子宮頸癌在細胞學的診斷與處理

➢日本東京國立癌症中心進修
➢國際細胞學會認證(CTIAC)
➢中山醫學大學生化暨生物科技研究所
➢現職: 台杏病理細胞中心

張森鈴 醫檢師
2010/11/28

# 96年與95年女性10大癌症發生率比較

序位	原發部位	96年			95年		96年與95年發生率增減*	
		個案數	年齡標準化發生率	年齡中位數	個案數	年齡標準化發生率		
1	女性乳房	7,502	53.1	51	6,895	50	6.2	↑
2	大腸癌	4,471	31.1	67	4,455	32.2	-3.4	
3	肺、支氣管及氣管	3,161	21.9	68	2,992	21.5	1.9	
4	肝及肝內膽管	2,900	20.5	69	2,925	21.6	-5.1	
5	子宮頸侵襲癌	1,749	12.2	54	1,828	13.2	-7.6	↓
6	甲狀腺	1,407	10.4	46	1,257	9.5	9.5	↑
7	胃	1,301	8.9	68	1,339	9.6	-7.3	
8	子宮體	1,165	8.3	53	1,159	8.5	-2.4	
9	皮膚	1,113	7.6	72	1,129	8.1	-6.2	↓
10	卵巢、輸卵管及寬韌帶	1,047	7.6	51	1,000	7.5	1.3	
	全癌症	32,439	229.7	59	31,276	228.8	0.4	

註：1.序位係以標準化發生率（每10萬人口）排序。
2.年齡標準化發生率，係以西元2000年世界標準人口為標準人口計算。
3.96年與95年發生率增減（%）公式：
（96年年齡標準化發生率-95年年齡標準化發生率）÷95年年齡標準化發生率*100%。
4.女性前五大癌症發生年齡最年輕的為女性乳癌。

女性五大癌症發生率趨勢
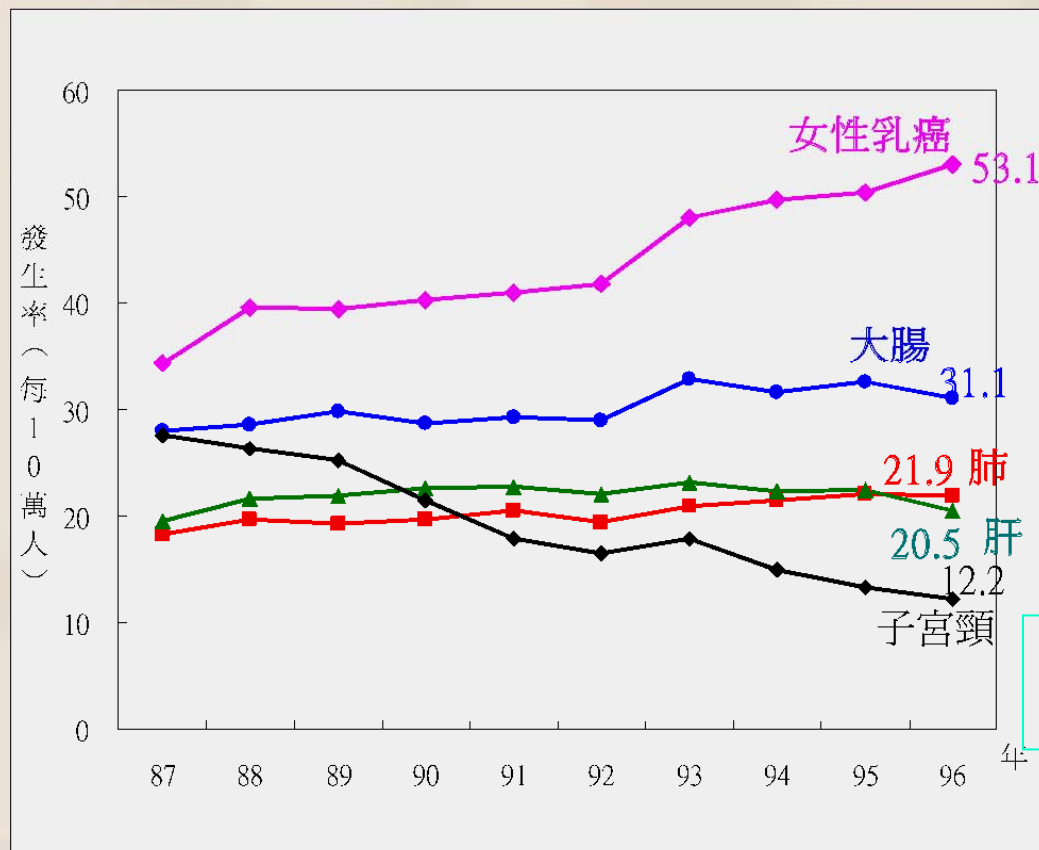
10 大癌症死亡率（每 10 萬人口），民國 96 年

順位	ICD-9	原發部位	個案數（人）	粗死亡率	年齡標準化死亡率[2]	年齡標準化死亡率[3]
1	155	肝及肝內膽管	7,809	34.01	24.59	27.69
2	162	肺、支氣管及氣管	7,993	34.82	23.25	27.48
3	153-154	結腸、直腸、乙狀結腸連結部及肛門	4,470	19.47	12.95	15.30
4	174	女性乳房	1,552	13.67 [1]	10.00	10.90
5	151	胃	2,474	10.78	7.04	8.40
6	140-149[4]	口腔、口咽及下咽	2,312	10.07	7.51	8.18
7	185	攝護腺	1,003	8.64 [2]	5.12	6.58
8	180	子宮頸	833	7.34 [1]	4.95	5.69
9	150	食道	1,438	6.26	4.63	5.09
10	157	胰	1,354	5.9	4.00	4.68
	140-208	全癌症	40,306	175.56	122.20	140.54

註：
1. 自 96 年癌症登記報告起，淋巴瘤從各部位獨立出來計算發生率，並納入排名。淋巴瘤：ICD-O-3 M-95903 - M-97293、M-97503 - M-97583、M-97643。
2. 年齡標準化率[2] 係使用 1976 年世界標準人口為標準人口。
3. 年齡標準化率[3] 係使用 2000 年世界標準人口為標準人口。
4. 口腔、口咽及下咽原發部位代碼包括 ICD-O-3：C00-C06、C09-C10、C12-14；ICD 9：140-141、143-146、148-149。
5. 皮膚原發部位包括基底細胞癌個案。
6. 原位癌：組織形態之分類碼第 5 碼（性態譯碼）為 2。
7. (1)每 10 萬女性人口粗發生率及粗死亡率；(2)每 10 萬男性人口粗發生率及粗死亡率

➢民國96年死亡率約為每十萬名人口7.34例，死亡人數為833人,佔第八位
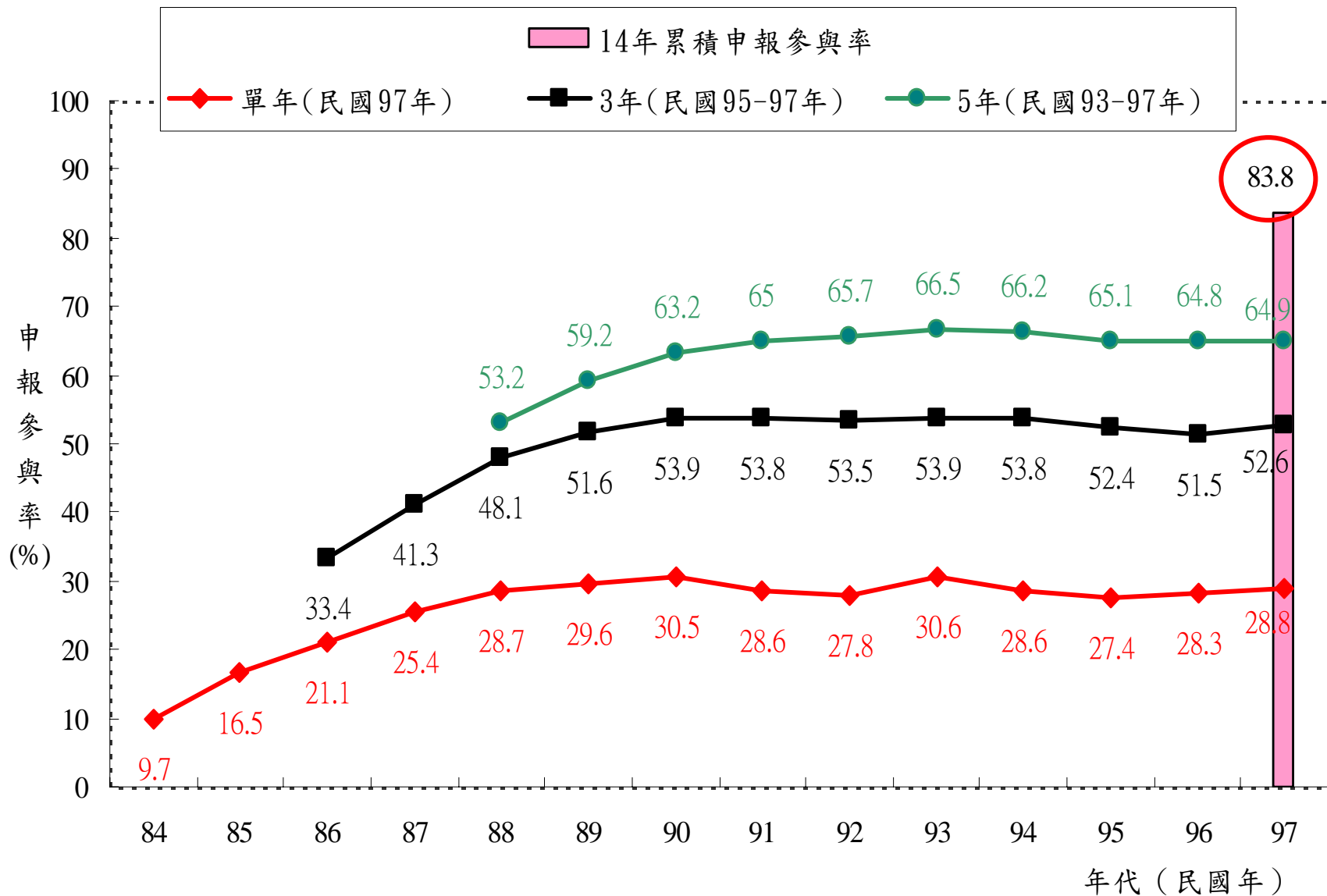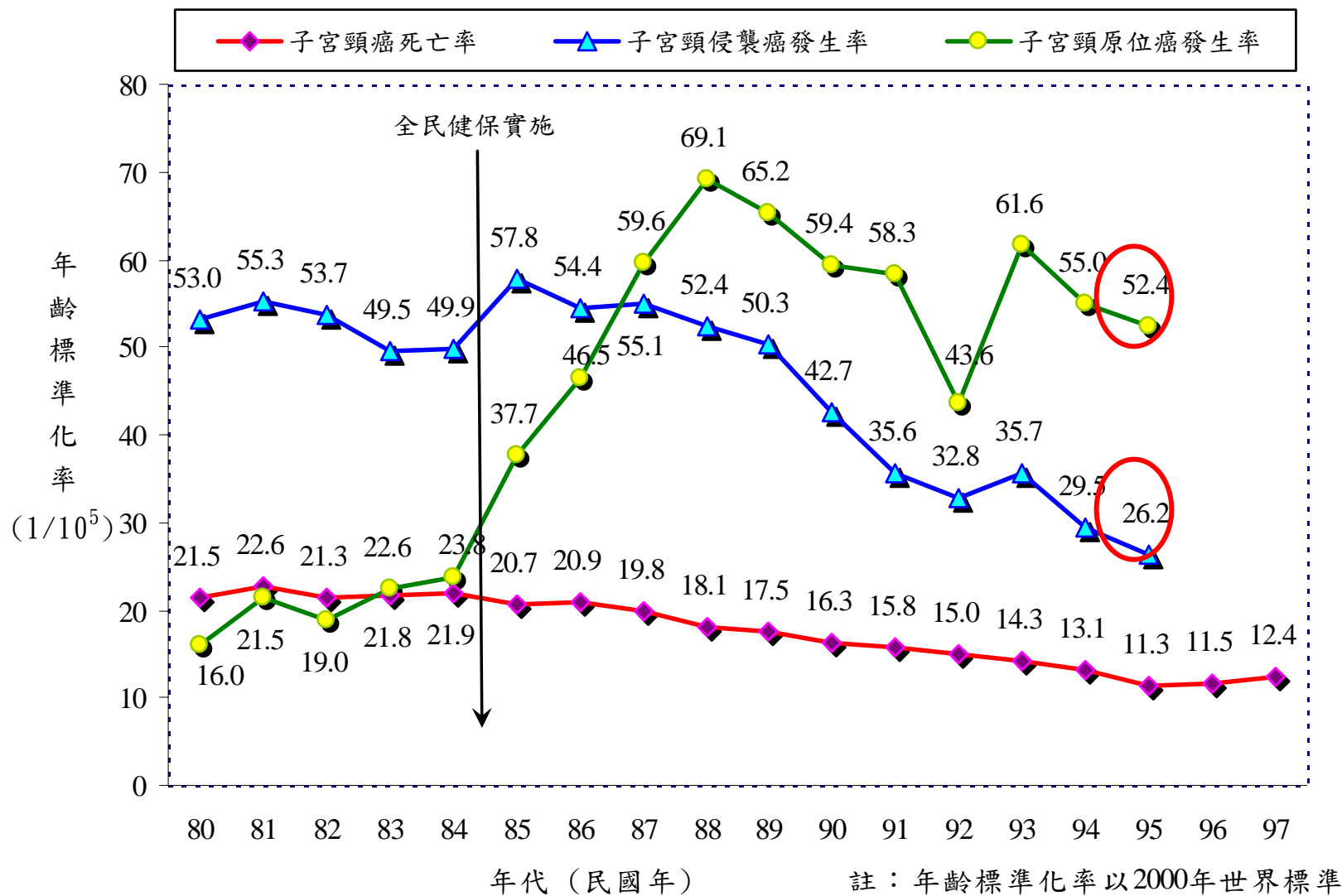
台灣30歲以上婦女子宮頸癌篩檢申報參與率長期趨勢，民國84年至97年

DEPARTMENT OF HEALTH THE EXECUTIVE YUAN, TAIWAN ,2010

98-100癌症篩檢

篩檢項目	98年	99年	100年
大腸癌篩檢人數	29萬	130萬(4.5倍)	135萬
乳癌篩檢人數	24萬	40萬(1.7倍)	60萬
子宮頸癌篩檢人數	192萬	204萬*(1.1倍)	204萬*
口腔癌篩檢人數	88萬	108萬(1.2倍)	108萬
總篩檢人數	333萬	482萬(1.4倍)	507萬
預計檢出癌症人數（含原位癌）	6千人	1萬人(1.7倍)	1.1萬人

註：含拒絕抹片婦女HPV自我檢測服務20萬人

預計99年比98年多篩檢150萬人，

多找出4千名癌症病人

台灣30歲以上婦女子宮頸癌發生率及死亡率之年齡標準化率長期趨勢，民國80年至97年

DEPARTMENT OF HEALTH THE EXECUTIVE YUAN, TAIWAN ,2010

診斷依據與組織形態

　　1,749位子宮頸惡性腫瘤個案中，經細胞學或組織病理證實者為1,733位，證實率為99.09%。

　　其組織形態分布，以鱗狀細胞癌最多，占1,749位個案之76.73%。

　　民國96年子宮頸原位癌個案3,503位，詳見本年報第132、133頁。

組 織 形 態	女性			
	個案數	百分比	百分比 (含惡性淋巴瘤)	顯微鏡檢 證實數
鱗狀細胞癌	1,342	76.73	76.60	1,341
腺性鱗狀癌	66	3.77	3.77	66
腺癌	235	13.44	13.41	234
明亮細胞癌	6	0.34	0.34	6
絨毛膜癌	1	0.06	0.06	1
其他明示癌	41	2.34	2.34	41
未明示癌	41	2.34	2.34	40
惡性黑色素瘤	2	0.11	0.11	2
明示之肉瘤	1	0.06	0.06	1
其他惡性腫瘤	14	0.80	0.80	1
惡性淋巴瘤	3		0.17	
總計 [2]	1,749	100.00	100.00	1,733

註：1. 自96年癌症登記報告起，惡性淋巴瘤（ICD-O-3 M-95903 - M-97293、M-97503 - M-97583、M-97643）從各部位獨立出來計算發生率，並納入排名。

