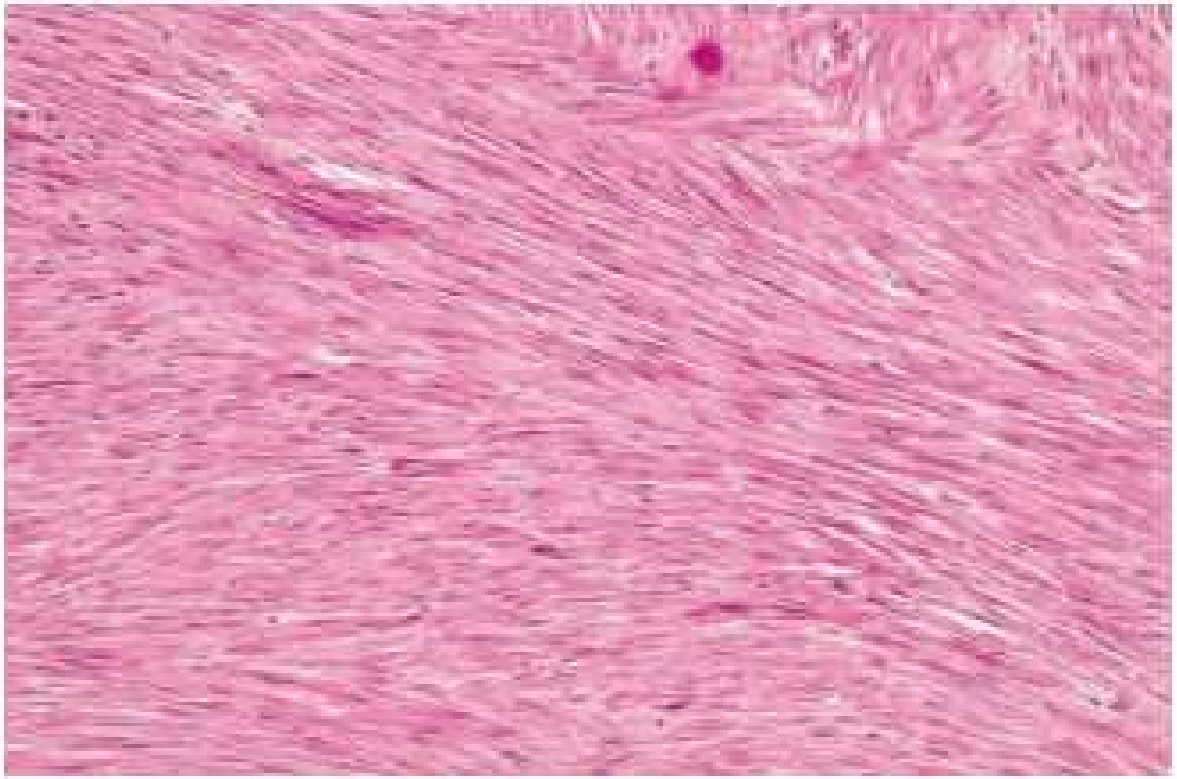
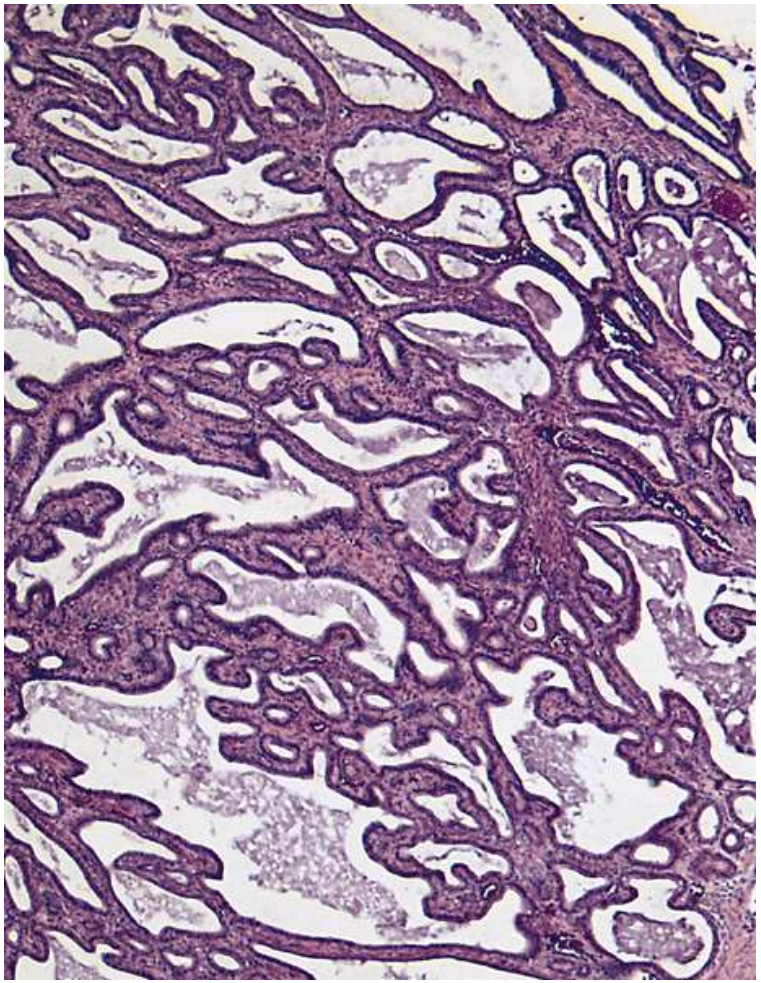


Figure 7-4 Leiomyoma of the uterus. This benign, well-differentiated tumor contains interlacing bundles of neoplastic smooth muscle cells that are virtually identical in appearance to normal smooth muscle cells in the myometrium.

Endometrial polyp

- Stroma is neoplastic
- Glands may be atrophic or hypeplastic
- Little response to progesterone

Endometrioid polyp



The glands are lined by benign epithelium and are separated by small amounts of fibrous stroma.

Fig. 5-11

Scully, Robert E, Young, Robert H, Clement, Phillip B. Tumors of the ovary, maldeveloped gonads, fallopian tube, and broad ligament. Atlas of Tumor Pathology, Third Series, Fascicle 23. Armed Forces Institute of Pathology. Washington, D.C, 1998.

Endometrial hyperplasia

- Presents as a proliferation of glands and stroma, with crowding of glands, increase in mitotic figures, and prominent nucleoli in nucleus.
- Unopposed estrogen stimulation
- Pap smear rarely shows hyperplasia but it may be suggested by AGUS result (abnormal glandular cells of undetermined significance) on Pap smear.
- A pre-malignant lesion.

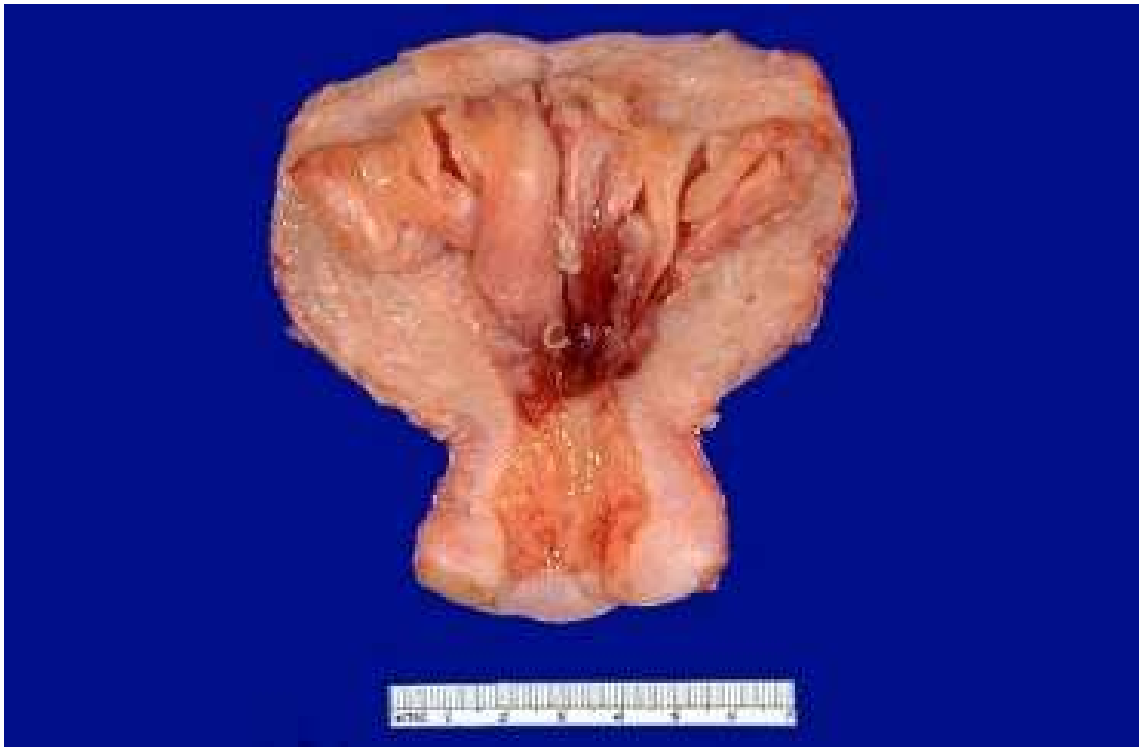
Endometrial hyperplasia

- Non-atypical endometrial hyperplasia
- Simple.
- Regular glandular pattern. No cytologic atypia.
- 1% will progress to cancer.
- Complex.
- Irregular glands crowded back to back. No atypia.
- 3% will progress to cancer.