2. 個案數的總計不包含惡性淋巴瘤個案數。

What is the Normal Structure of the Cervix?
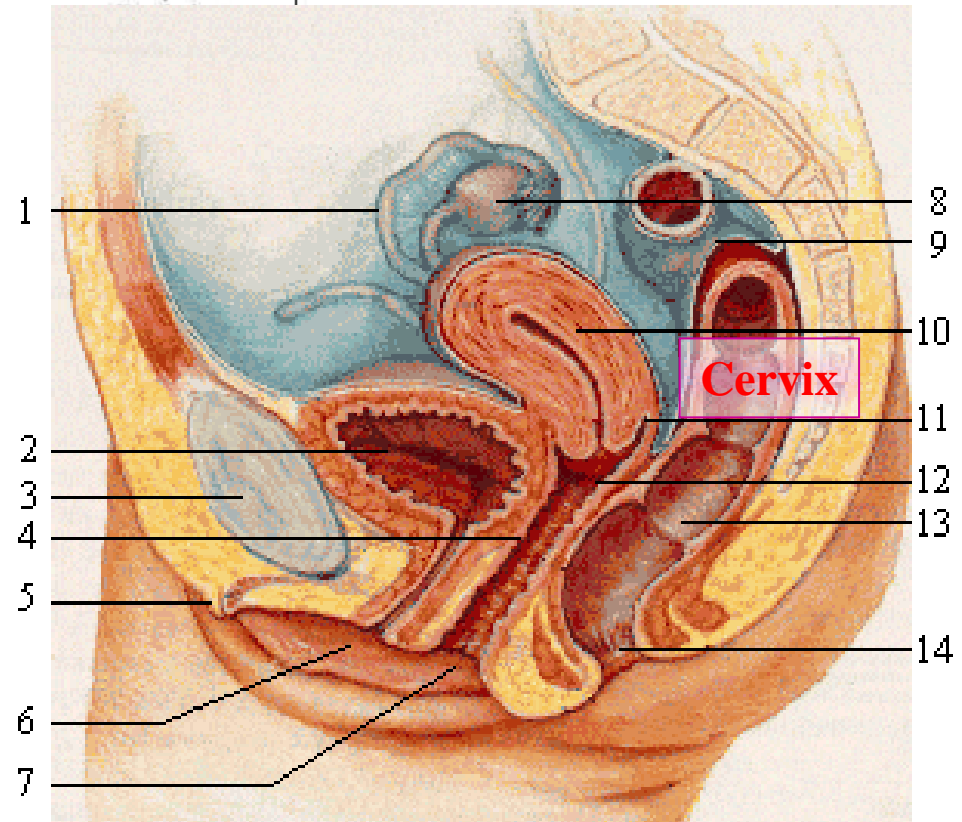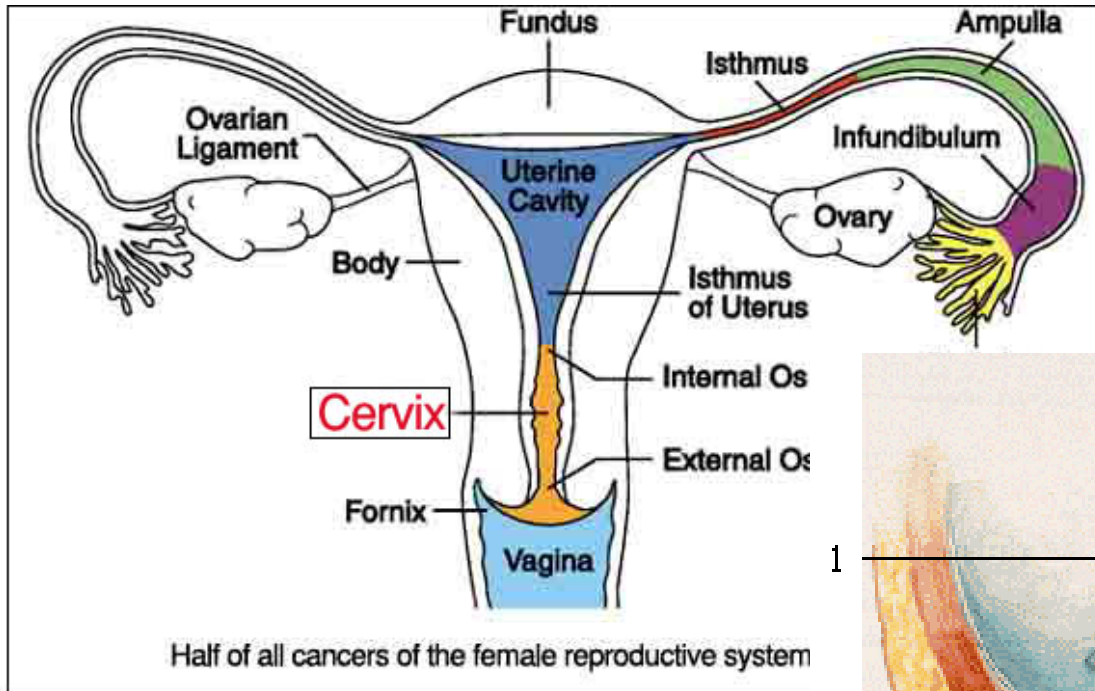
Image copyright 2000 by Nucleus Communications

Cervix Structure

Transformation Zone & Squamocolumnar Junction (SCJ)

內頸部
columnar cells of the endocervix
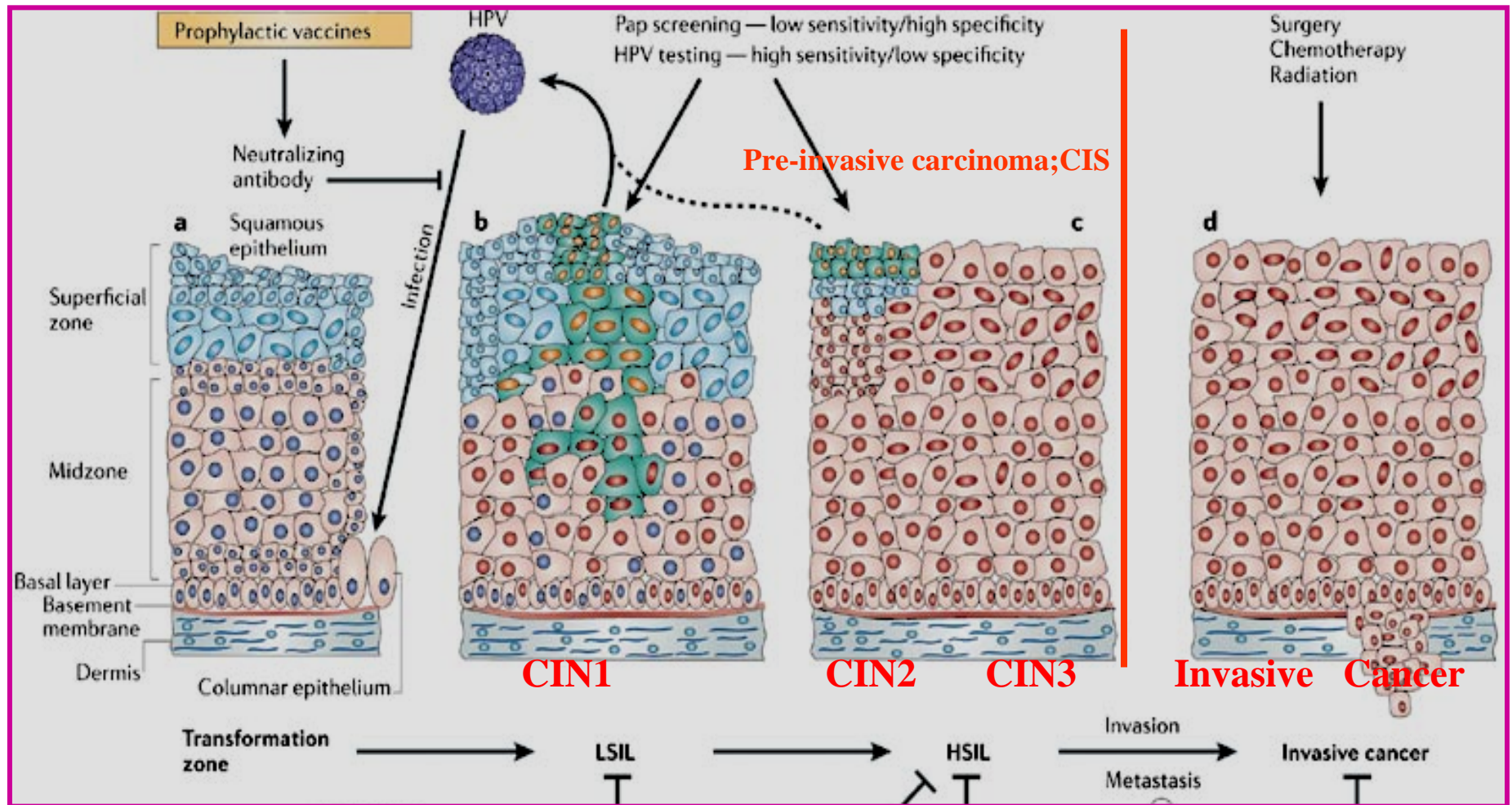
外頸部
squamous cells of the exocervix

current SCJ
transformation zone

transformation zone

SCJ
original SCJ

Jason Bratcher, MD, MBA Advanced Endoscopy Fellow Beth Israel Medical Center New York, New York
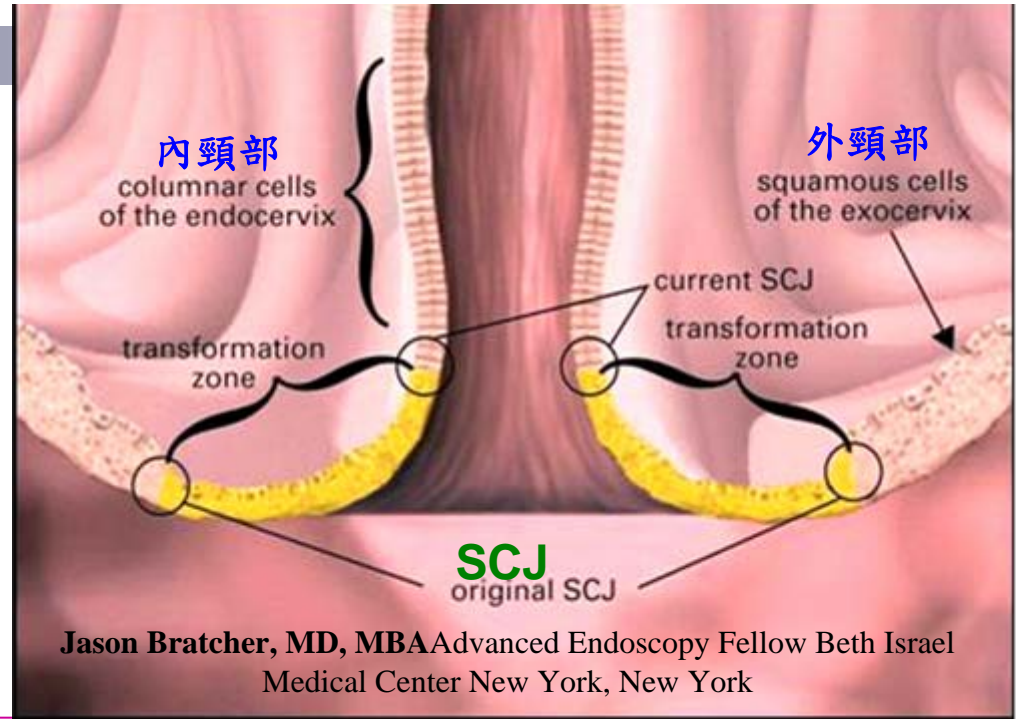
鱗狀-柱狀上皮接合處
(squamous-columnar，junction)

multi-layered squamous cell epithelium, S1

S1

S2

transformation zone ,S2

G

single-cell mucus-producing columnar epithelium ,G

In 1965, Victorian Cytology Service (VCS)

CIN (Cervical Intraepithelial Neoplasia)的分級

Nature Reviews Cancer 6, 753-763 (October 2006)

Cervical Intraepithelial Neoplasia(CIN)

Normal	CIN1	CIN2	CIN3
	Mild dysplasis	Morderate dysplasis	Severe dysplasis

Labels on image: 1/3, 2/3

Cervical Cancer: Pathology Report and Staging
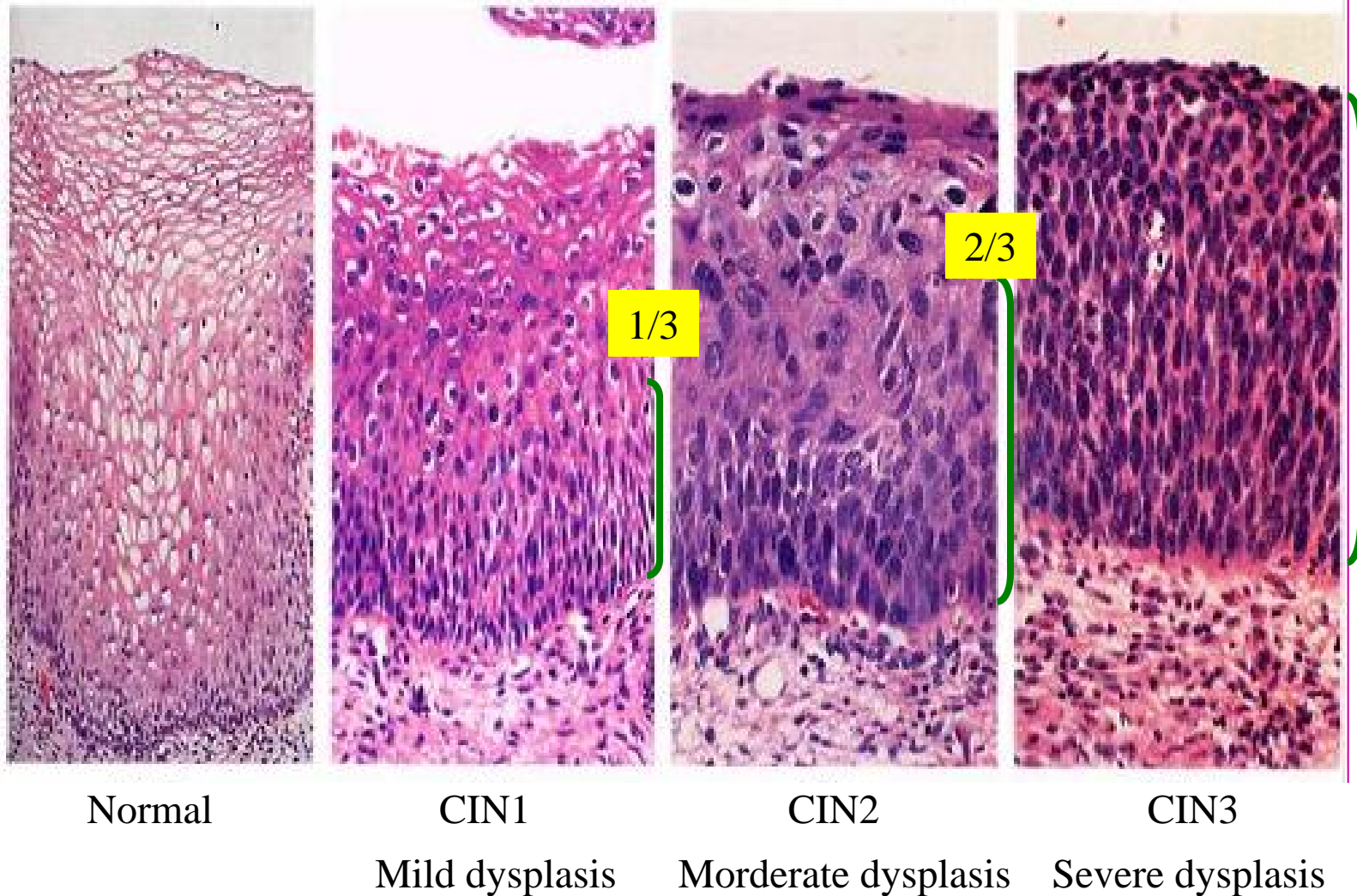
HPV– human papilloma virus

HPV has a circular, double stranded DNA, protected by capsid proteins.

More than 100 HPV-types are known. HPV16 and 18 cause 70% of all cervix cancers.