Endometrial hyperplasia

- Atypical endometrial hyperplasia (endometrial intraepithelial carcinoma)
- Simple with atypia.
- 8% will progress to cancer.
- Complex with atypia.
- 29% will progress to cancer.
- PTEN lost (PI3K/AKT overactive)
- Enhances the ability of the estrogen receptor to turn on the expression of its target gene
- Up to 20% of hyperplasias and 80% of endometrial carcinomas

Endometrial hyperplasia



Endometrial hyperplasia usually results with conditions of prolonged estrogen excess and can lead to metrorrhagia (uterine bleeding at irregular intervals), menorrhagia (excessive bleeding with menstrual periods), or menometrorrhagia.
https://webpath.med.utah.edu/FEMHTML/FEM019.html Accessed 05/05/2020

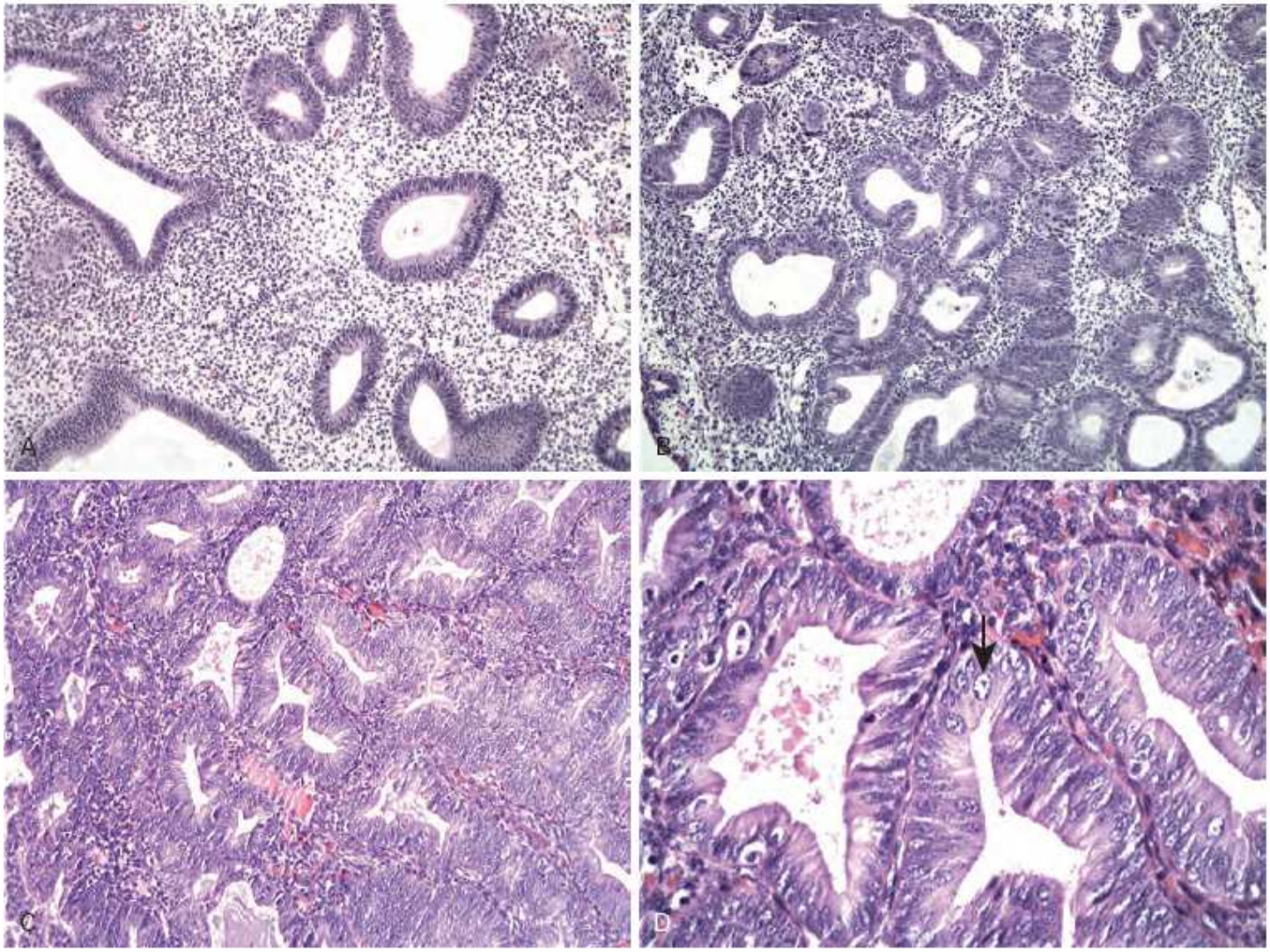


Figure 22-23 Endometrial hyperplasia. **A,** Hyperplasia without atypia. Note architectural abnormalities including mild glandular crowding and cystic glandular dilatation. **B,** Hyperplasia without atypia demonstrating increased glandular crowding with areas of back-to-back glands and cytologic features similar to proliferative endometrium. **C,** Atypical hyperplasia with further increase in glandular crowding and abnormal cytologic features. **D,** High magnification of atypical hyperplasia showing rounded, vesicular nuclei with prominent nucleoli *(arrow)*.

Endometrial carcinoma

- Most common invasive cancer of female genital tract
- 75% are Type I (endometrioid carcinoma)
- Related to hyper-estrogen state
- 81% of endometrial cancers associated with a BMI>30
- Diabetes mellitus, nulliparity, polycystic ovary syndrome and tamoxifen administration as other risk factors.
- Insulin resistance common

Endometrial carcinoma

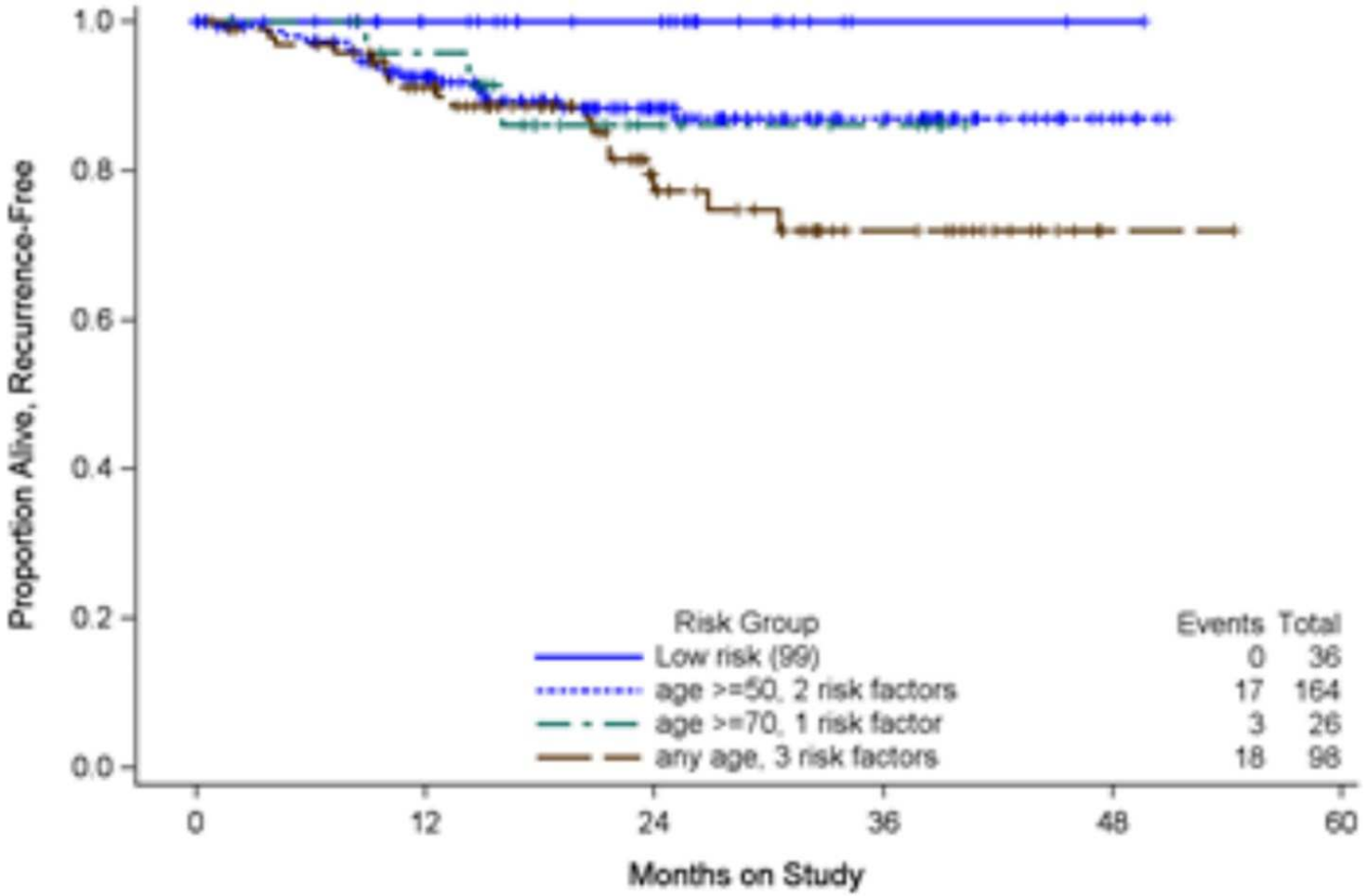
- Lynch syndrome and hereditary non-polyposis colon cancer are other risk factors.
- Protective factors include the use of oral contraception, increasing age at menarche, number of delivered children and smoking.
- Twice as common in those of African descent
- Peak incidence 50-65 years of age
- Presents with abnormal vaginal bleeding

Endometrioid carcinoma

- Ultrasonography of uterus as screening test
- >3mm endometrial thickness as cutoff
- Tampon collections or uterine swabs may collect cells to identify GYPC mutation noted in endometrioid cancer.
- Can take the form of a localized polypoid tumor or a tumor that diffusely infiltrates the endometrial lining.
- Uterine risk factors included grade 2 or 3, presence of lymph vascular space invasion, and depth of invasion to the outer one-third of the myometrium.
- May be associated with extensive peritoneal disease

Endometrioid carcinoma

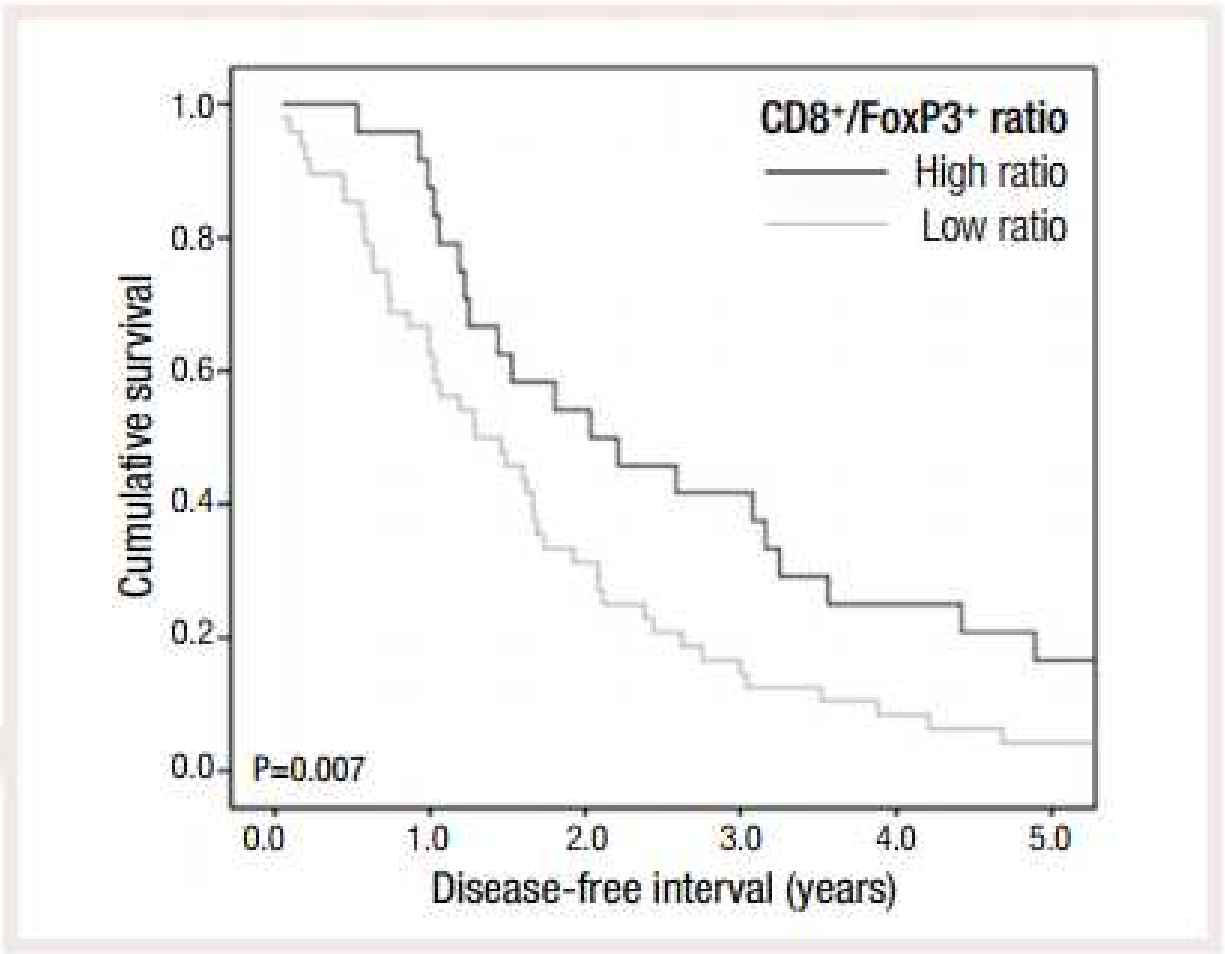
- Spread generally occurs by myometrial invasion followed by direct extension to adjacent structures.
- Invasion of the broad ligaments may create a palpable mass.
- Disseminates to regional lymph nodes
- Hematogenous spread



https://ascopubs.org/doi/full/10.1200/EDBK_175666

Endometrioid carcinoma

- Usually PI3K/AKT and BCL-2 pathways involved together with K-RAS mutations and microsatellite instability.
- PTEN mutated in up to 80%
- PI3CKA mutated in 40%
- KRAS mutated in 25%
- ARID1A mutated in 33%
- MLH mutated in 20%
- TP53 mutated in 50% of poorly differentiated lesions



Recurrent disease

High expression of cyclin A associated with poor prognosis

Endometrioid carcinoma

- Demonstrates glandular growth patterns resembling normal endometrial epithelium.
- If fewer than 50% of the tumor is composed of solid growth, it is moderately well differentiated.
- If >50%, poorly differentiated
- 20% have areas of squamous differentiation

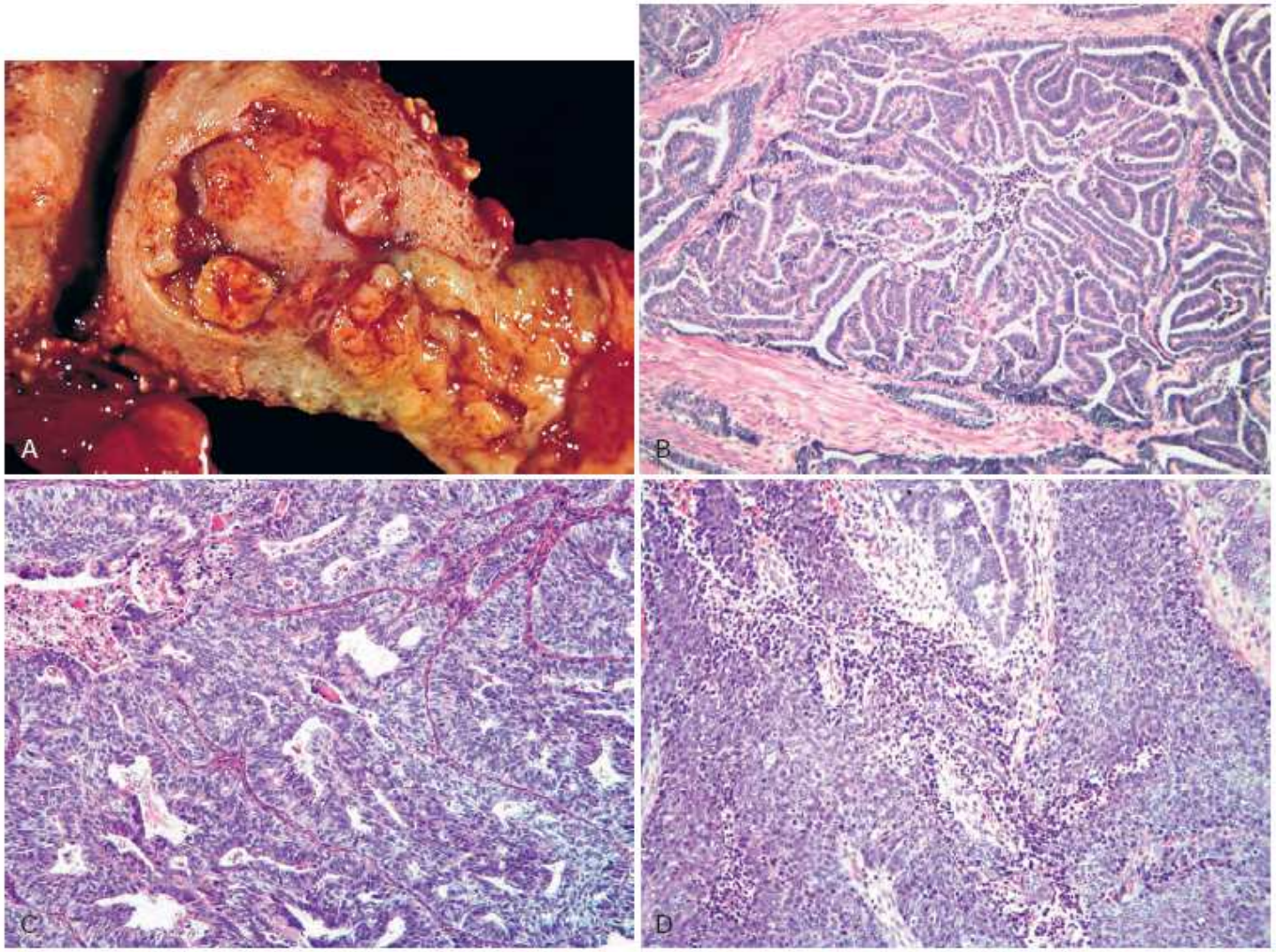


Figure 22-25 Type I endometrial carcinoma. **A,** Endometrial adenocarcinoma presenting as a fungating mass in the fundus of the uterus. **B,** Well-differentiated (grade 1) endometrioid adenocarcinoma with preserved glandular architecture but lack of intervening stroma. **C,** Moderately differentiated (grade 2) endometrioid adenocarcinoma with glandular architecture admixed with solid areas. **D,** Poorly differentiated (grade 3) endometrioid adenocarcinoma with a predominantly solid growth pattern.

Endometrial carcinoma

- Type II
- 15% of cases
- Not related to estrogen
- Arise in endometrial atrophy
- Risk factors as in Type I with the exception of obesity and hereditary predisposition
- 90% have mutated TP53
- HER2/neu often expressed
- Serous carcinoma is most common subtype
- Arise in serous endometrial intraepithelial carcinoma

Endometrial carcinoma

- WHO 2020 classification adds:
- Mesonephric adenocarcinoma
- Mesonephric-like adenocarcinoma
- squamous cell carcinoma
- Mucinous carcinoma, gastrointestinal type
- In each of these it is important to rule out extension from the cervix as this is overwhelmingly the more common site of a primary carcinoma with this morphology.

Serous carcinoma

- Malignant cells identical to those of serous carcinoma of the ovary are confined to the epithelial surfaces
- The invasive lesions may have a papillary growth pattern composed of cells with marked cytologic atypia, atypical mitotic figures, hyperchromasia, and prominent nucleoli
- May also have a predominantly glandular growth pattern
- Distinguished from endometrioid carcinoma by the marked cytologic atypia.
- More frequent if of African ancestry, not obese

Serous carcinoma

- Surgical staging as with serous epithelial ovarian cancer
- Sentinel node detection still not standardized
- Low-risk patients do not benefit from pelvic and para-aortic lymph node dissection
- In intermediate- and high-risk patients with higher risk of lymph node involvement, pelvic (and para-aortic) lymph node dissection will help to guide the necessity for and tailor the type of adjuvant therapy
- Micrometastases associated with worse prognosis

Serous carcinoma

- Laparoscopic surgical staging for uterine cancer results in fewer complications in obese patients, shorter hospital stay, with equivalent oncological outcome
- However, robotic surgery, which utilizes a reverse Trendellenberg position, poses an increased risk for ischemic retinal atrophy

Endometrial carcinoma

- Clear cell carcinoma as other common subtype
- Oxyphil or hobnail cells
- Low mitotic activity
- Solid, glandular, or papillary pattern
- No specific molecular profile