Virus DNA

Capsid protein
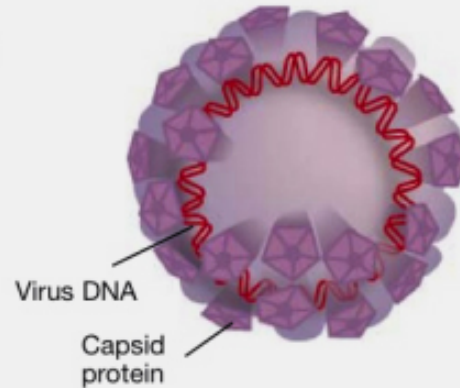
Discovery of HPV DNA in cancer cells

1   2   3   4

+   +   –   +

Probe for HPV DNA

Patient DNA

PNAS 1983
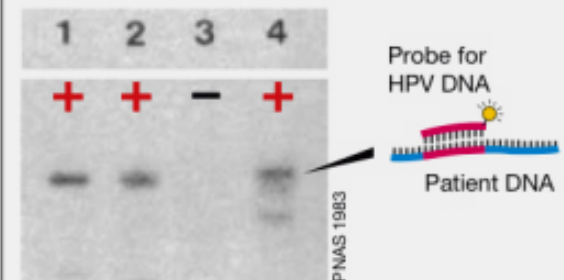
Harald zur Hausen found HPV DNA in patient DNA (+).

Cervix

Infection by HPV

Viral replication

~90% heal within two years

HPV DNA integrated into tumour cell DNA

0.8% develop cancer

Infection by HPV

HPV infects epithelial cells in the cervical mucosa. HPV DNA integrates into the cellular genome when causing cancer.

Weeks

10–30 years

Infected basal cell

HPV in epithelial cells

Invasive cancer
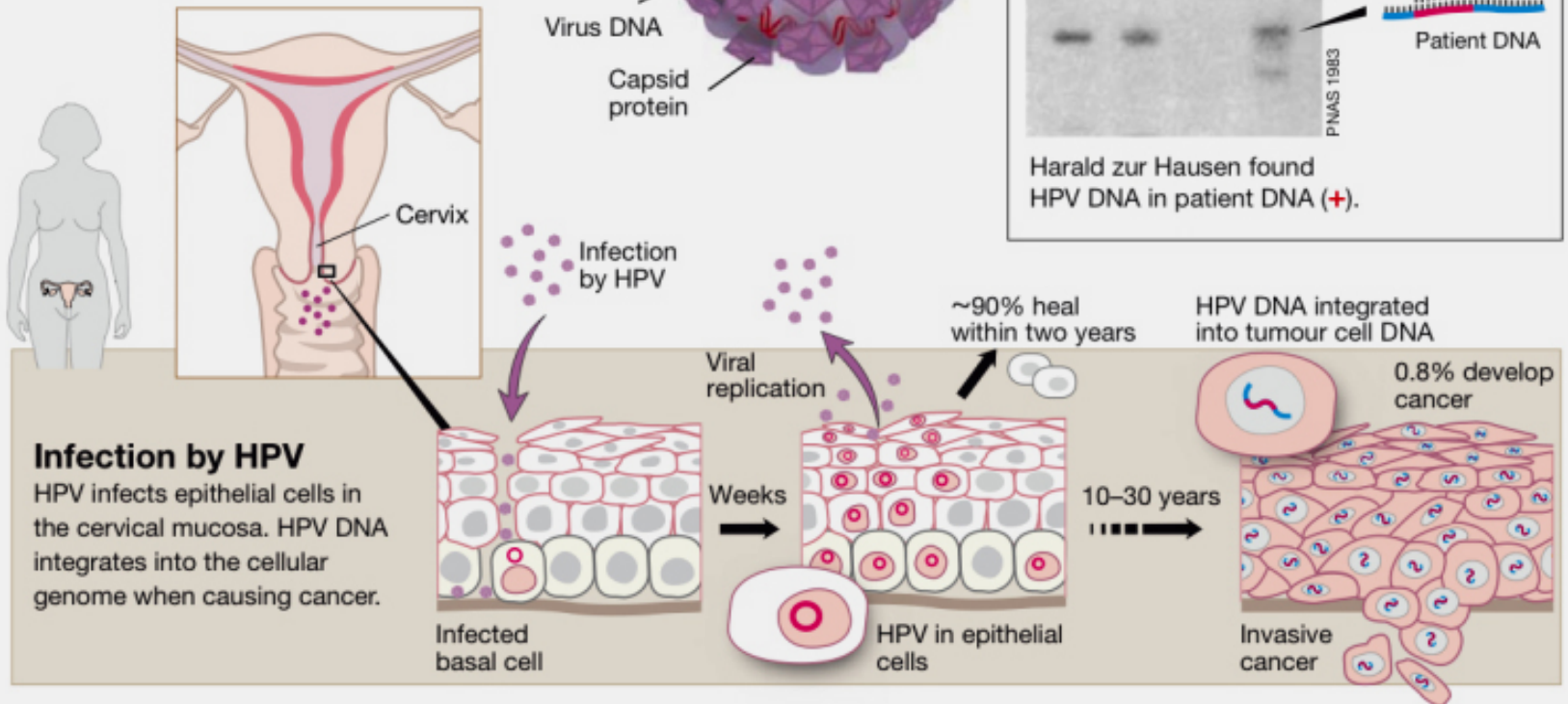
© The Nobel Committee for Physiology or Medicine 2008   Illustration: Annika Röhl

Human Papilloma Virus And Cancer, In 2008 Nobel Prize In Physiology Or Medicine ... Harald zur Hausen

HPV Prevalence in Cervical Cancer

- HPV DNA sequences are integrated to the host genome

- Integration occurs disrupting the HPV E1/E2 genes, which control viral transcription and replication

- HPV E6/E7 genes are always present and expressed

80 %

HPV-16

Other HPVs

HPV-18

No HPV
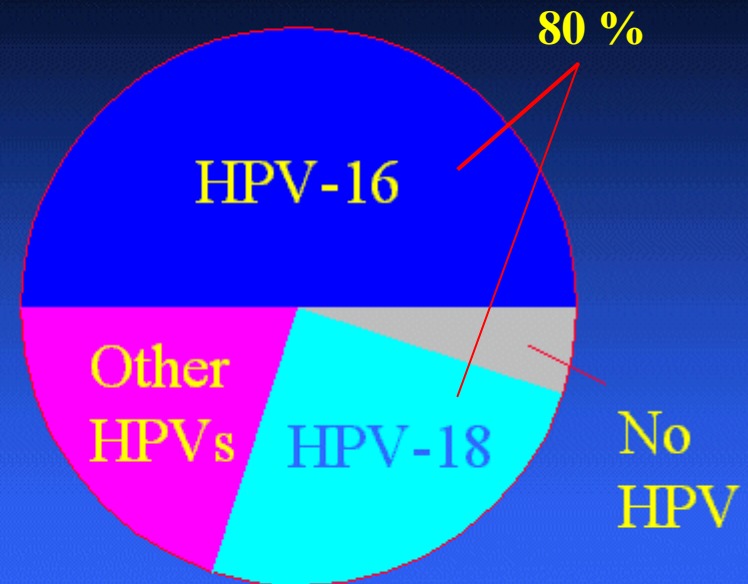
The most prevalent types in cervical carcinoma are the HPV-16 and HPV-18, which encompass as much as 80 % of the cases.

DiPaolo, J.A., Popescu, N.C., Alvarez, L. & Woodworth, C.D. (1993) Crit.Rev.Oncog. 4, 337-360.

Relationship between HPV Infection and Cancer

Sexual activity: woman and her male partners

Transient HPV infection

Co-factors: smoking, host

oral contraceptive(OC)

human immunodeficiency virus (HIV)

Co-factors: OC use, parity, other STDs

Persistent HPV infection with oncogenic types

Viral factors: copy number, variants

sexually transmitted diseases (STDs)

Normal cervical epithelium

Low grade CIN/SIL

High grade CIN/SIL

Invasive cervical cancer

Co-factors: nutrition

Factors affecting the persistence of HPV infection and cervical cancer onset.

人類乳突病毒在子宮頸癌發生過程中的角色

人類乳突病毒目前在臨床應用上有三個大方向：

(a) 輔助子宮頸抹片，可降低抹片的偽陰性率，也就是減少抹片誤差。

(b) 當抹片的報告出現模棱兩可（輕微異常）的情形時，人類乳突病毒的測定可以協助抹片判定，也就是給婦產科醫師一個較肯定的處理方式。

(c) 協助子宮頸癌或零期癌之治療前、後的追蹤。

PAP smear screening

Normal

Squamous metaplasia
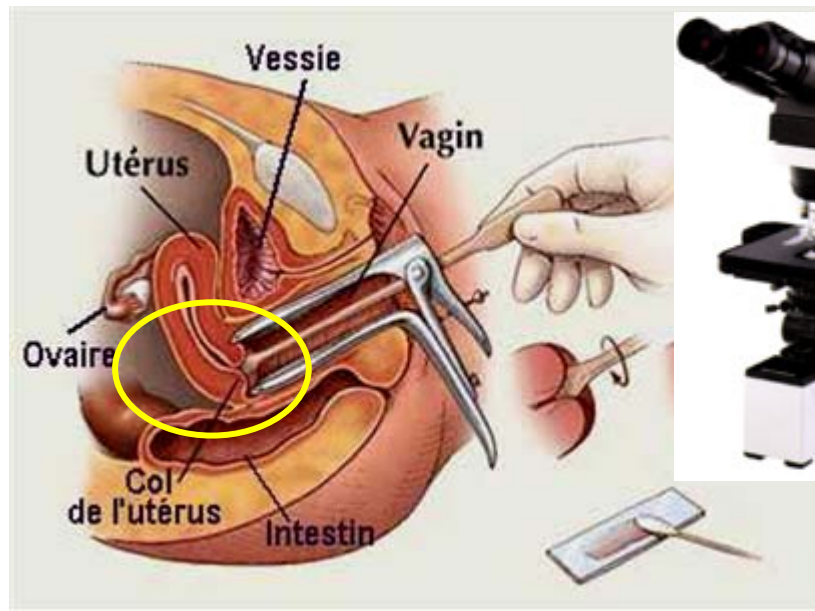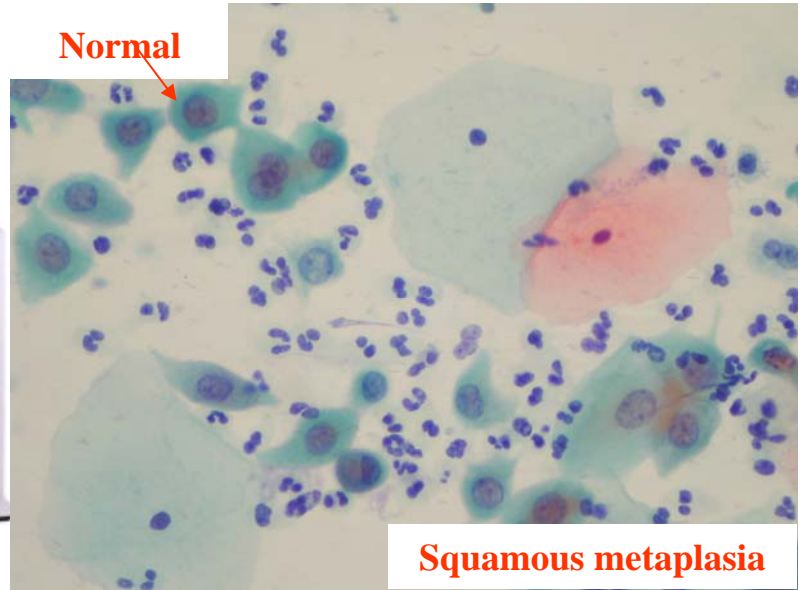
Abnormal

CIN3;HSIL
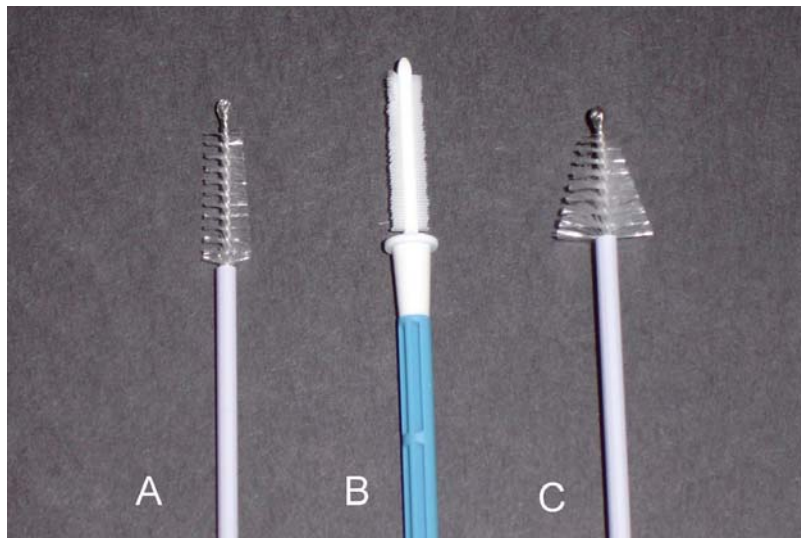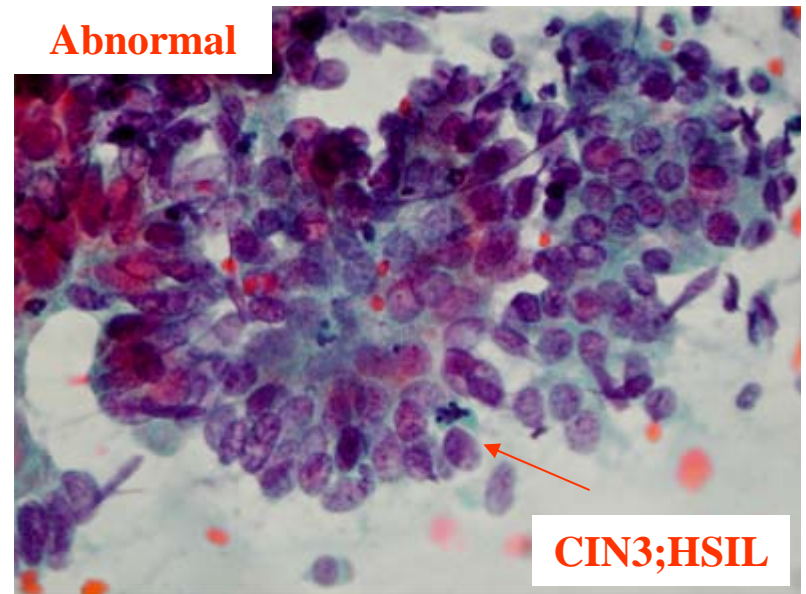
臨床處置與治療