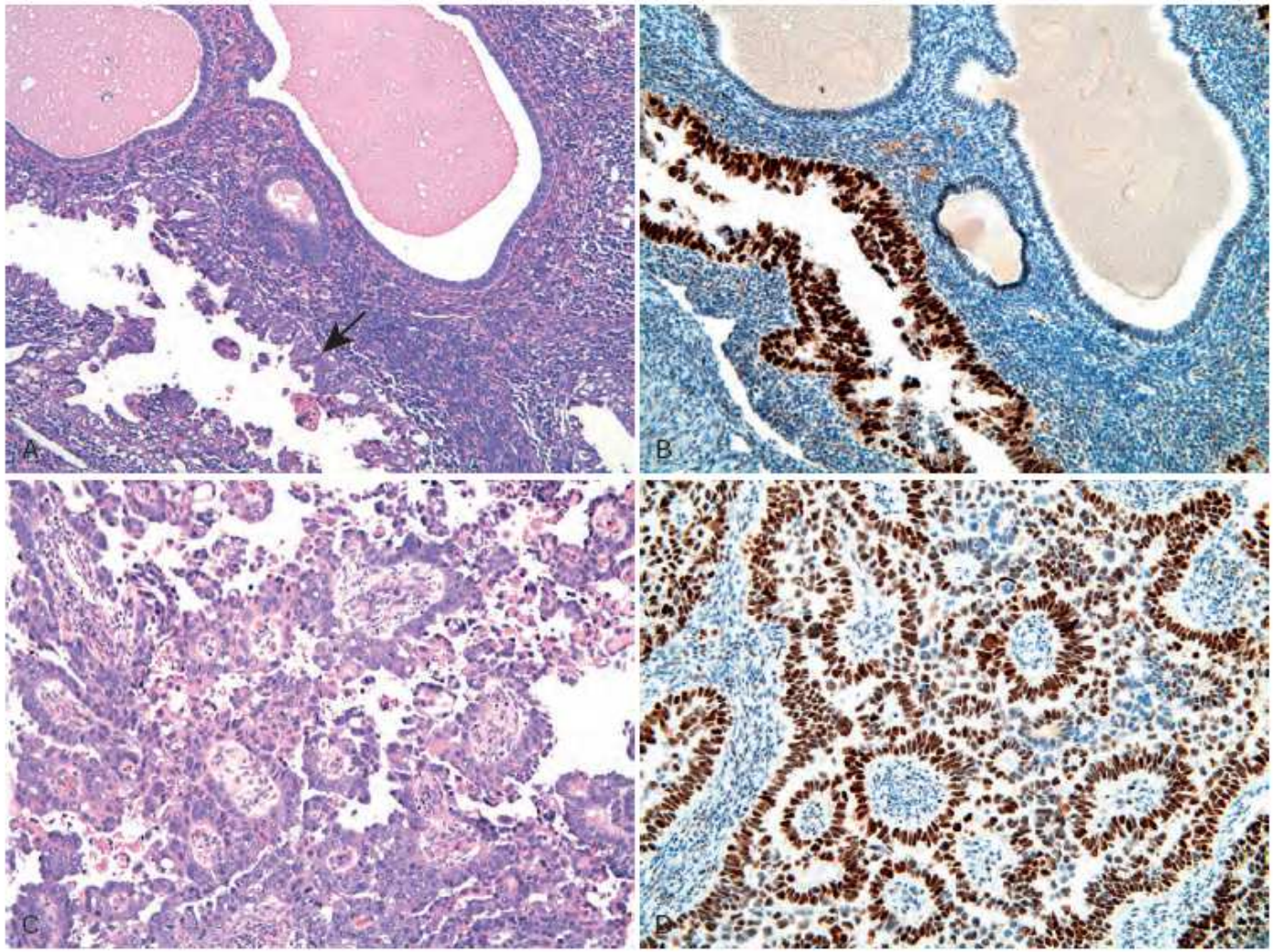
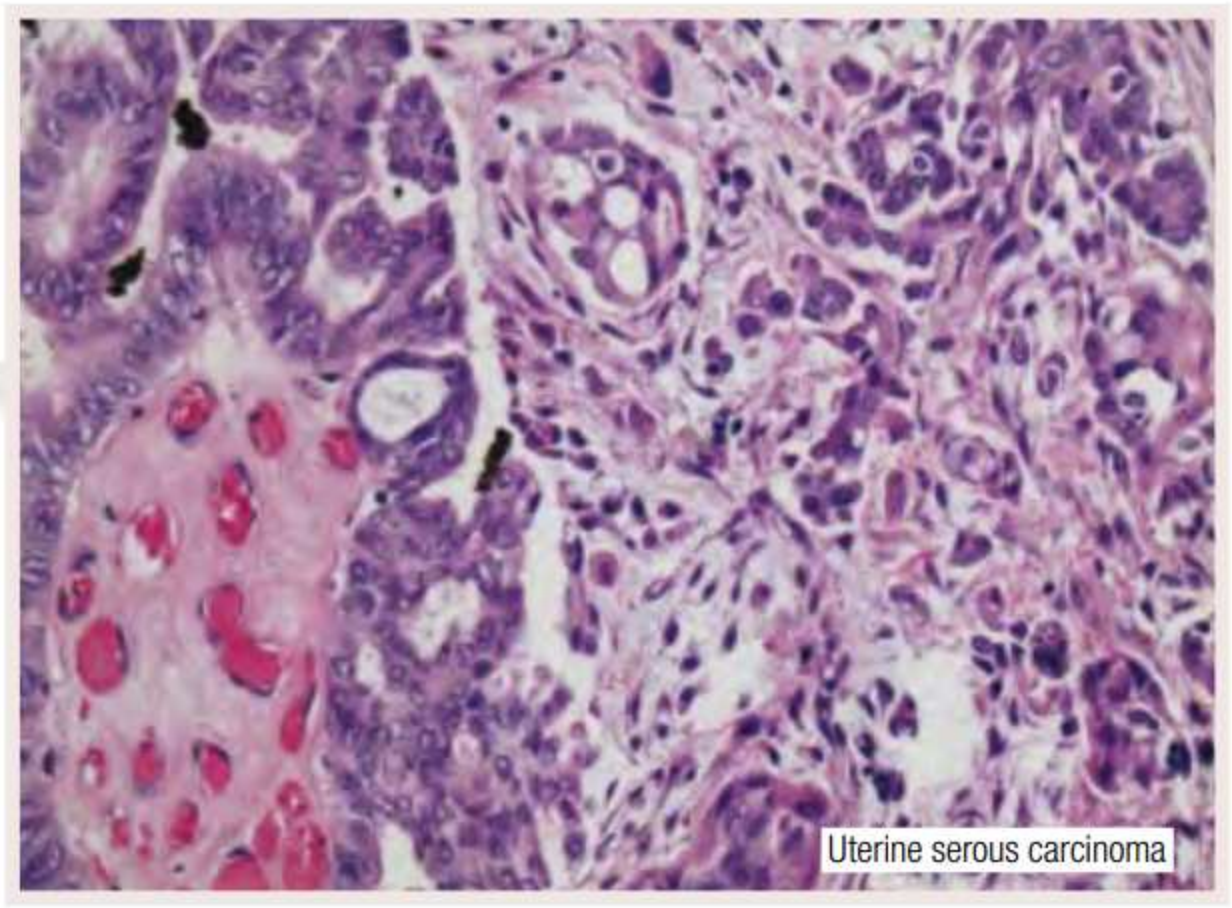
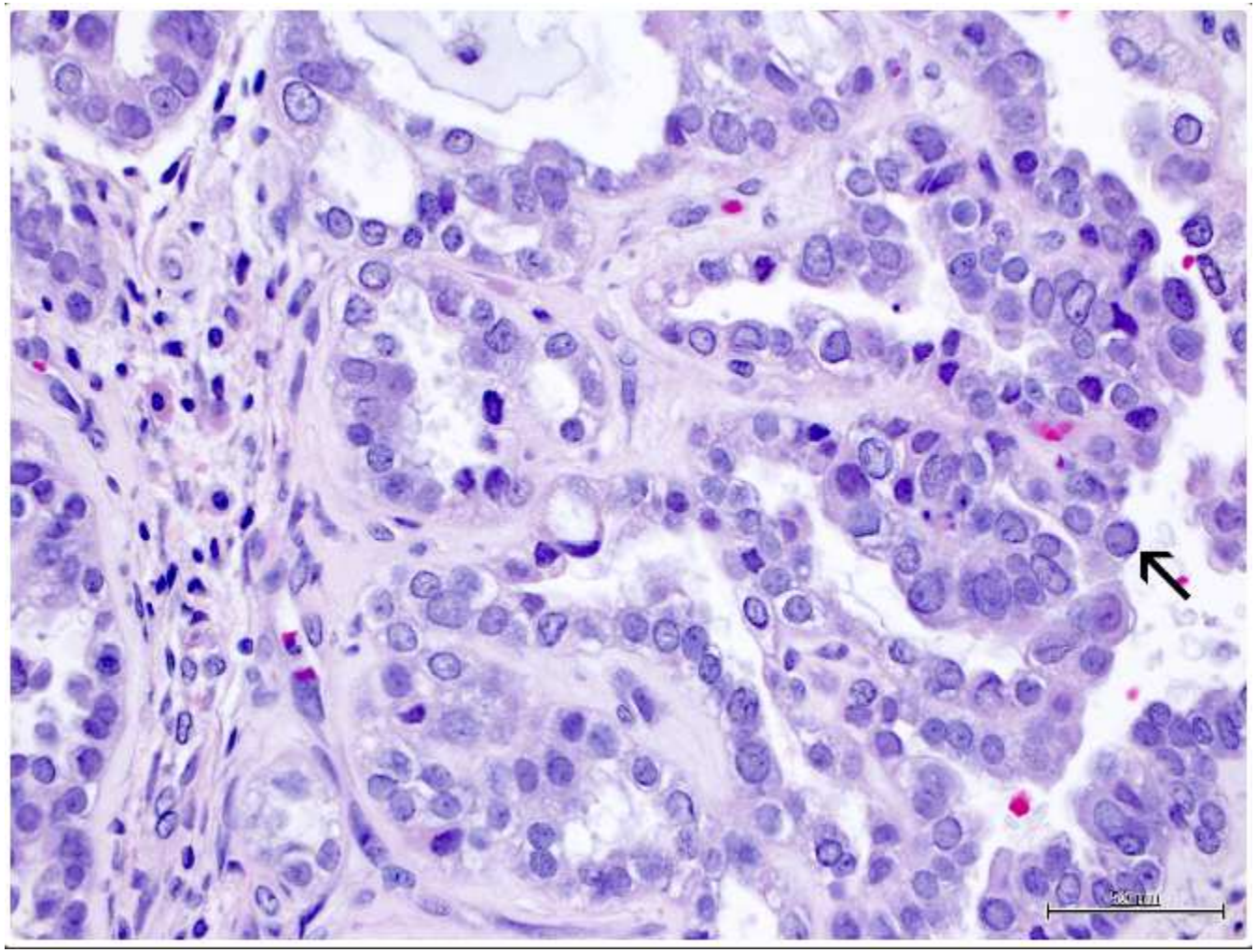


Figure 22-26 Type II endometrial carcinoma. **A,** Endometrial intraepithelial carcinoma, the precursor to serous carcinoma showing malignant cells *(arrow)* with morphologic features identical to serous carcinoma lining the surfaces of the endometrial glands without obvious stromal invasion. **B,** Strong, diffuse expression of p53 as detected by immunohistochemistry in endometrial intraepithelial carcinoma. **C,** Serous carcinoma of the endometrium with papillary growth pattern consisting of malignant cells with marked cytologic atypia including high nuclear-to-cytoplasmic ratio, atypical mitotic figures, and hyperchromasia. **D,** As with the previous lesion, there is an accumulation of p53 protein in the nucleus.


Uterine serous carcinoma

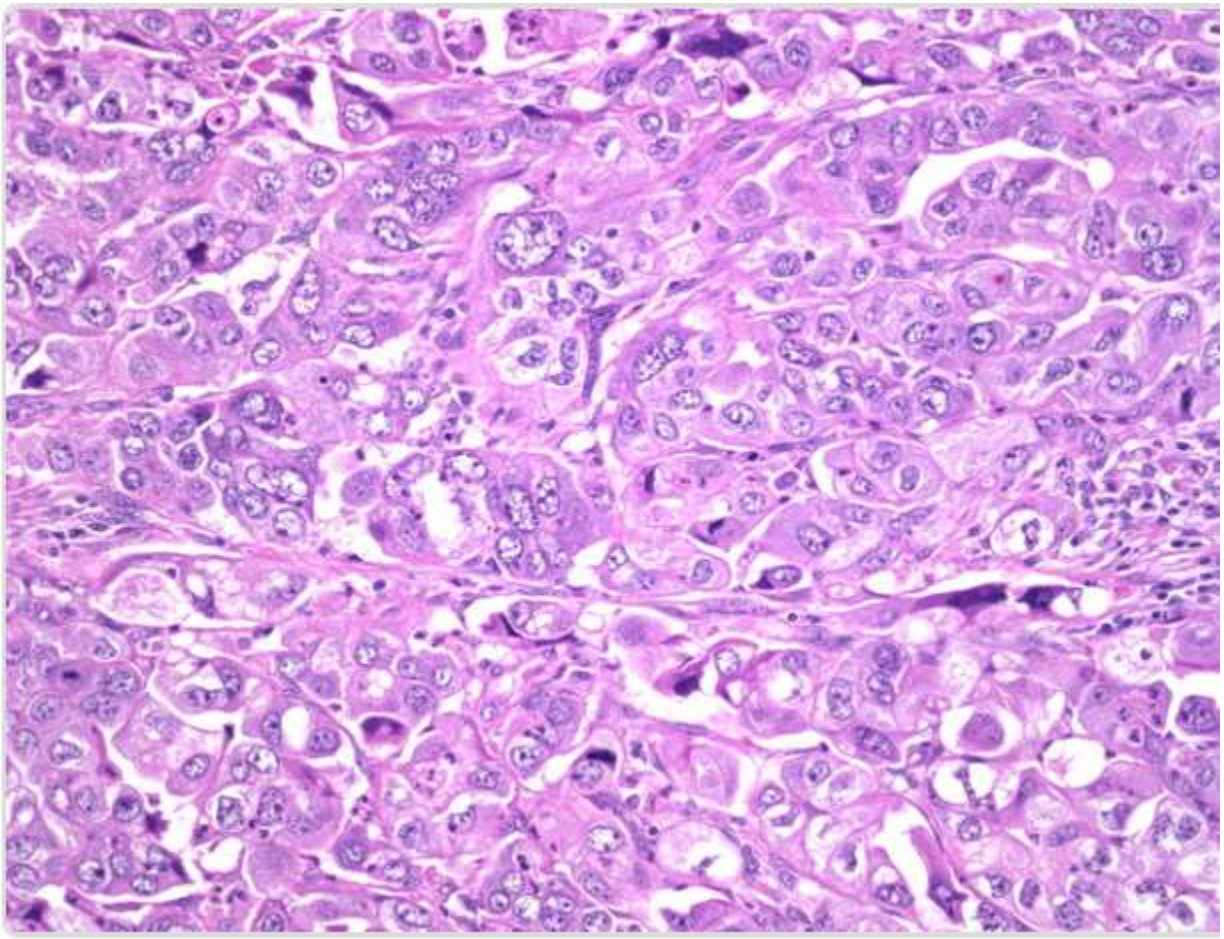
Clear cell carcinoma



Hobnail cell (arrow)

www.pathologyoutlines.com/uterus.htm
Contributed by Jutta Havila, MD

Clear cell carcinoma



http://webpathology.com/image.asp?case=569&n=28

Stage I	Tumour confined to the corpus uteri
I A	NO or less than half myometrial invasion
I B	Invasion equal to or more than half of the myometrium
Stage II	Tumour invades cervical stroma, but does not extend beyond the uterus
Stage III	Local and/or regional spread of the tumour
III A	Tumour invades the serosa of the corpus uteri and/or adnexae
III B	Vaginal and/or parametrial involvement
III C	Metastasis to pelvic and/or para-aortic lymph nodes
III C1	Positive pelvic nodes
III C2	Positive para-aortic lymph nodes with or without positive pelvic lymph nodes
Stage IV	Tumour invades bladder and/or bowel mucosa, and/or distant metastases
IV A	Tumour invasion of bladder and/or bowel mucosa
IV B	Distant metastases, including intra-abdominal metastases and/or lymph nodes

A categorisation of patients by ESMO-ESGO-ESTRO 2016 guidelines based on the risk of LN metastasis is used for the indication of surgical staging and also for the indication of adjuvant treatment.

	IA	IB	II
G1	Low	Intermediate	High
G2	Low	Intermediate	High
G3	High-intermediate	High	High

Para-aortic metastases in Stage I patients are rare and usually present together with positive pelvic lymph nodes.

New risk groups to guide adjuvant therapy use

Risk group	Description	LOE
Low	Stage I endometrioid, grade 1-2, <50% myometrial invasion, LVSI negative	I
Intermediate	Stage I endometrioid, grade 1-2, ≥50% myometrial invasion, LVSI negative	I
High-intermediate	Stage I endometrioid, grade 3, <50% myometrial invasion, regardless of LVSI status	I
	Stage I endometrioid, grade 1-2, LVSI unequivocally positive, regardless of depth of invasion	II
High	Stage I endometrioid, grade 3, ≥50% myometrial invasion, regardless of LVSI status	I
	Stage II	I
	Stage III endometrioid, no residual disease	I
	Non-endometrioid (serous or clear-cell or undifferentiated carcinoma, or carcinosarcoma)	I
Advanced	Stage III residual disease and Stage IVA	I
Metastatic	Stage IVB	I

LOE, Level of evidence; LVSI, lymphovascular space invasion.

Endometrial Cancer: Molecular Subtypes

***POLE* ultramutated**	• Ultra-high somatic mutation frequency; MSS; frequent mutations in the exonuclease domain of *POLE*; high ASNS and CCNB1 expression • Represents ~4% of endometrioid tumors* • Best prognosis
MSI hypermutated	• High mutation rate and few copy number alterations; high rate of *MLH1* promoter methylation; high phospho-AKT; low PTEN expression; frequent *PIK3CA* and *PIK3R1* mutations co-occurring with *PTEN* mutations • Represents ~39% of endometrioid tumors*†
Copy-number low‡	• High frequency of mutations in *CTNNB1, KRAS, SOX17*; frequent *PIK3CA* and *PIK3R1* mutations co-occurring with *PTEN* mutations; elevated levels of progesterone receptor and RAD50 expression • Represents ~49% of endometrioid tumors*
Copy-number high‡	• Greatest transcriptional activity; frequent *TP53* mutations; decreased levels of phospho-AKT; mutually exclusive *PIK3CA, PIK3R1,* and *PTEN* mutations • Represents ~9% of endometrioid tumors* • Worst prognosis

G Getz *et al. Nature* **497**, 67-73 (2013) doi:10.1038/nature12113

Endometrial carcinoma

- Four molecular types identified
- Polymerase Epsilon exonuclease domain mutated (POLE EDM)
- Mismatch repair deficient (MMRd)
- p53 wild-type/copy-number-low (p53 wt)
- p53-mutated/copy-number-high (p53 abn)
- Benefit of external beam radiotherapy limited to this group
- Bevacizumab plus chemotherapy if p53 overexpressed
- In those with none of the above molecular types, vaginal brachytherapy beneficial

Therapy

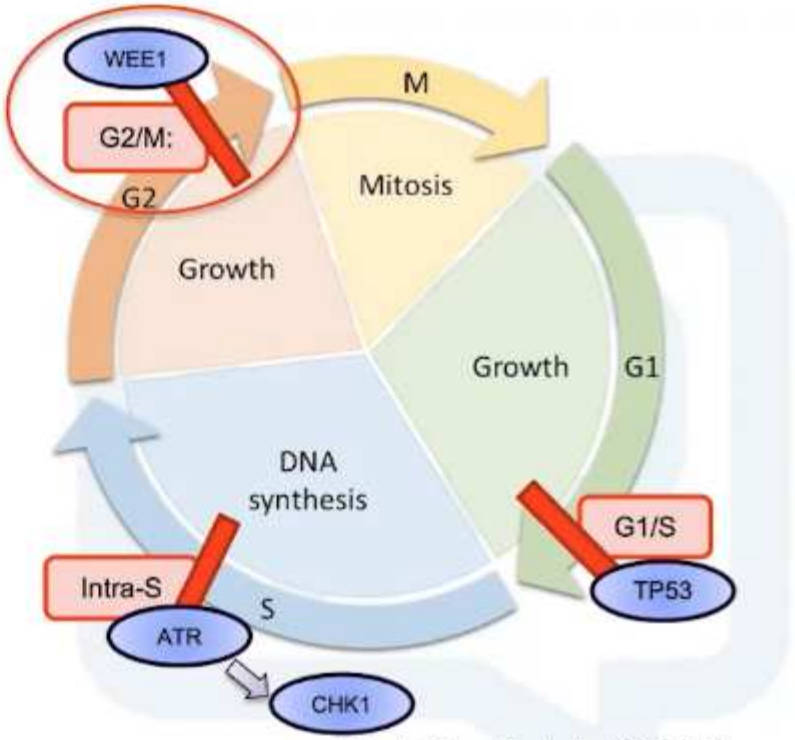
- Adjuvant radiotherapy confers better local control.
- BUT, significantly inferior survival in patients receiving adjuvant radiotherapy.
- Double the risk of a second cancer.
- Adjuvant chemotherapy may not be beneficial.
- Chemotherapy with carboplatin and paclitaxel as standard
- 88% of serous tumors are incurable
- Majority die within one year
- Endocrine therapy of no benefit
- In advanced or recurrent disease, 30% will benefit by progesterone administration (ER/PR positive)

Therapy

- Pembrolizumab and levatinib in recurrent disease in patients in microsatellite stable disease as well as those mismatch repair proficient.
- If HER+, add trastuzumab
- Benefit appears in chemotherapy naive
- If recurrence, measure TMB; immunotherapy
- Anti-angiogenic therapy may be useful if TP53 mutated
- Evorlimus with letrozole beneficial in endometrioid carcinoma
- Palcociclib (CDK 4/6 inhibitor) beneficial