PAP Smear : HSIL
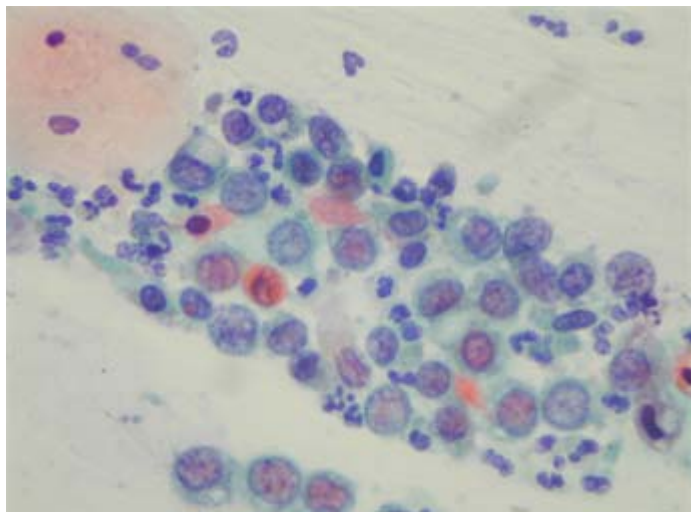
Corposcopy finding
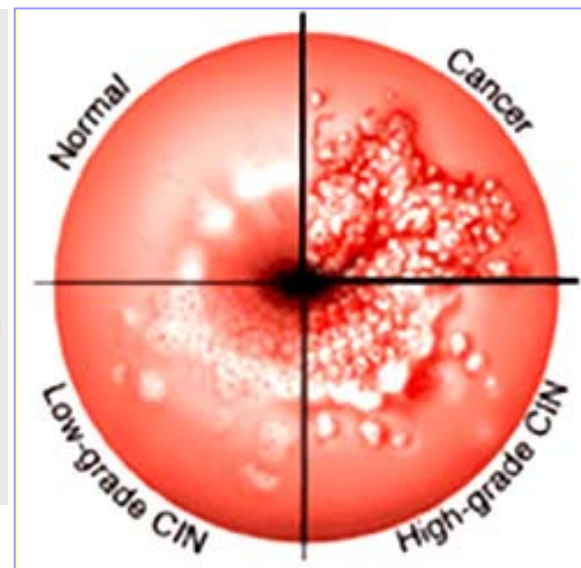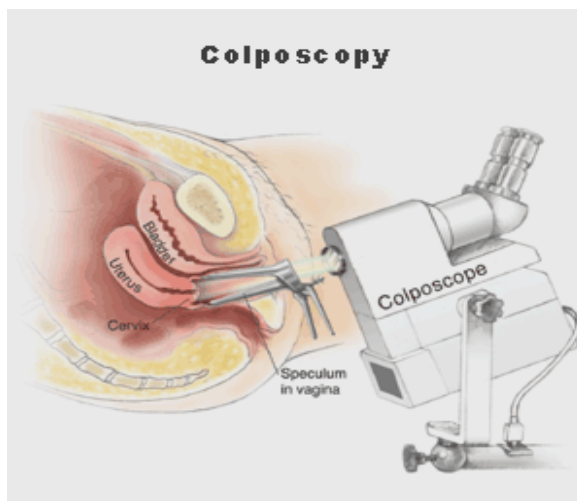
Leep biopsy
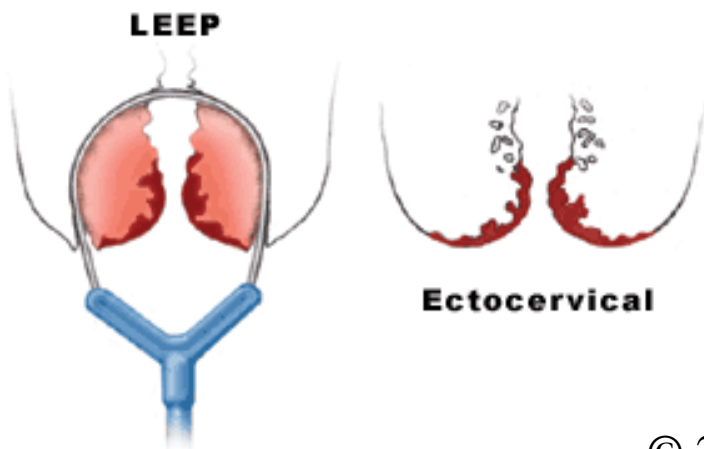
Pre-invasive stage... *Carcinoma in situ (Stages 0)*
➢**Laser surgery.**
➢**Cryosurgery.** (冷凍手術)
➢**Hysterectomy.** (子宮切除術)
➢**Loop electrosurgical excision procedure (LEEP)**
➢**Conization**(椎狀切除)

FIGO staging system for cervical cancer
(Estimated 4-year survival)

Stage IV

Preinvasive disease
(carcinoma in situ)
(stage 0)

26%

0%

99%

39%

Stage III

Stage II

Stage O

Stage IB

Stage IA

79%

94%

Invasive carcinoma
(stage I , II , III , IV)

Carcinoma of the cervix uteri. *Int J Gynaecol Obstet*. Oct 2003;83(Suppl 1):41-78.
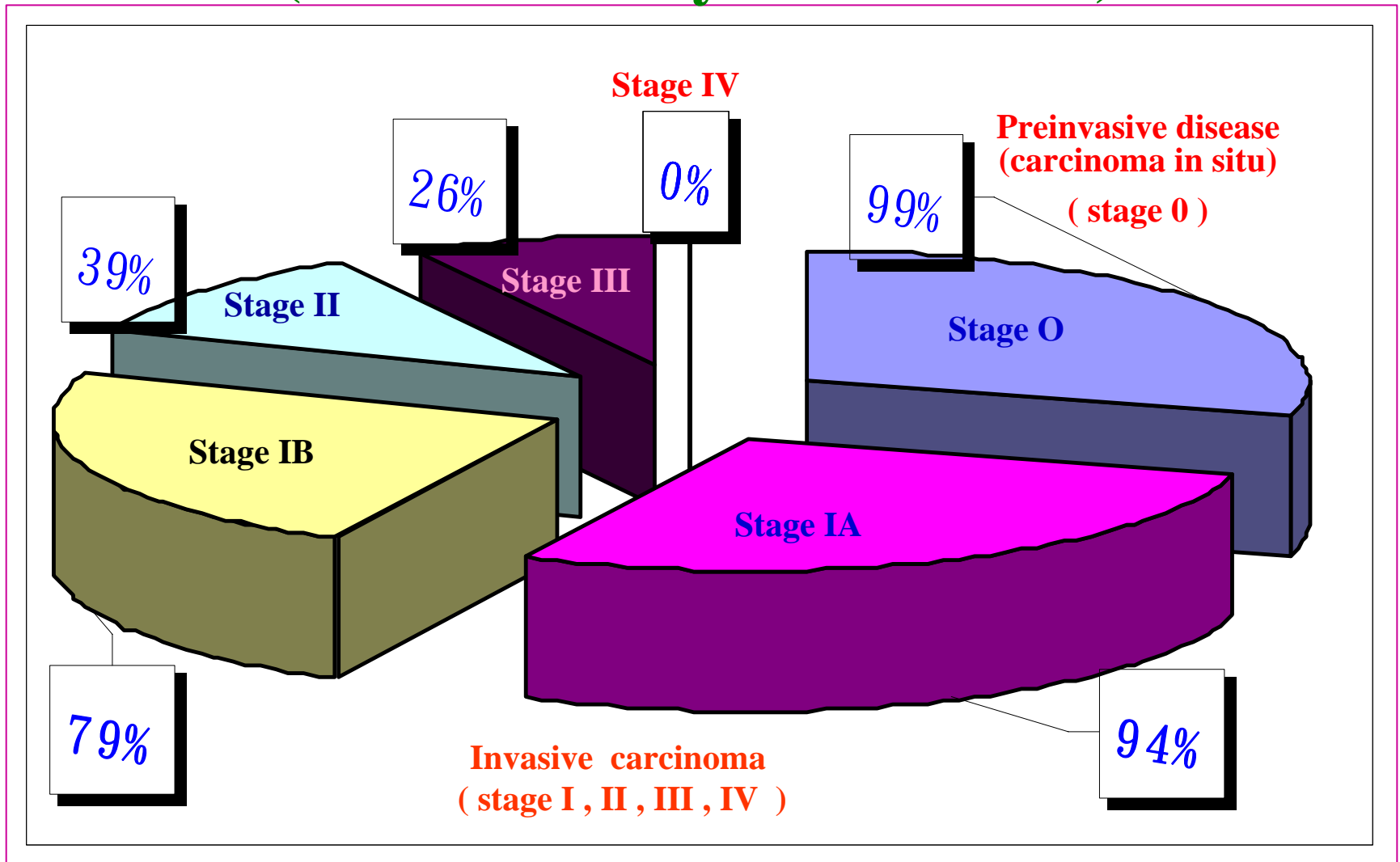
The Bethesda System for Reporting Cervical Cytology, Second Edition.

New York: Springer-Verlag, 2004.

http://nih.techriver.net/atlas.php
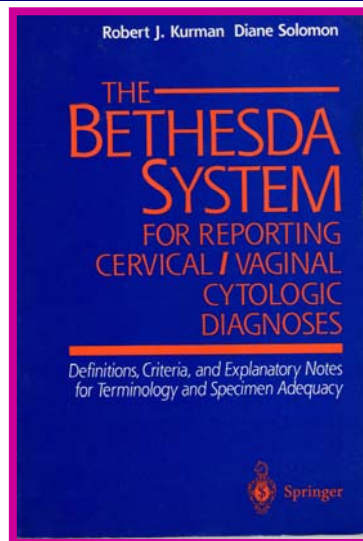
Specific inflammations

- ➢ *Organisms:*

- ■ *Trichomonas vaginalis*

- ■ **Fungal organisms morphologically consistent with *Candida* spp**

- ■ **Shift in flora suggestive of bacterial vaginosis**

- ■ **Bacteria morphologically consistent with *Actinomyces* spp.**

- ■ **Cellular changes consistent with *Herpes* simplex virus**

Other non-neoplastic findings

- **Reactive cellular changes associated with**
  - ☐ inflammation (includes typical repair)
  - ☐ radiation
  - ☐ intrauterine contraceptive device (IUD)
- **Glandular cells status post hysterectomy**
- **Atrophy**

Abnormalities of squamous cell

- **Atypical squamous cells**
  - of undetermined significance (ASC-US)
  - cannot exclude HSIL (ASC-H)
- **Low grade squamous intraepithelial lesion (LSIL)** (encompassing: HPV/mild dysplasia/CIN 1)
- **High grade squamous intraepithelial lesion (HSIL)** (encompassing: moderate dysplasia,CIN 2 and severe dysplasia ,CIN 3 and CIS,CIN 3) - with features suspicious for invasion (if invasion is suspected)
- **Squamous cell carcinoma (SCC)**
  - **non- keratinizing Squamous cell carcinoma**
  - **keratinizing Squamous cell carcinoma**

Abnormalities of glandular cell

- **Atypical**
  - ☐ endocervical cells (not otherwise specified (NOS) or specify in comments)
  - ☐ endometrial cells (NOS or specify in comments)
  - ☐ glandular cells (NOS or specify in comments)
- **Atypical**
  - ☐ endocervical cells, favor neoplastic
  - ☐ glandular cells, favor neoplastic
- **Endocervical adenocarcinoma *in situ***
- **Adenocarcinoma:**
  - ☐ endocervical
  - ☐ endometrial
  - ☐ extrauterine
  - ☐ not otherwise specified (NOS)

Cytology diagnosis?

superficial cells

intermediate cells

parabasal cells

Sup

int

pb

Mild dysplasia;CIN1,LSIL

Moderate dysplasia; CIN2,HSIL

Severe dysplasia;CIN3,HSIL

Carcinoma in situ;CIN3,HSIL
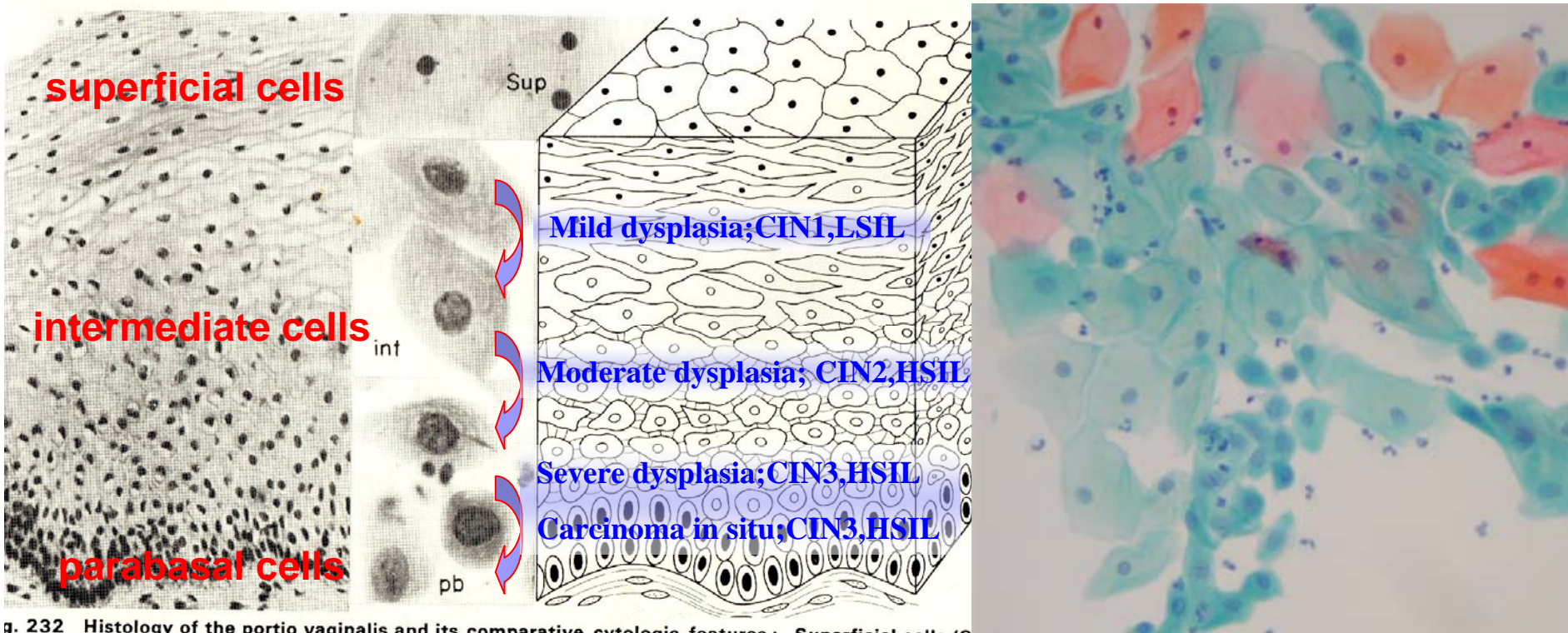
g. 232   Histology of the portio vaginalis and its comparative cytologic features :   Superficial cells (Sup), intermediate cells (int), and parabasal cells (pb).

Color Atlas of Cancer cytology,Second Edition .MasayoshiTakahashi,M.D.,.I.A.C.F

Normal squamous cells
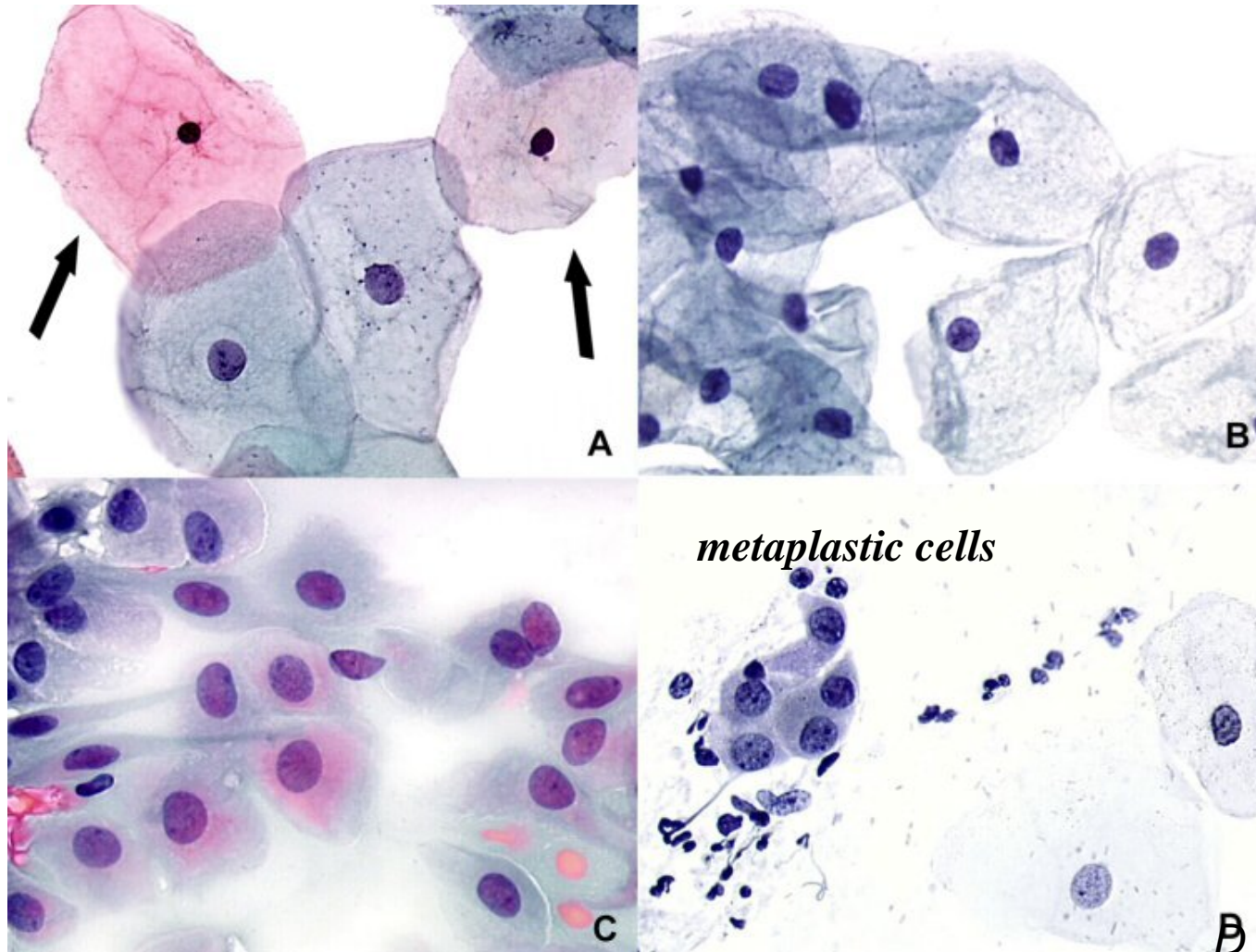
metaplastic cells

Different types of squamous cells - A: superficial cells (arrows); B: intermediate cells; C: parabasal cells; D: metaplastic cells. (obj. 20x) **http://screening.iarc.fr/atlascyto.ph**

Normal endocervical glandular cells
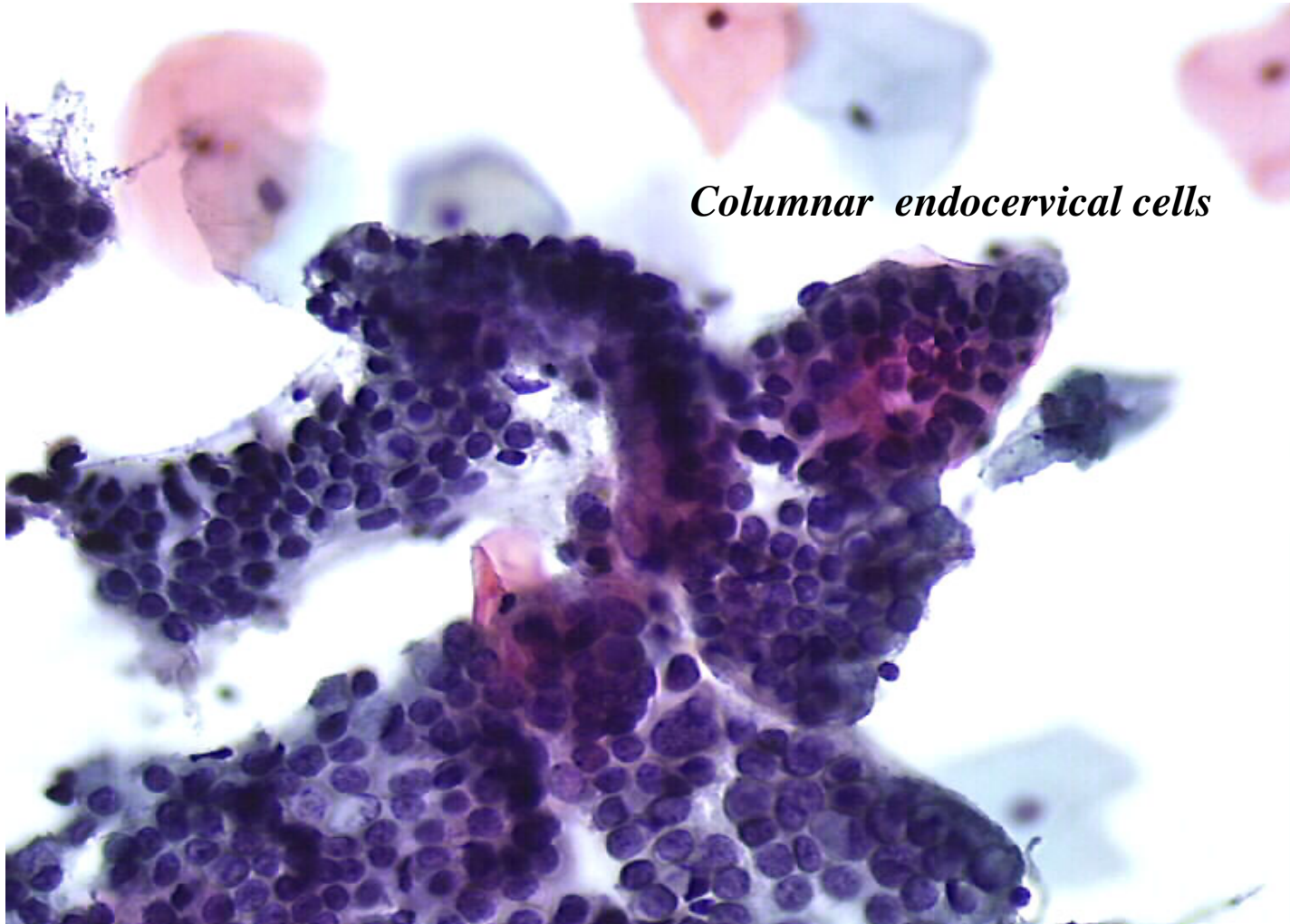
Columnar endocervical cells

Liquid-based cytology: morphological details of a cluster of columnar endocervical cells. (obj. 20x)

http://screening.iarc.fr/atlascyto.php

Other (endometrial cells after 40 years)
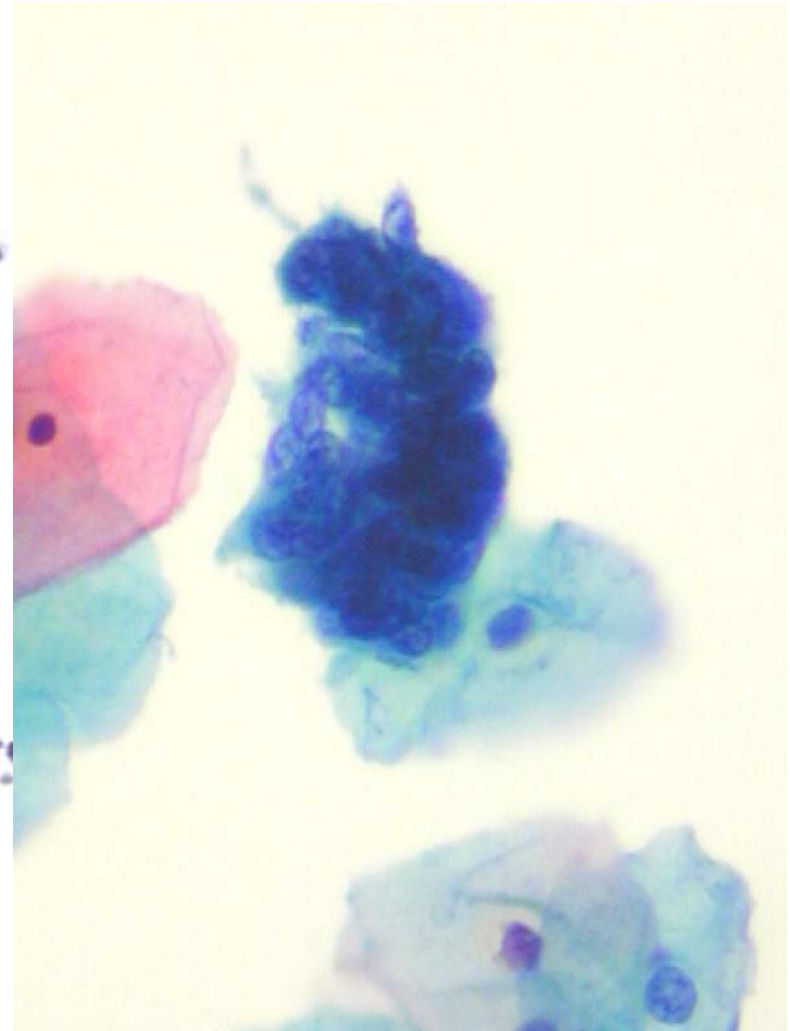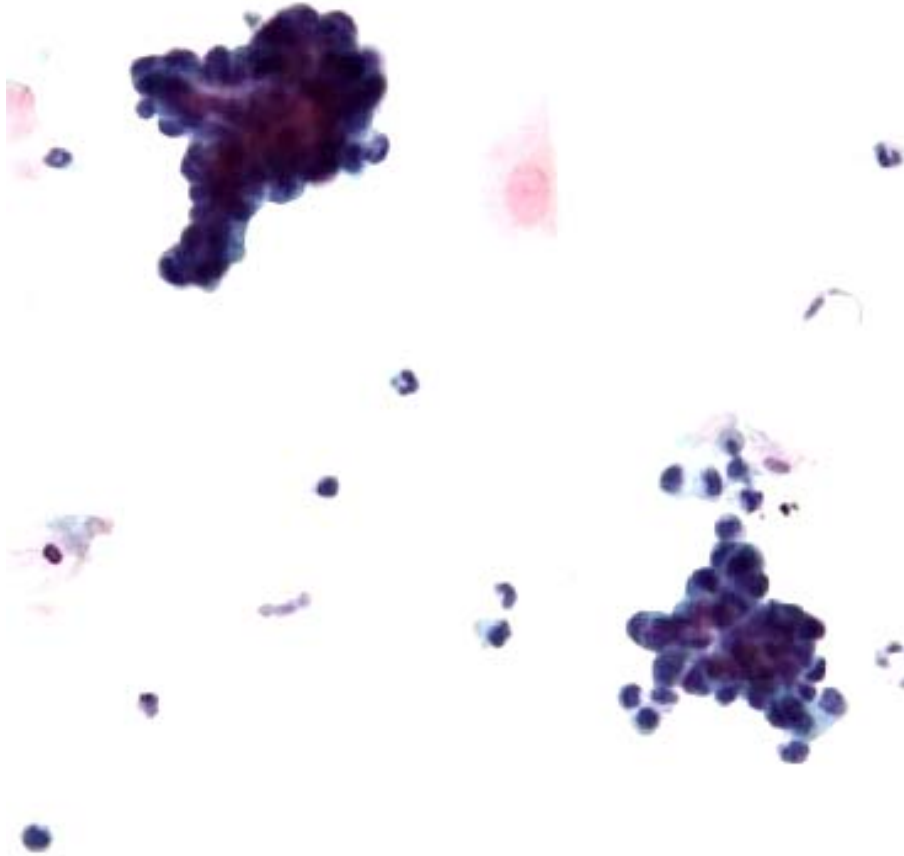
48 year-old woman. Presence of endometrial cells. Bethesda recommendation: endometrial biopsy. (obj. 20x)

Mature squamous metaplasia
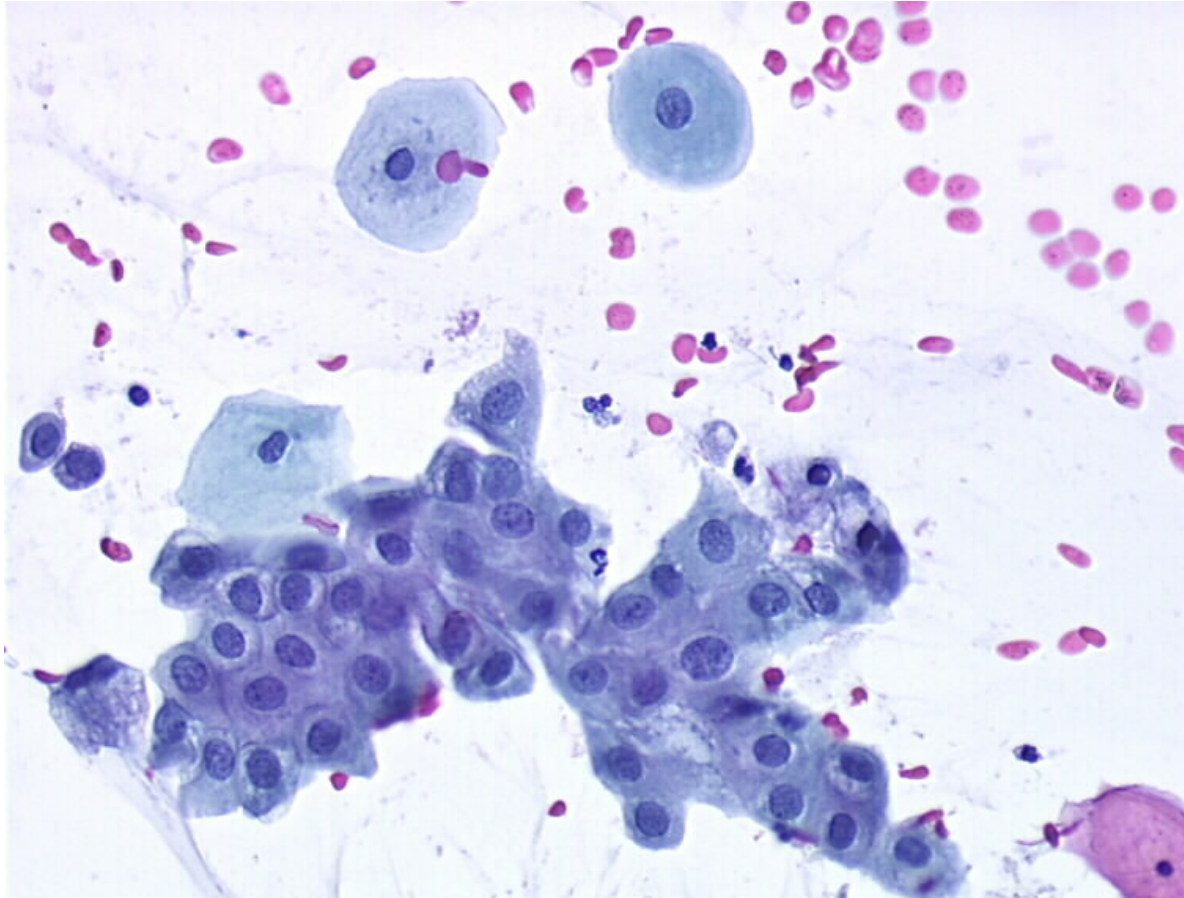
Transition zone smear with a sheet of metaplastic squamous cells. (obj. 20x)

Immature squamous metaplasia
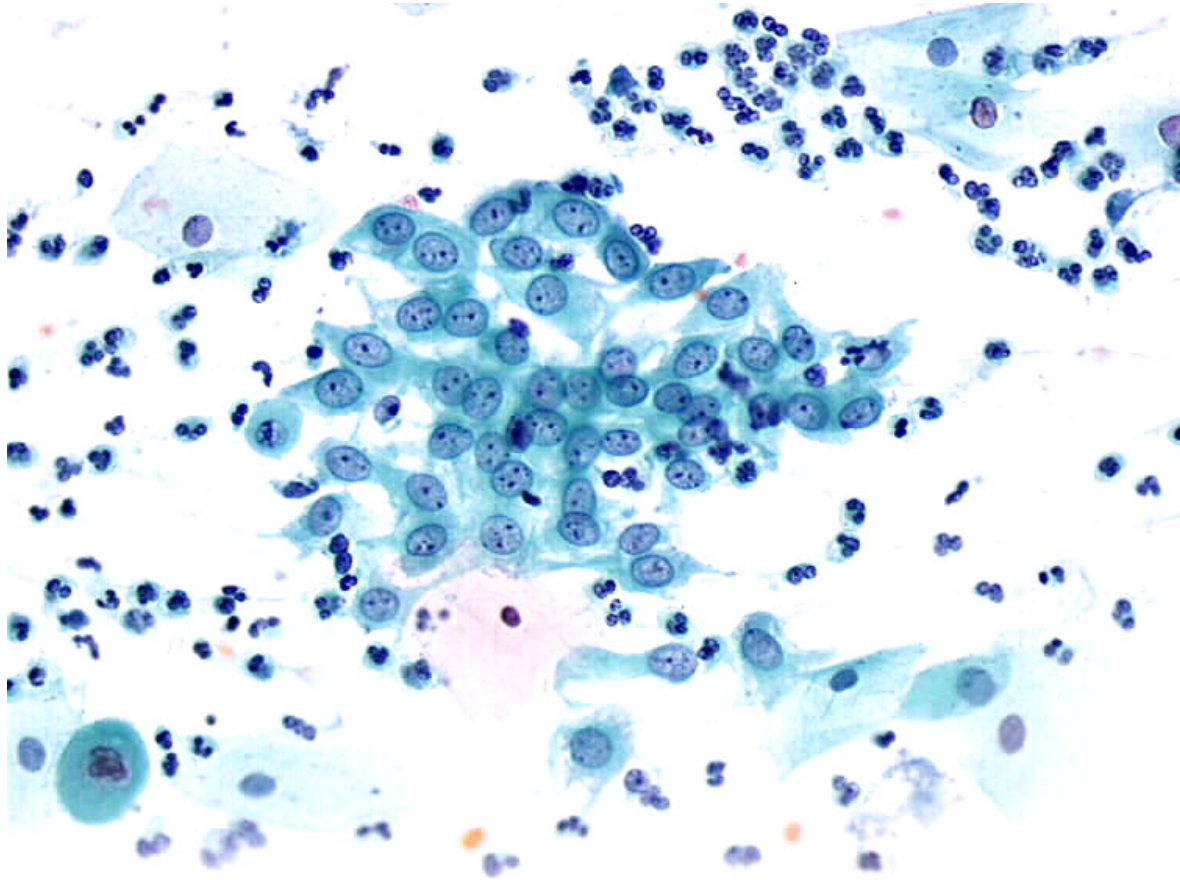
Transition zone: a sheet of immature metaplastic cells (repair cells), nuclei with clear chromatin and visible nucleoli. Inflammatory background. (obj. 20x)