WEE1 is a potential target in cells with high replication stress

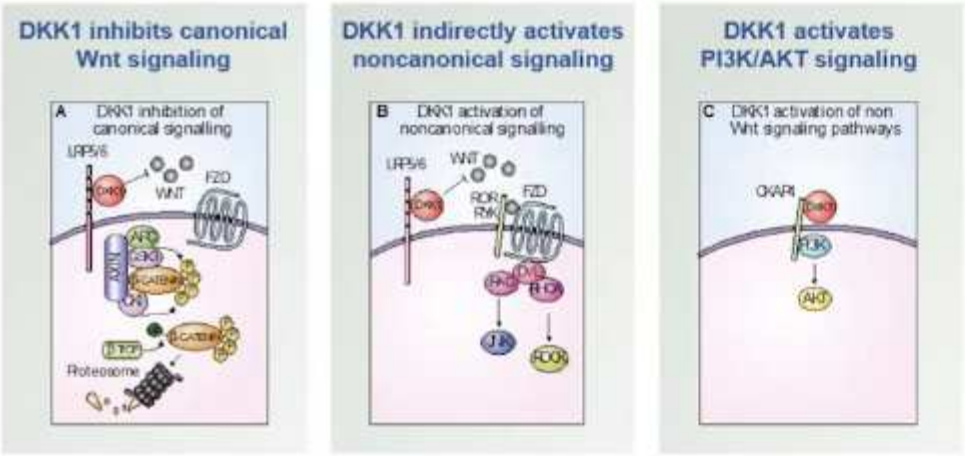
- Replication stress
  - Occurs when DNA replication is hindered
  - Multiple causes, including unrepaired DNA damage or oncogenic drivers
- High replication stress can increase dependency on cell cycle checkpoints
  - Slow down cell cycle
  - Prevent progression to mitosis with underreplicated DNA
- Inhibition of WEE1 abrogates the G2/M checkpoint and can also directly increase replication stress



Adapted from Liu et al., ASCO 2020

Targeting DKK1 in endometrial cancers

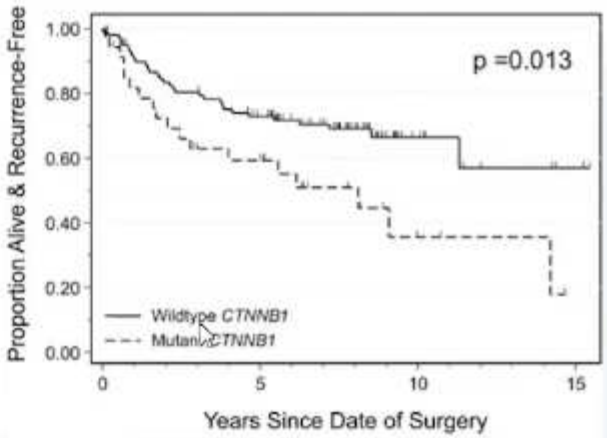
Model of DKK1 Regulation of Signaling Pathways



Mataldi et al., Cell, 2016; D'Amico et al., J Exp Med, 2016; Kimura et al., J Clin Invest, 2016; Krause et al., Cell Death Dis, 2014; Tao et al., Dig Liver Dis, 2013; Thudi et al., Prostate, 2011; Wang and Zhang, Clin Exp Metastasis, 2011

- DKN-01 is a humanized monoclonal antibody [IgG4] targeting DKK1

Arend et al., 2021 SGO Annual Meeting



Kurnit et al., Mod Pathol 2017

Endometrial carcinoma

- Mixed-Müllerian tumors (carcinosarcomas)
- Endometrial carcinoma with malignant mesenchymal component:
- Stromal sarcoma or leiomyosarcoma
- Rhabdomyosarcoma or chondrosarcoma
- Occur in post-menopausal women
- Present with abnormal vaginal bleeding

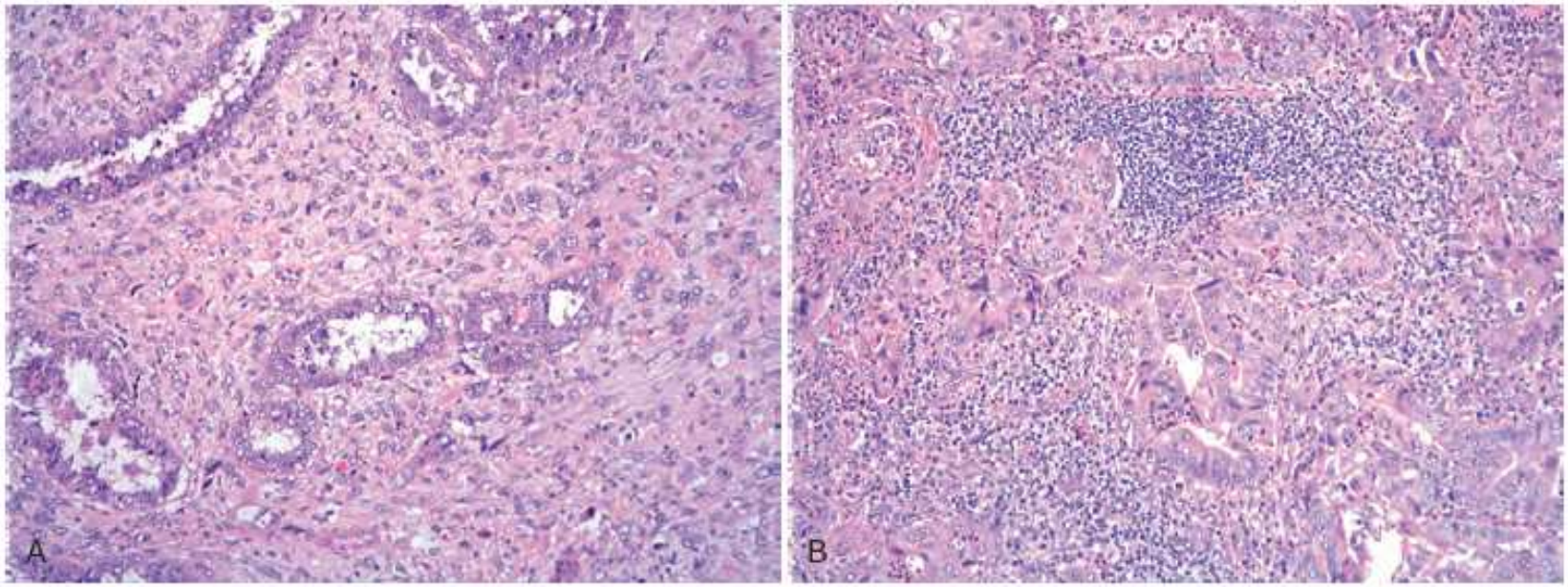


Figure 22-27 Malignant mixed müllerian tumor (MMMT). **A,** Micrograph showing both malignant epithelial and stromal components. **B,** Lymph node metastasis from a MMMT showing only the epithelial component, as is typically the case.

Table 22-4 Characteristics of Type I and Type II Endometrial Carcinoma

Characteristics	Type I	Type II
Age	55-65 yr	65-75 yr
Clinical setting	Unopposed estrogen Obesity Hypertension Diabetes	Atrophy Thin physique
Morphology	Endometrioid	Serous Clear cell Mixed müllerian tumor
Precursor	Hyperplasia	Serous endometrial intraepithelial carcinoma
Mutated genes/ genetic abnormalities	*PTEN* *ARID1A* (regulator of chromatin) *PIK3CA* (PI3K) *KRAS* *FGF2* (growth factor) MSI* *CTNNB1* (Wnt signaling) *TP53*	*TP53* Aneuploidy *PIK3CA* (PI3K) *FBXW7* (regulator of MYC, cyclin E) *CHD4* (regulator of chromatin) *PPP2R1A* (PP2A)
Behavior	Indolent Spreads via lymphatics	Aggressive Intraperitoneal and lymphatic spread