Reactive cellular changes associated with Radiation
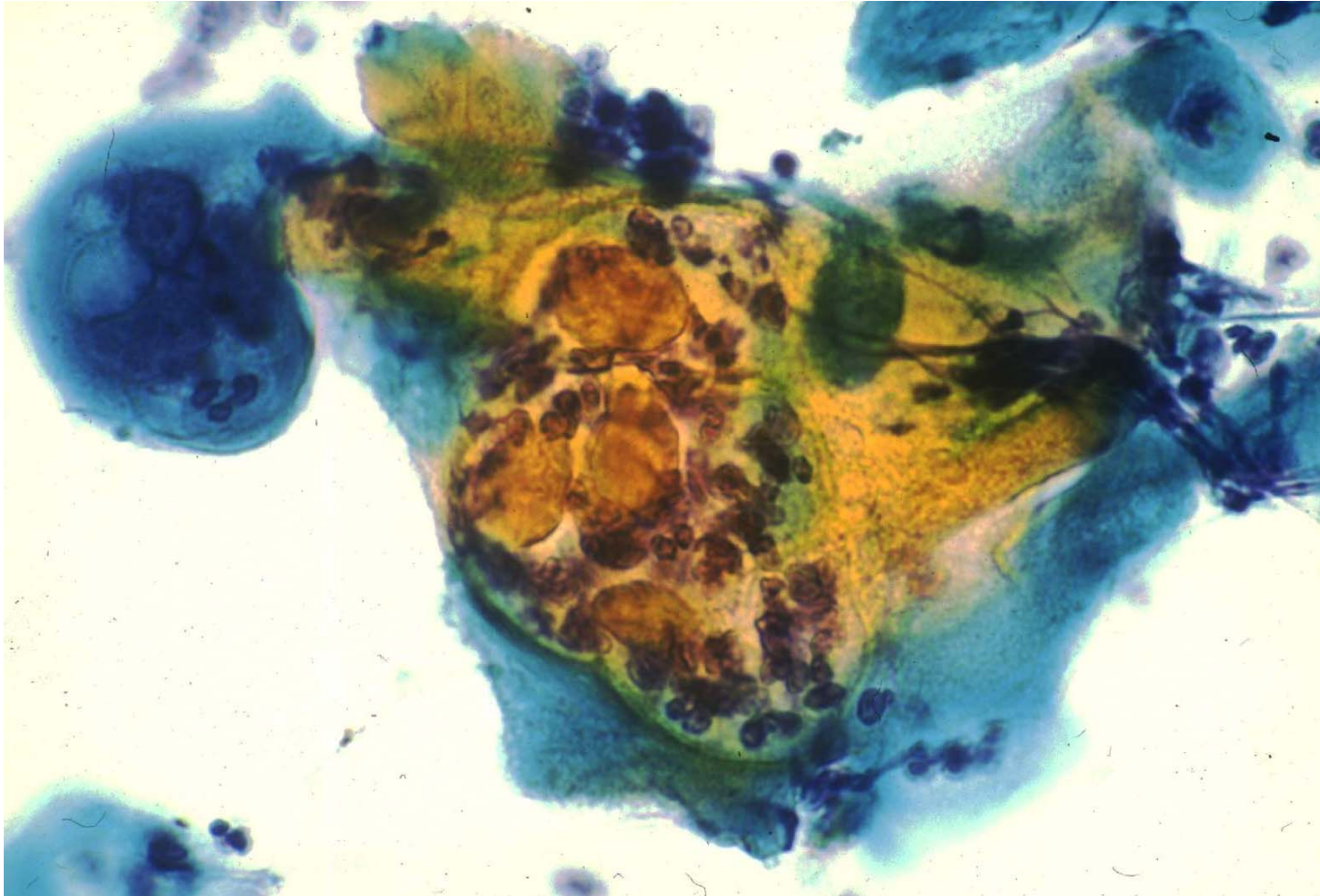
Glandular cells status post-hysterectomy
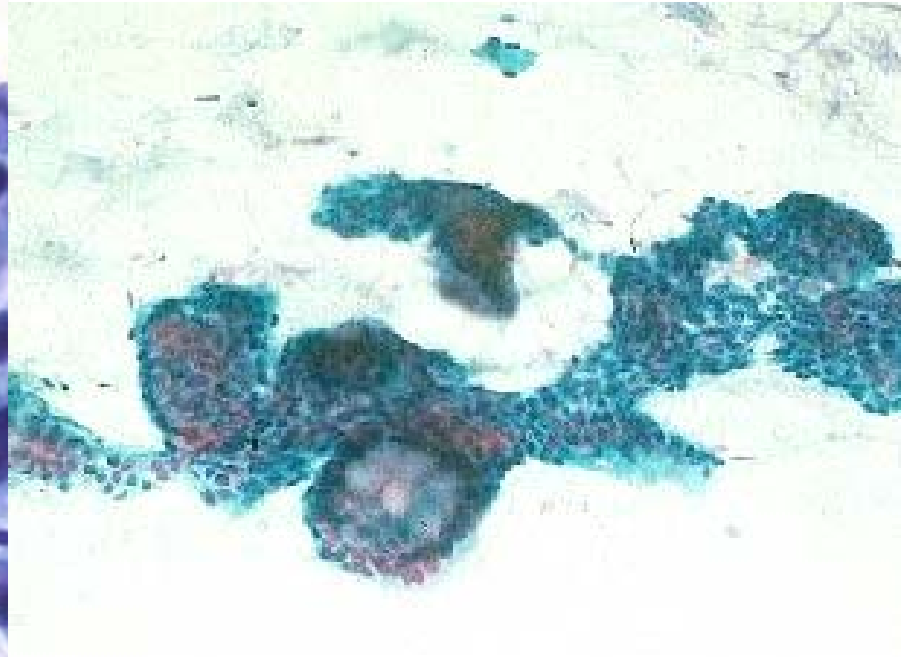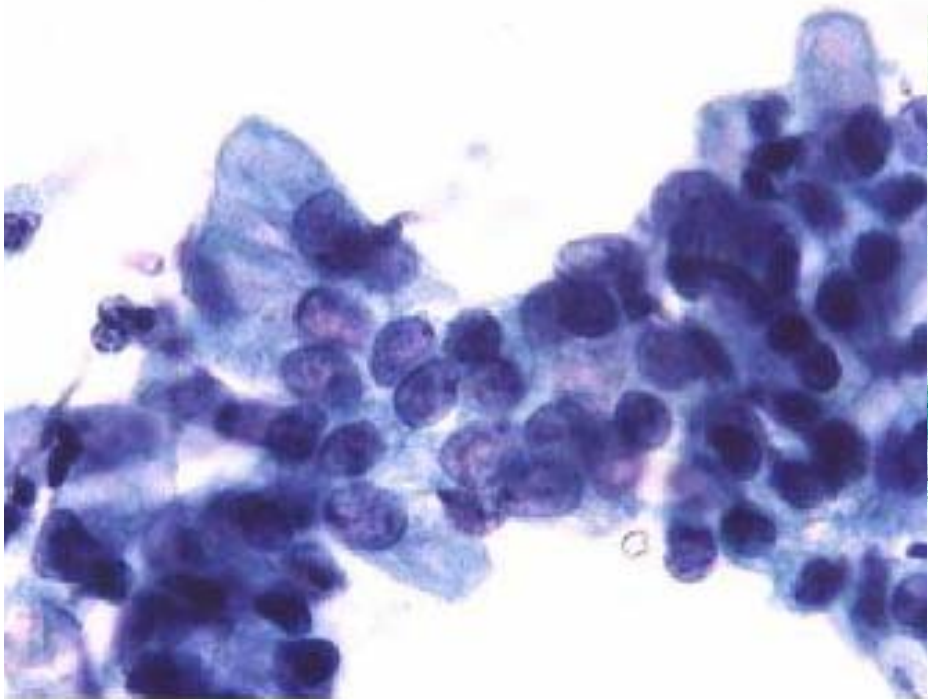
Goblet cell metaplasia and bland cellular features

Trichomonas vaginalis
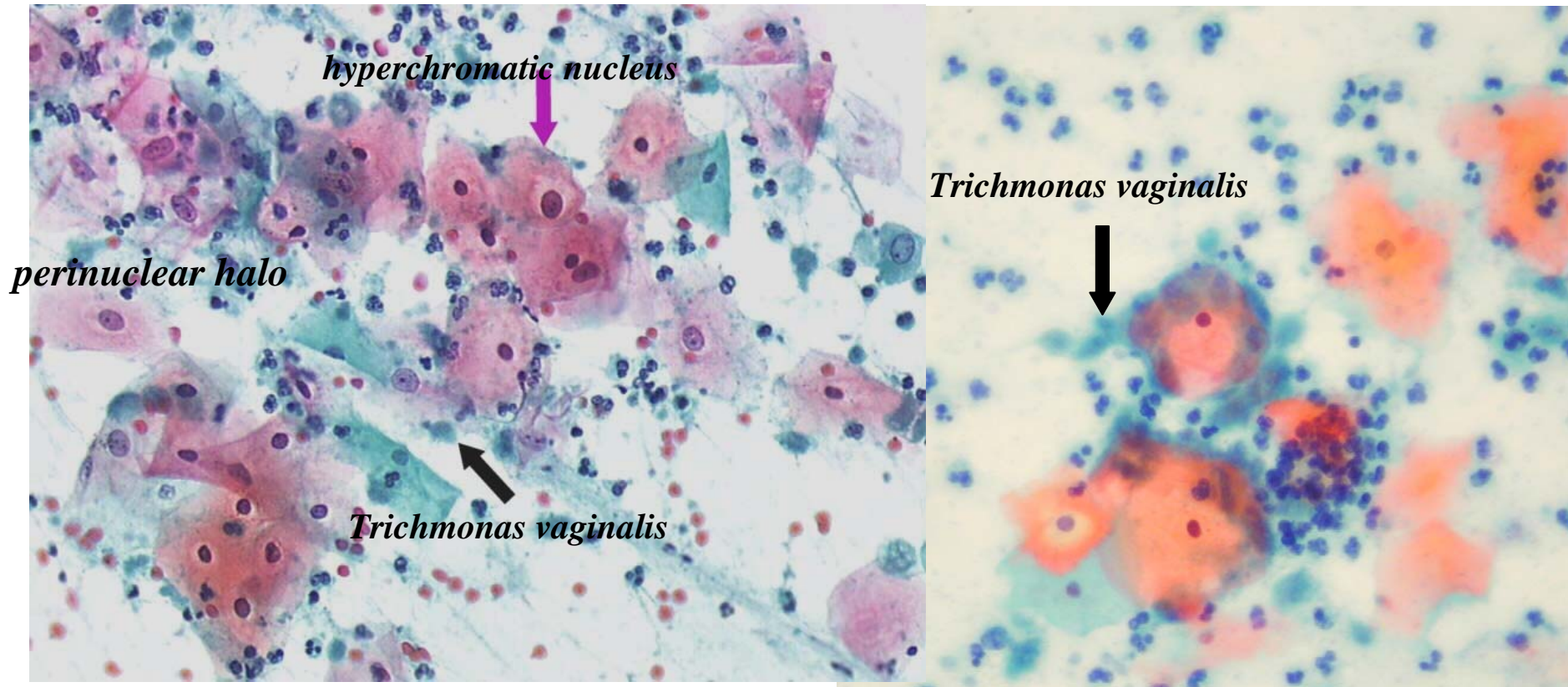
Inflammatory background, squamous cells with a clear perinuclear halo and an enlarged hyperchromatic nucleus (purple arrow): Trichomonas vaginalis infection (black arrow: parasite). (obj. 10x)

Mycosis: Candida
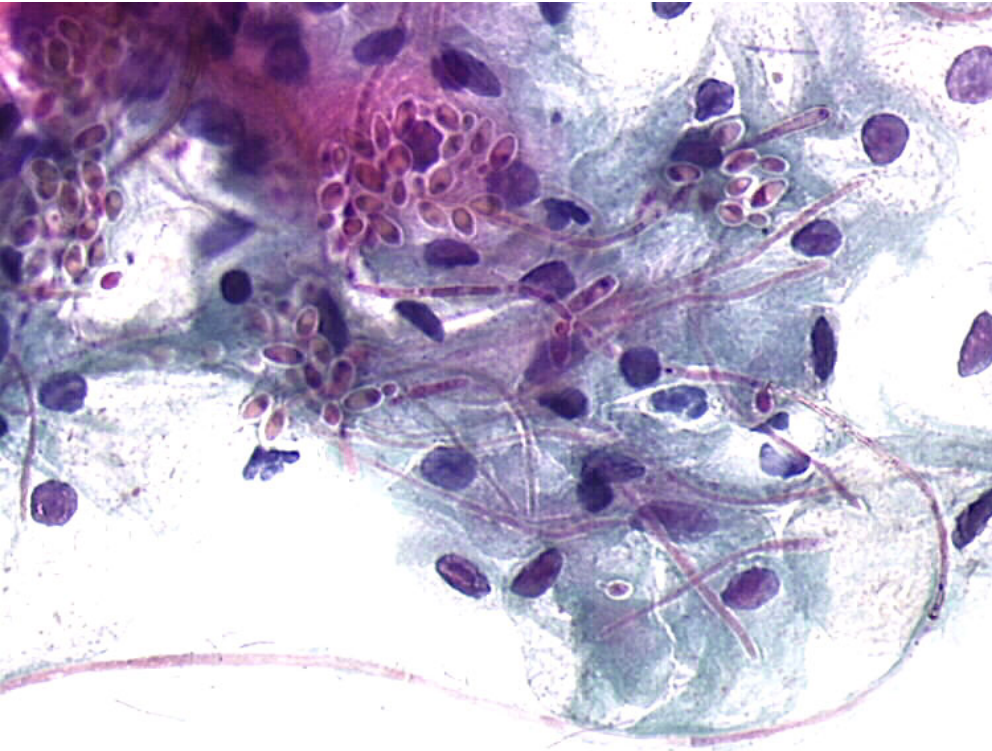
Moniliasis: details of hyphae and yeasts.
Compare sizes of yeasts and squamous cell nuclei.
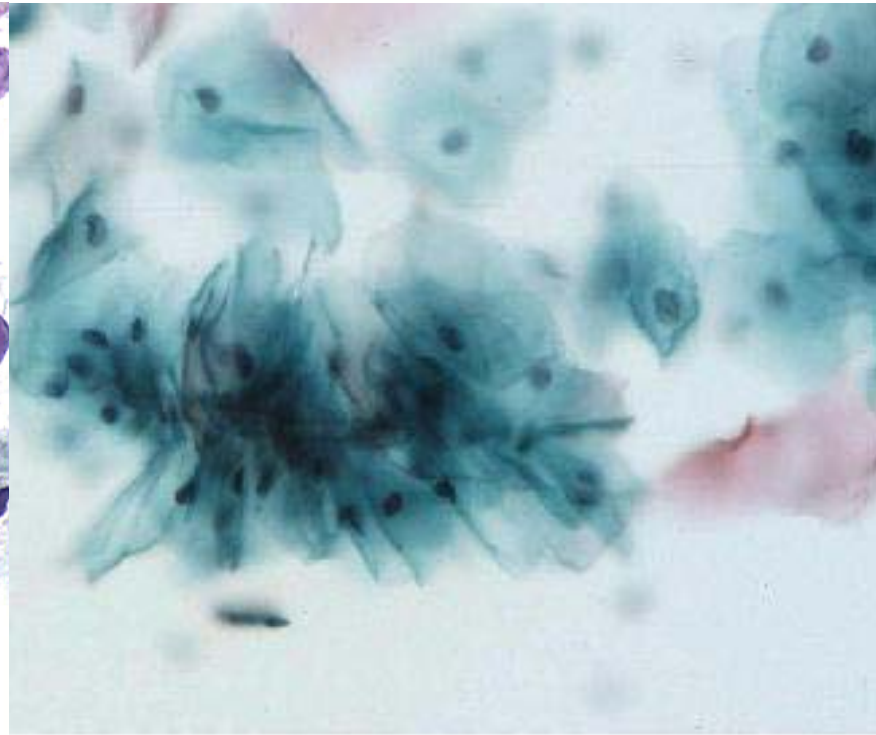
Spearing of epithelial cells by candida pseudohyphae ("shish kebob" effect).

Vaginal bacteriosis
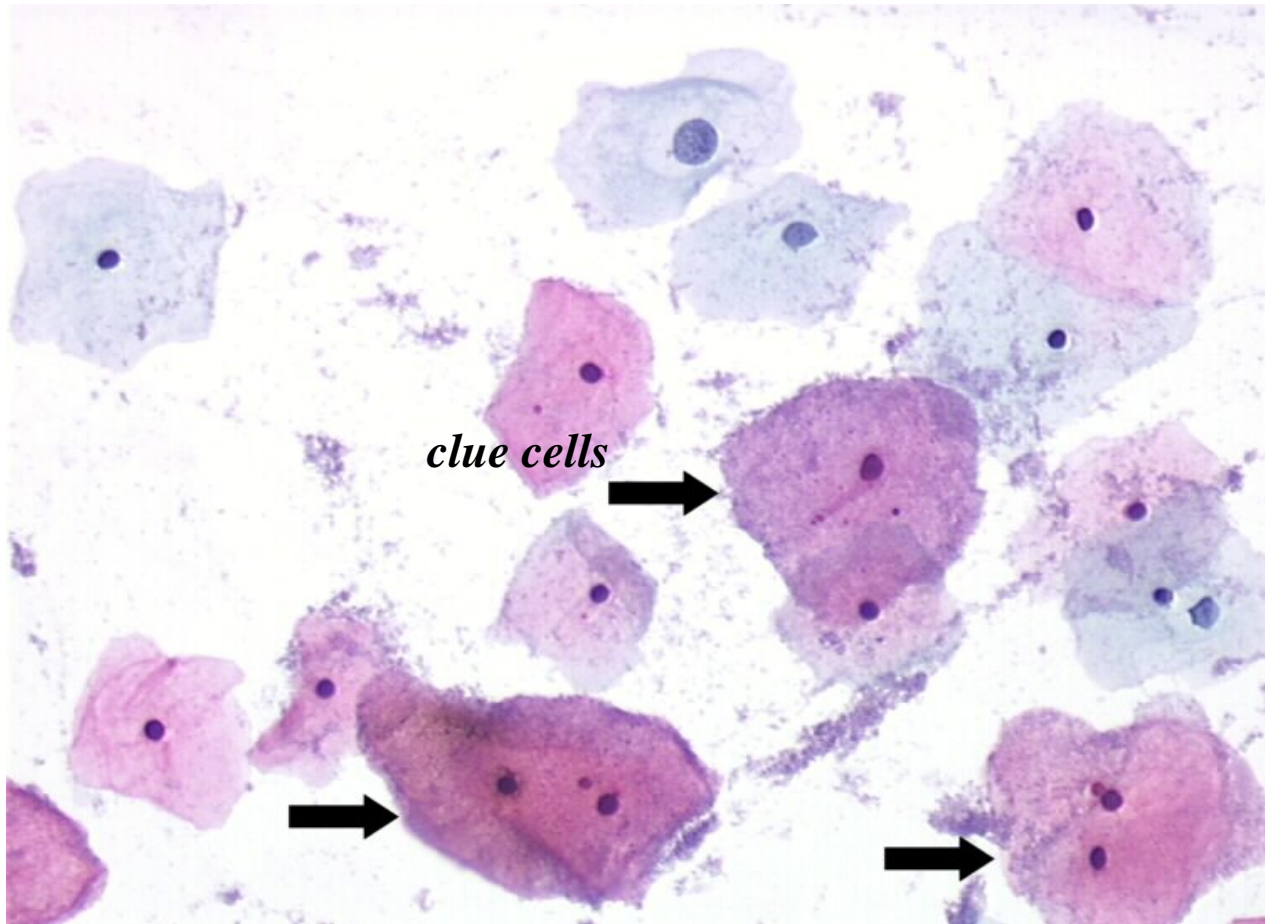
Gardnerella vaginalis: bacteria are seen in the background, mainly covering the squamous cells resulting in clue cells (arrows). No cytolysis. Polymorphs are absent or rare. (obj. 20x)

Actinomyces

pseudofilamentous
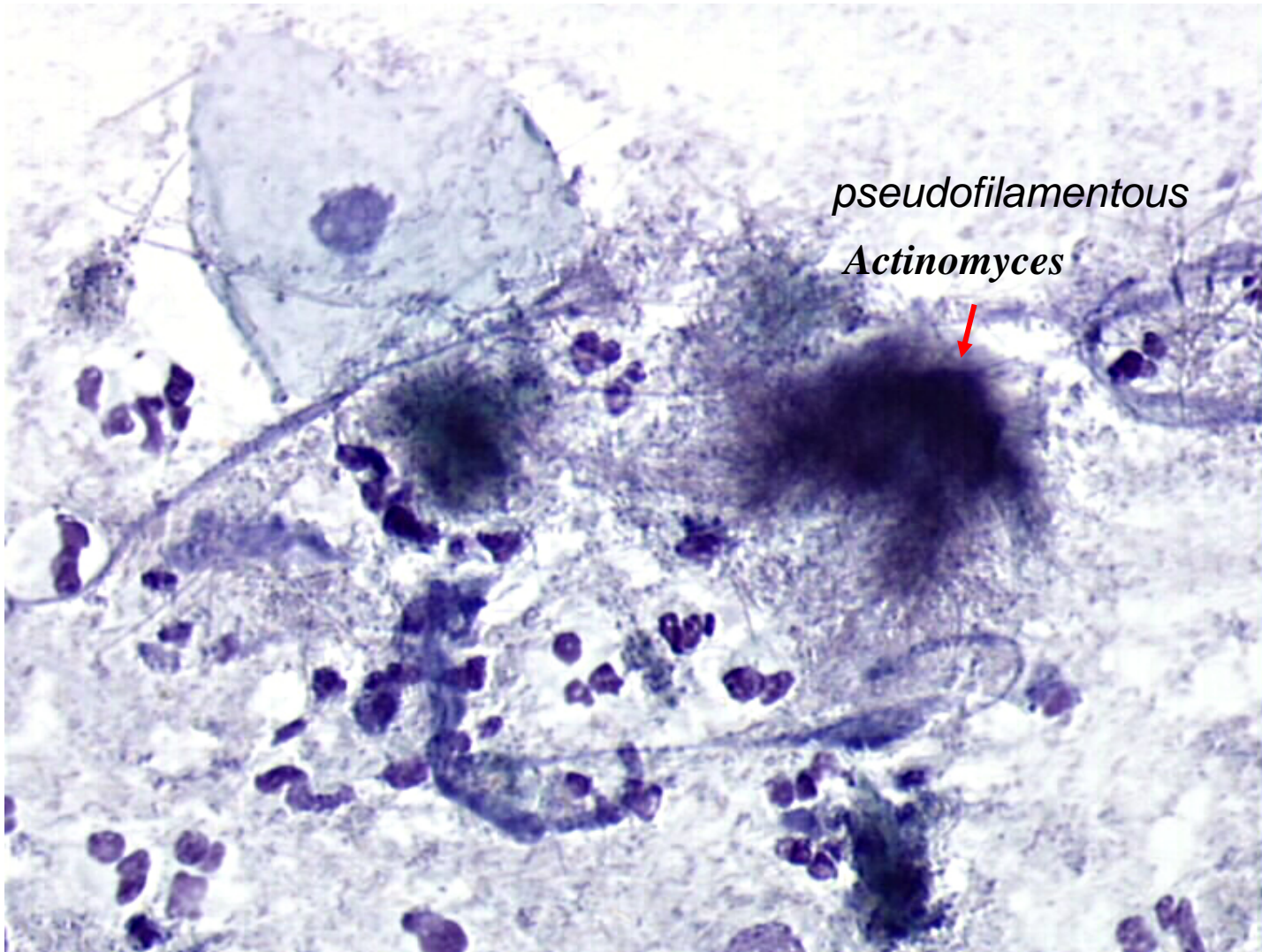
Actinomyces

Actinomyces: typical aggregates of pseudofilamentous material. Smear from a woman with an IUD. (obj. 40x)

Herpes simplex virus

multinucleate cells

intranuclear viral inclusions
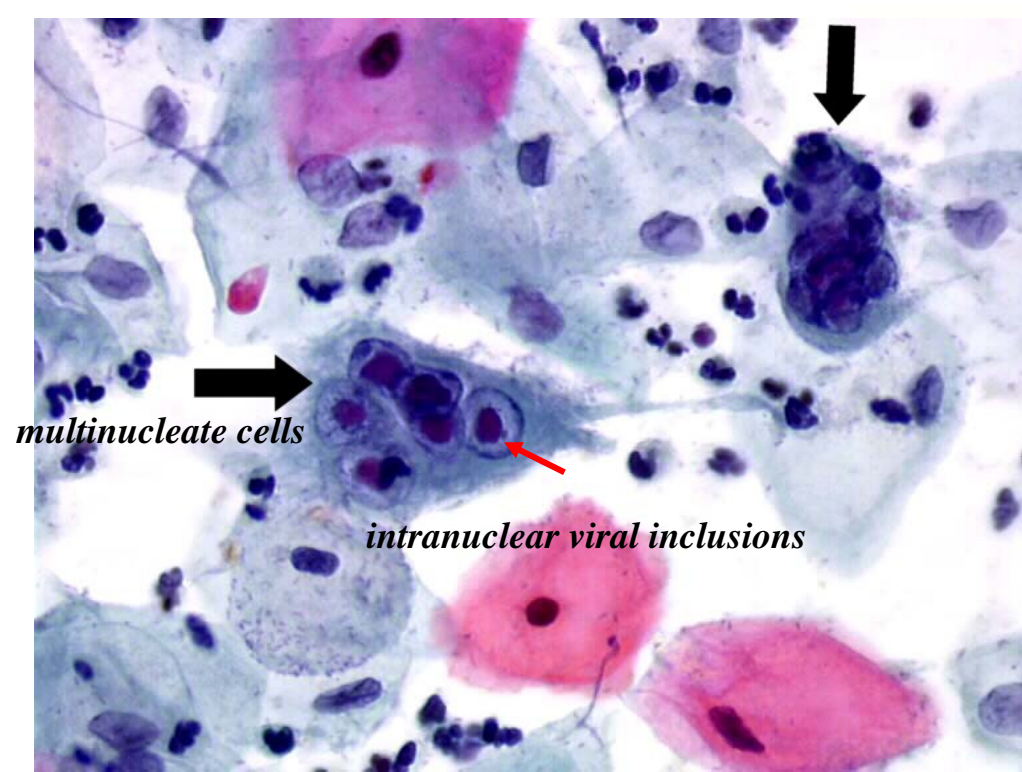
ground glass

Herpetic infection: two multinucleate cells (arrows) with intranuclear viral inclusions.
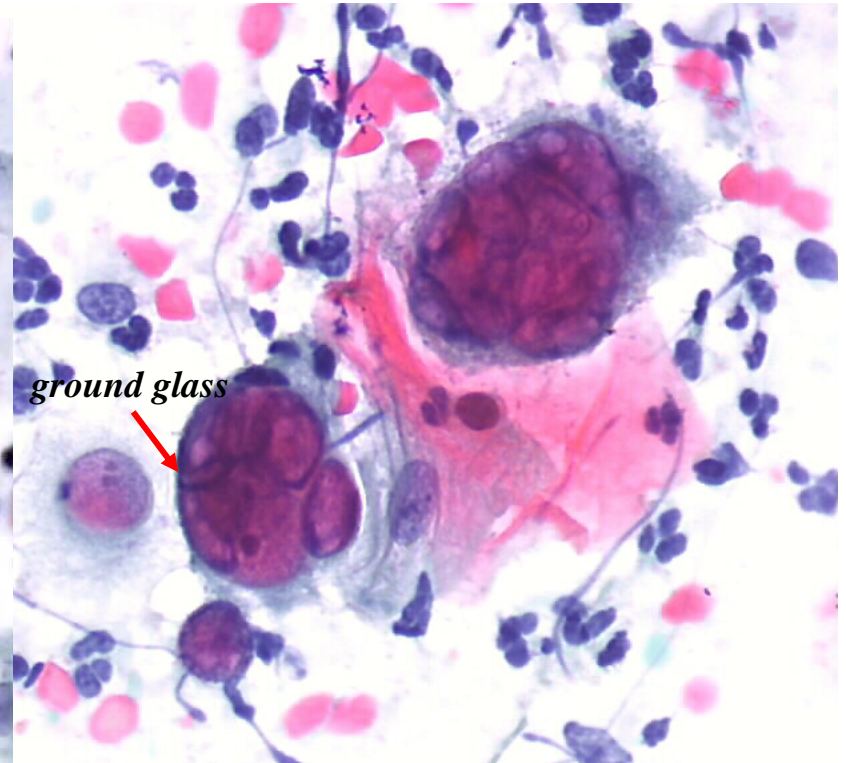
Herpetic infection: multinucleated cells with smudgy nuclei looking like ground glass

Inflammation and repair cells
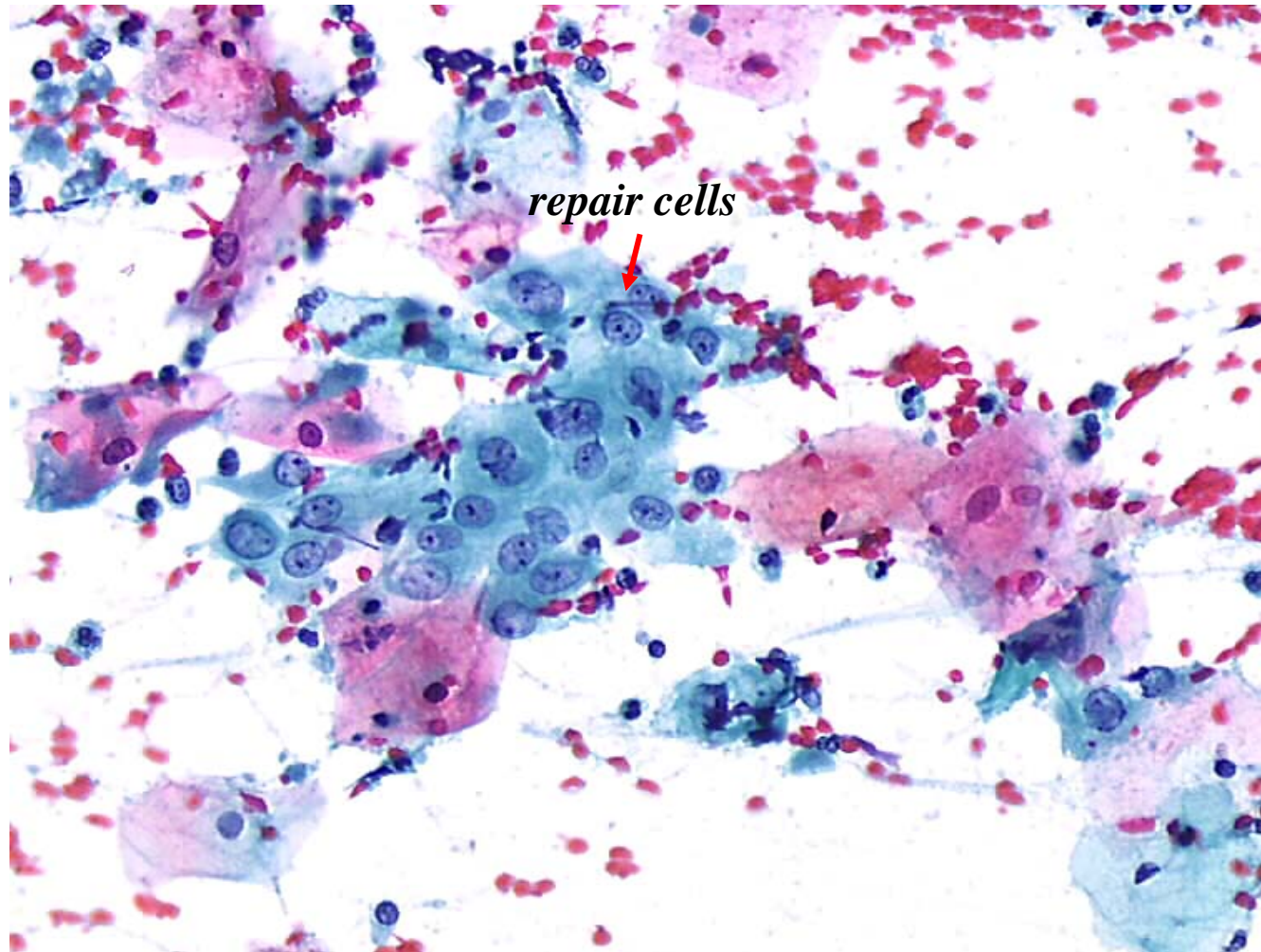
repair cells