*MSI, Microsatellite instability; CTNNB1, beta-catenin gene

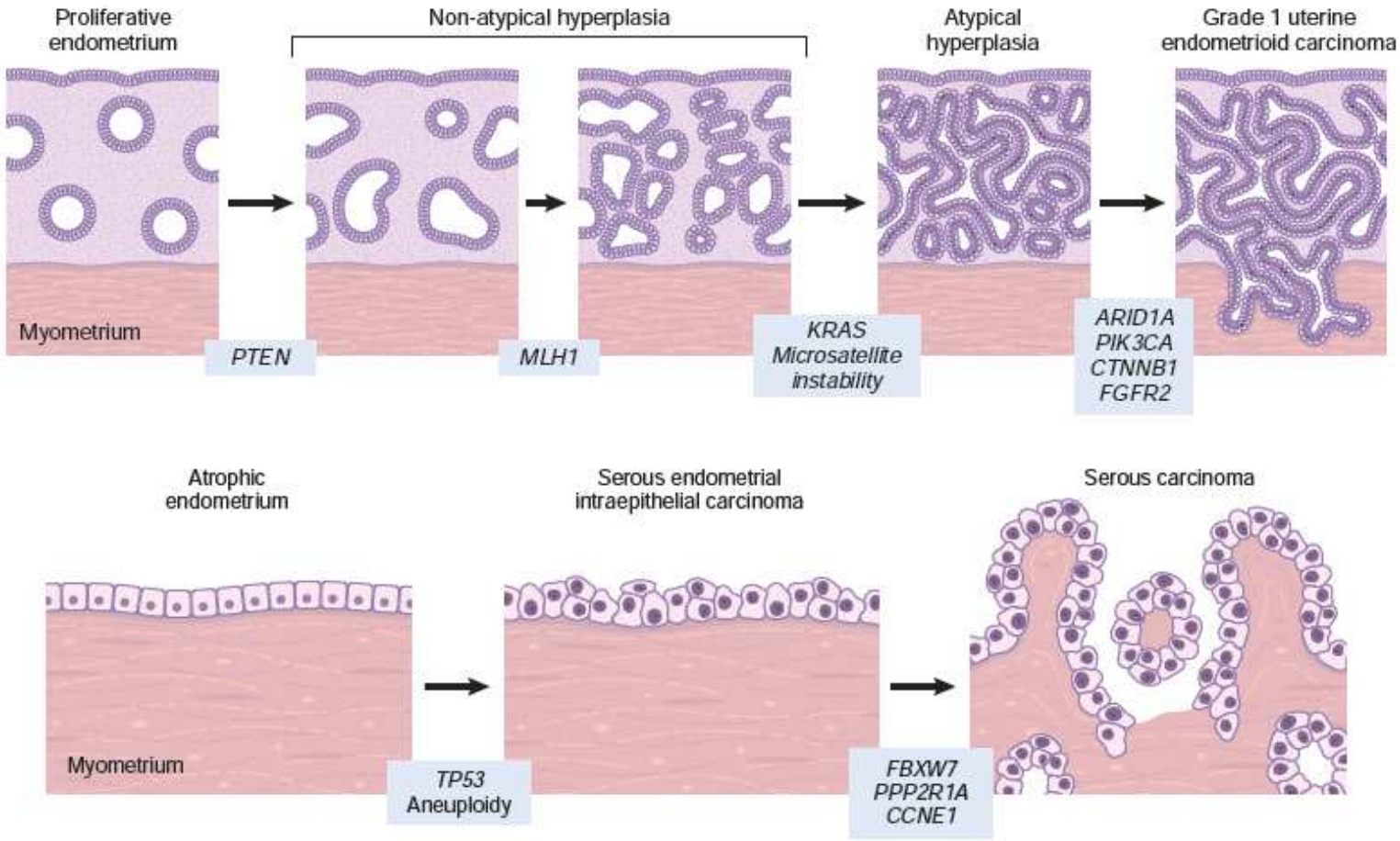
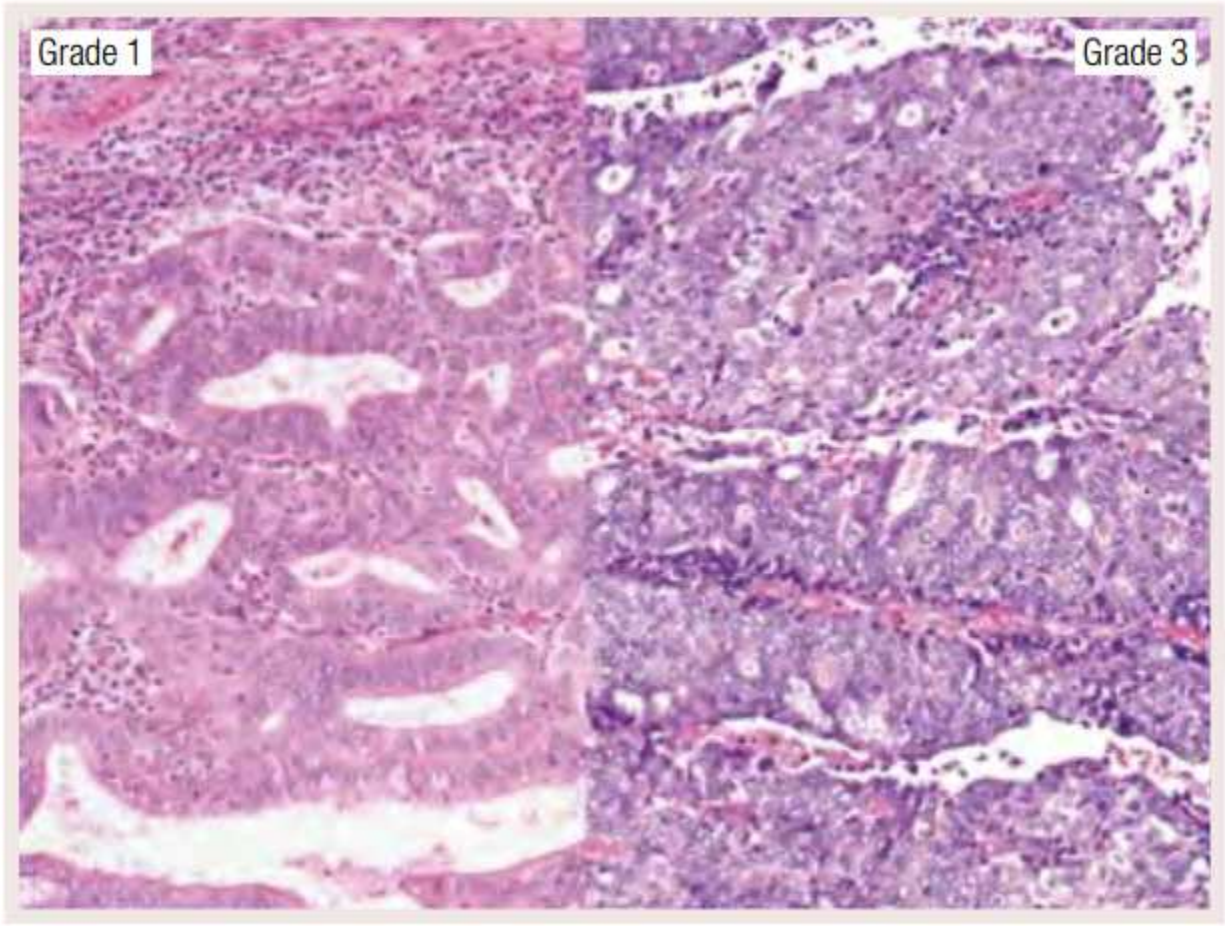


Figure 22-24 **A,** Schematic depicting the development of type I endometrial carcinoma arising in the setting of hyperplasia. **B,** Schematic diagram of the development of type II endometrial carcinoma. The most common molecular genetic alterations are shown at the time they are most likely to occur during the progression of the disease. *MI, Microsatellite instability. *CTNNB1*, beta-catenin gene; *PPP2R1A*, PP2A gene; *CCNE1*, cyclin E gene.


Grade 1
Grade 3

Stage I—Carcinoma is confined to the corpus uteri itself.

Stage II—Carcinoma involves the corpus and the cervix.

Stage III—Carcinoma extends outside the uterus but not outside the true pelvis.

Stage IV—Carcinoma extends outside the true pelvis or involves the mucosa of the bladder or the rectum.

Molecular genetics

- 4 prognostic subgroups of endometrial carcinoma:
- 7% POLE ultramutated
- 28% MISH (hypermutated)
- 39% Copy number low (endometrioid, Type I)
- 26% Copy number high (serous like, Type II)
- PD-L1 abnormalities high, but not prognostic

Stromal tumors

- Adenosarcoma
- Present as broad based endometrial polyp
- 30-40 years of age
- Low-grade
- Estrogen sensitive
- 25% recur
- Endometrial stromal tumor
- JAZF1 fusion genes silence placement of repressive histone marks into chromatin (Polycomb complex)
- Generally low-grade
- Up to 80% recur
- 15% die from late distant metastases

Leiomyosarcoma

- Peak incidence 40-60 years of age
- High recurrence rate
- High metastatic rate
- Distinction from leiomyoma is based on mitotic index (>10 mitoses/high power field) or mitotic index (5-9 mitoses/high power field) with nuclear atypia and zonal necrosis

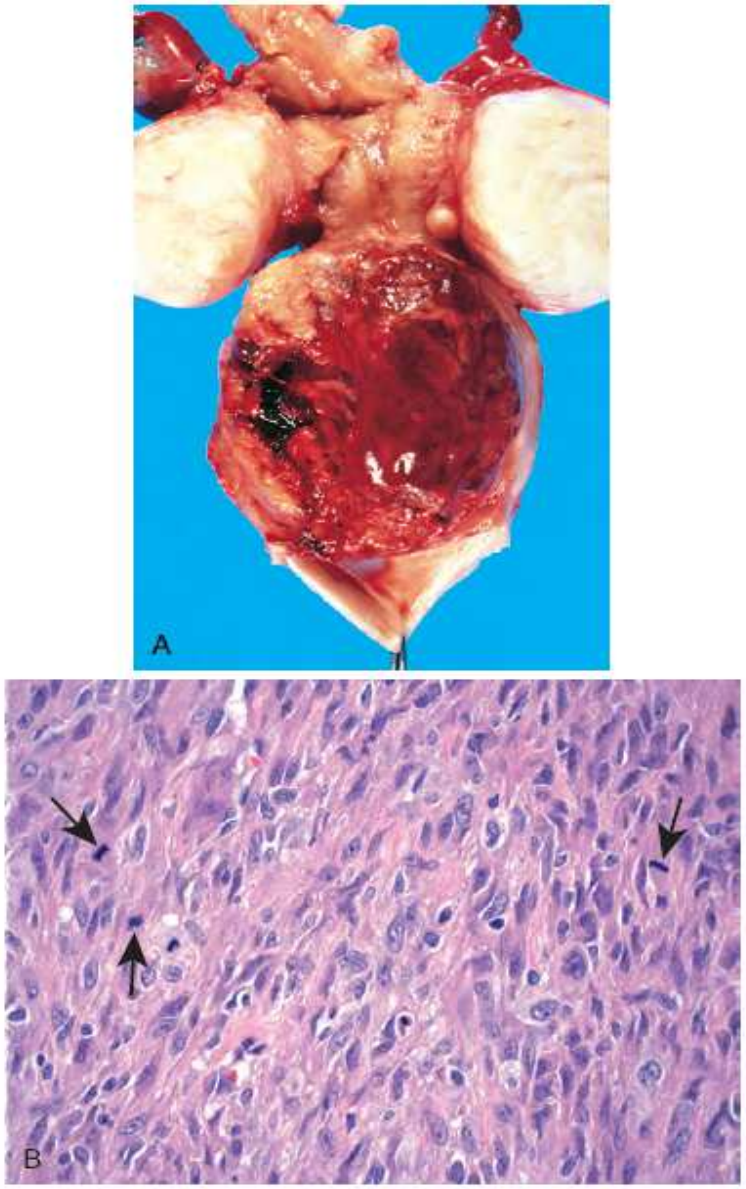
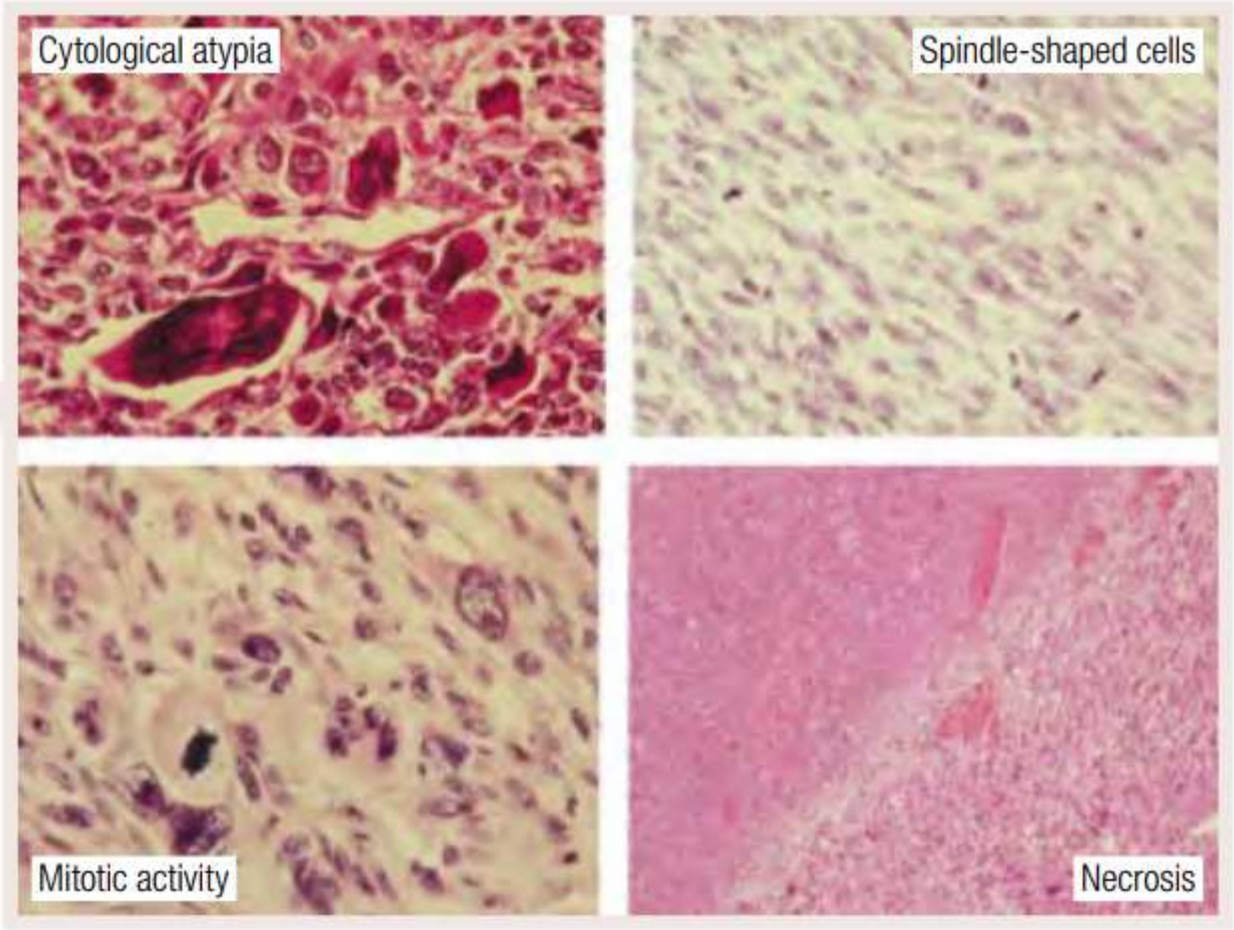


Figure 22-29 Leiomyosarcoma. **A,** A large hemorrhagic tumor mass distends the lower corpus and is flanked by two leiomyomas. **B,** The tumor cells are irregular in size and have hyperchromatic nuclei. Numerous mitotic figures are present *(arrows)*.


Cytological atypia
Spindle-shaped cells
Mitotic activity
Necrosis

Molar pregnancy

- Presents with irregular or heavy bleeding, often early in pregnancy.
- Uterine contractions noted.
- May see hyperemesis.
- Hydaditiform mole.
- Grape-like tissue clusters may be seen protruding from cervical canal.

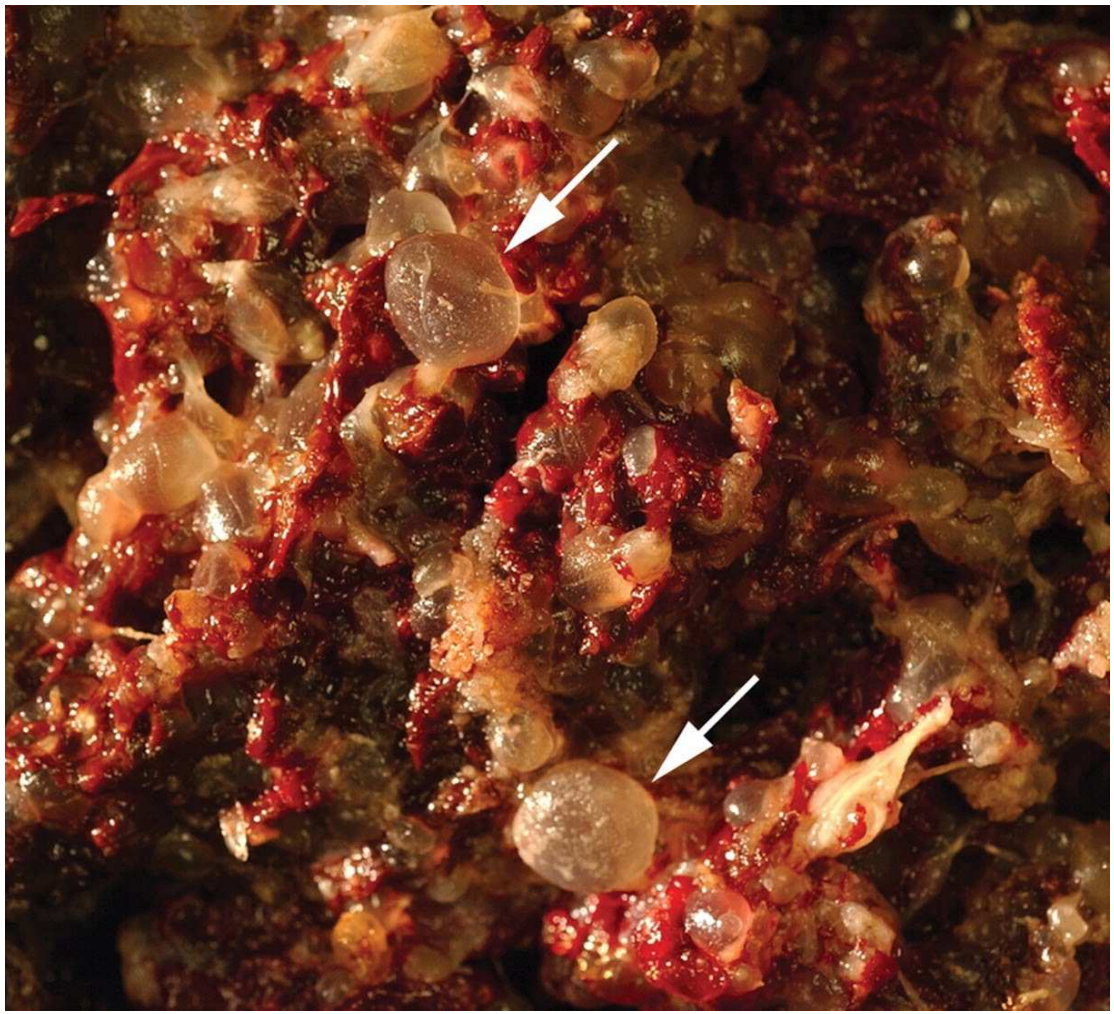
Molar pregnancy

- A complete mole
- Arises from syncytiotrophoblast cells.
- No embryoblast.
- Results from fertilization of an empty oöcyte.
- An incomplete mole
- Contains trophoblastic tissue with abnormal fetus.
- Always triploid.

Molar pregnancy

- HCG elevated.
- Ultrasound shows a “snowstorm” pattern in uterus with no fetus present.
- Bilateral, large theca-lutein cysts.
- Trophoblastic tissue embolism may lead to ARDS.
- If trophoblastic tissue functional, may see hyperthyroid state.
- Evacuate uterus.
- Follow with HCG levels for one year. No pregnancy permitted during that time.
- 5% will evolve to choriocarcinoma.

Hydaditiform mole



https://gyn101.files.wordpress.com/2011/10/37237511.jpg

Choriocarcinoma

- Gestational choriocarcinoma is a malignant neoplasm of trophoblastic cells derived from a previously normal or abnormal pregnancy, such as an extrauterine ectopic pregnancy.
- Choriocarcinoma is rapidly invasive and metastasizes widely, principally to lungs and vagina
- Choriocarcinoma is a soft, fleshy, yellow-white tumor that usually has large pale areas of necrosis and extensive hemorrhage.
- Histologically, it does not produce chorionic villi and consists entirely of proliferating syncytiotrophoblasts and cytotrophoblasts

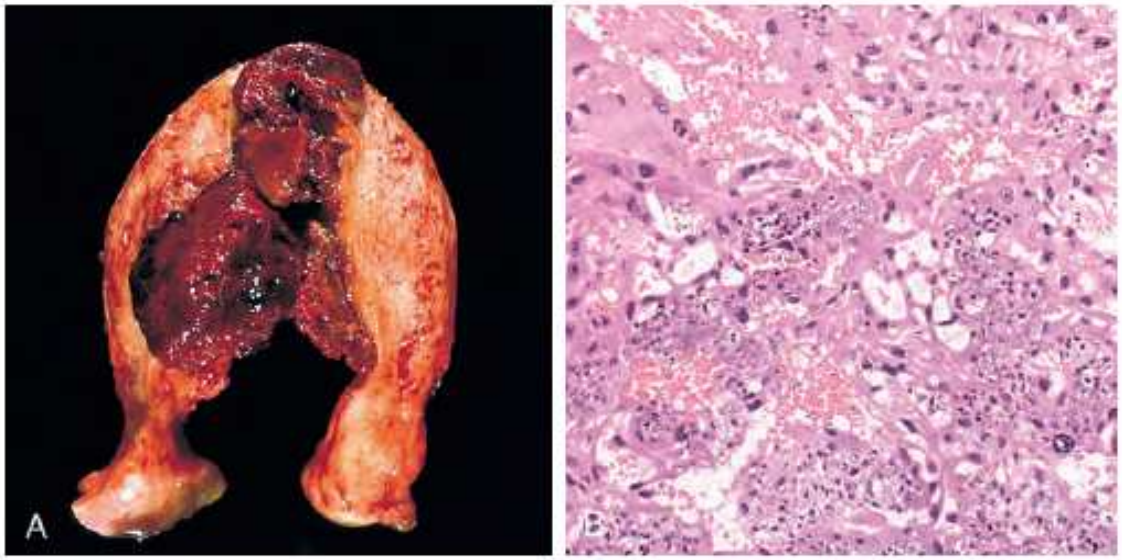


Figure 22-55 Choriocarcinoma. **A,** Choriocarcinoma presenting as a bulky hemorrhagic mass invading the uterine wall. **B,** Photomicrograph illustrating neoplastic cytotrophoblasts and syncytiotrophoblasts. (Courtesy Dr. David R. Genest, Brigham and Women's Hospital, Boston, Mass.)