Inflammatory and bloody exocervical smear: sheet of repair cells with a clear nuclear chromatin and a visible nucleolus. (obj. 20x)

Atrophy
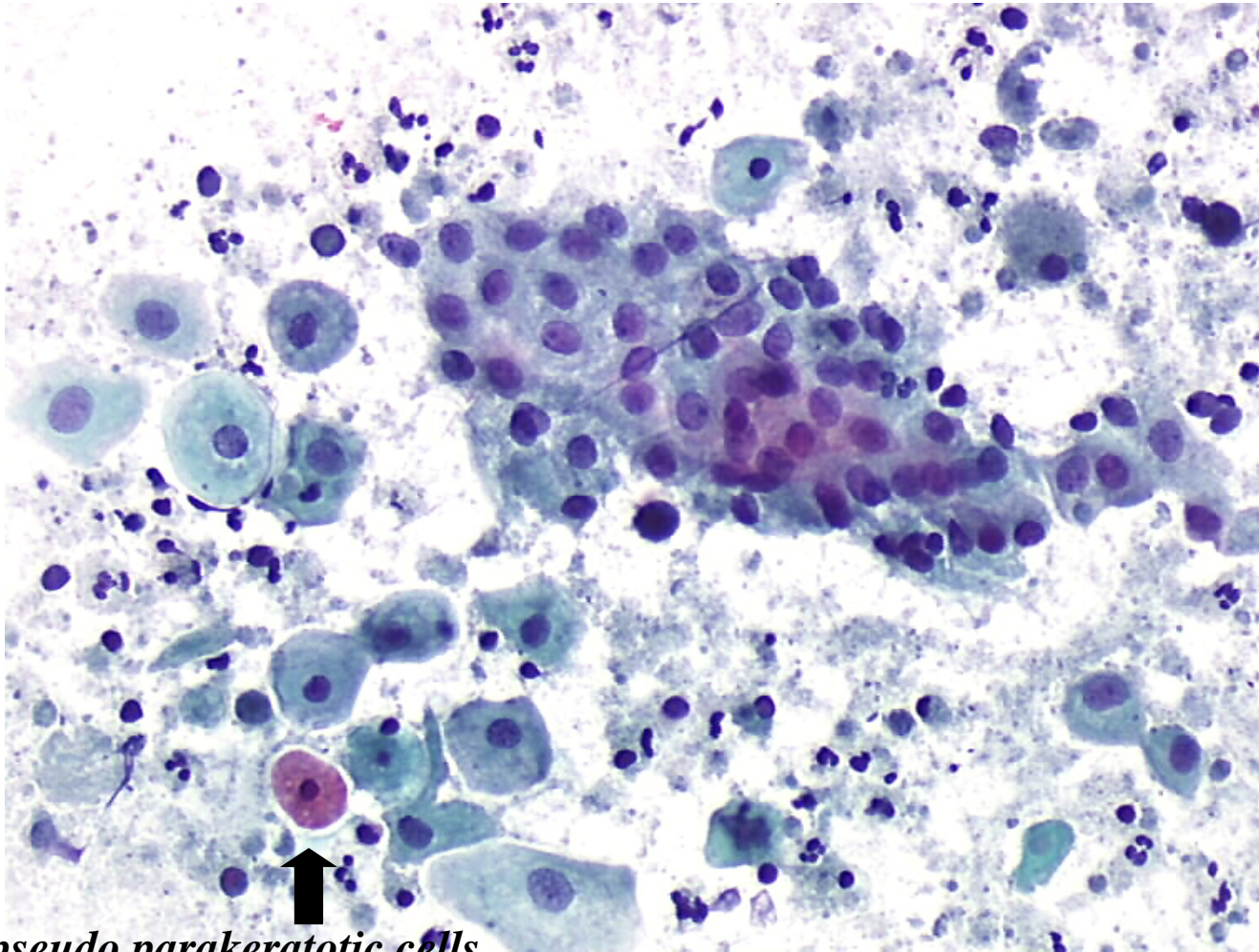
pseudo parakeratotic cells

Atrophic, inflammatory and necrotic menopausal smear, containing small pseudo parakeratotic cells (red necrosis) and nuclear degenerative changes. A cluster of basal squamous or columnar cells. (obj. 10x)

ASC-US suggesting a LSIL
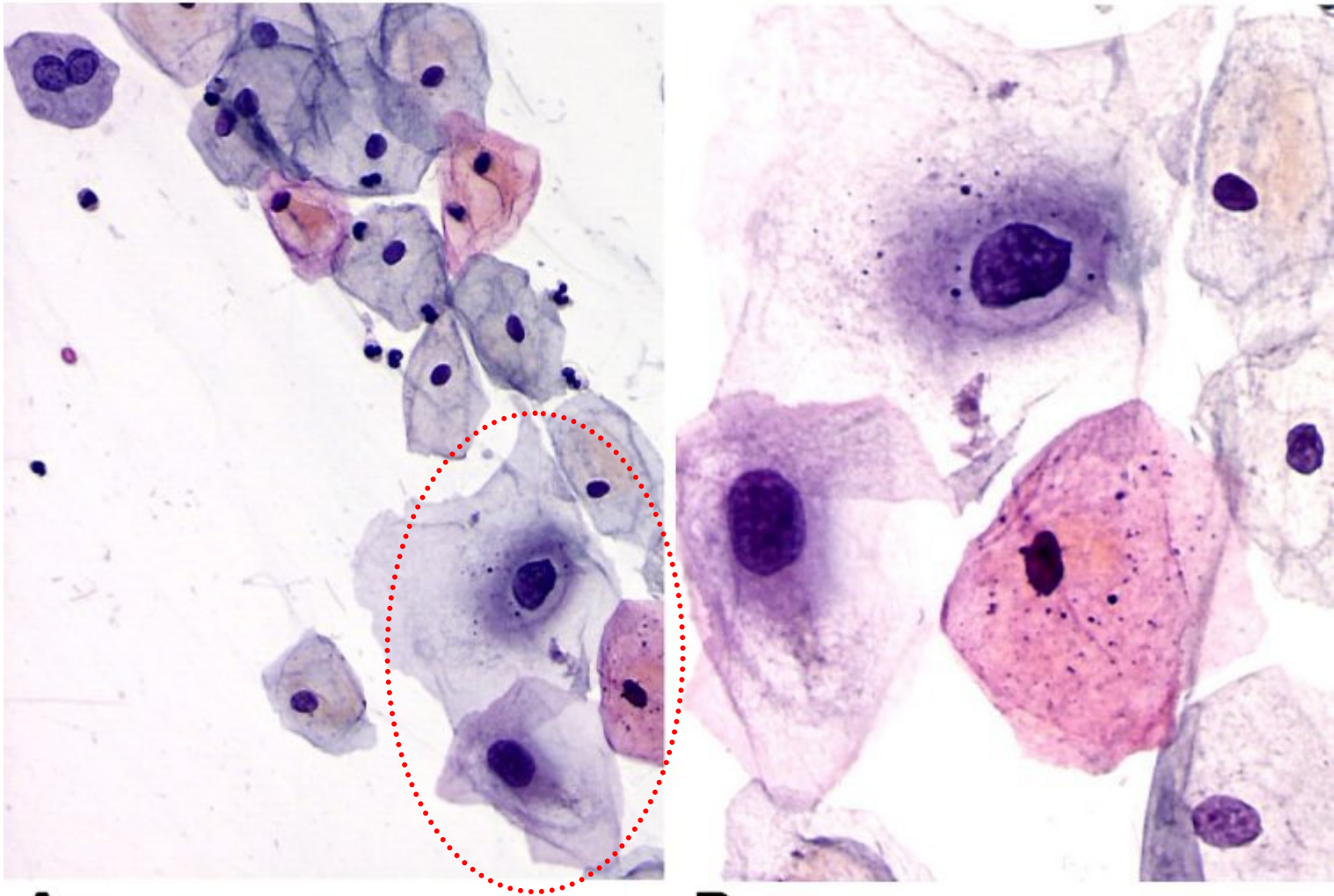
Two intermediate squamous cells with nuclear enlargement, irregular outlines and dense chromatin: ASC-US (rule out LSIL). (obj. 40x)

ASC cannot exclude a high-grade lesion ;ASC-H
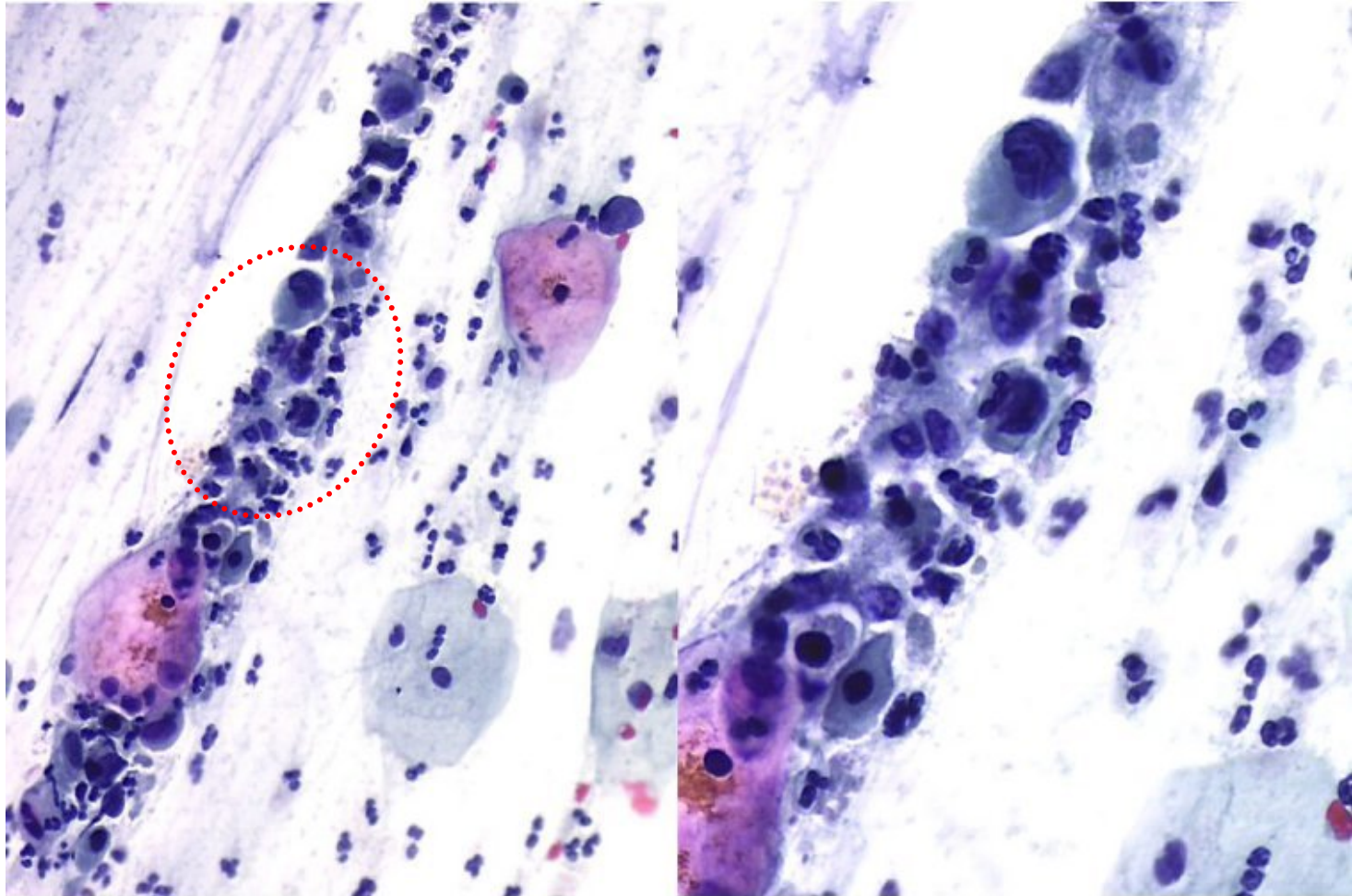
Smear containing isolated basal cells, with enlarged and irregular nuclei and a dense chromatin, suggesting high grade SIL: ASC-H vs HSIL. (A: obj. 20x, B: obj. 40x)

Low-grade Squamous Intraepithelial Lesion ;LSIL

Atomic Model of
Papillomavirus Capsid

Pap Smear with HPV

Koilocytosis (perinuclear cavitation)
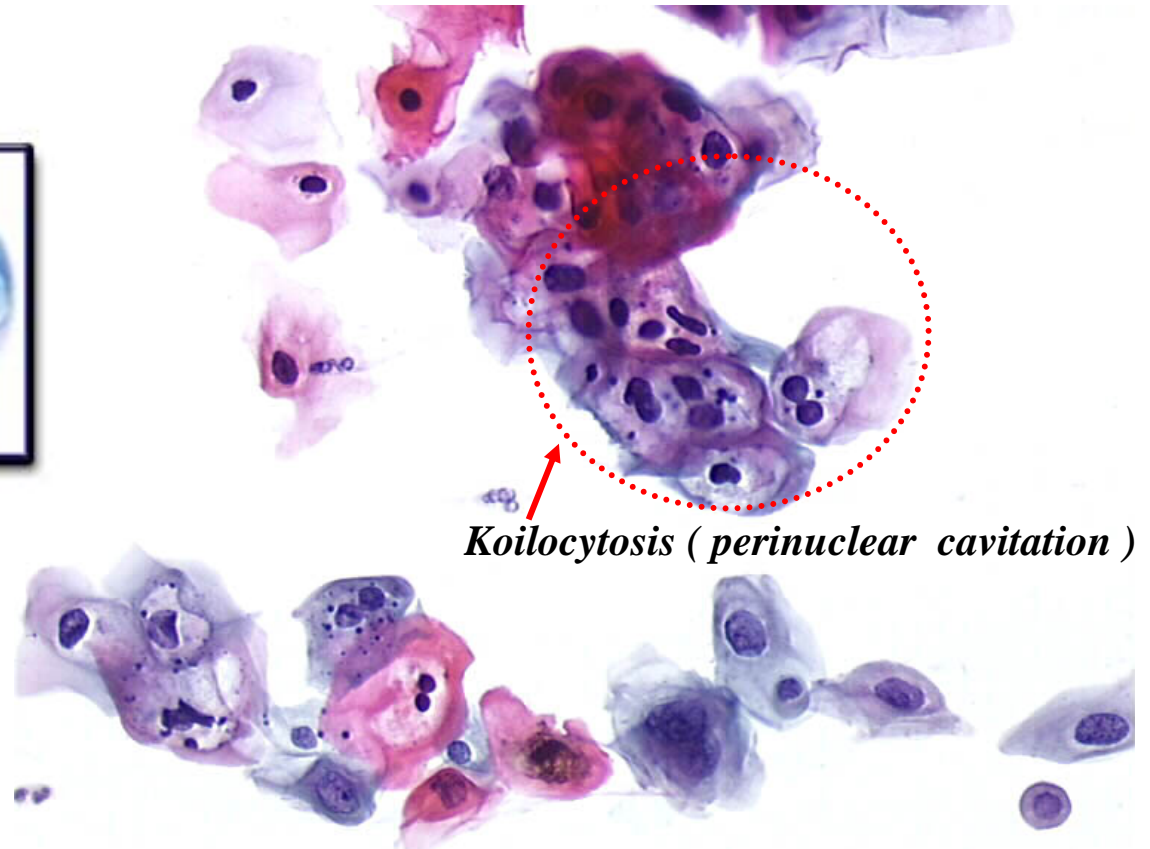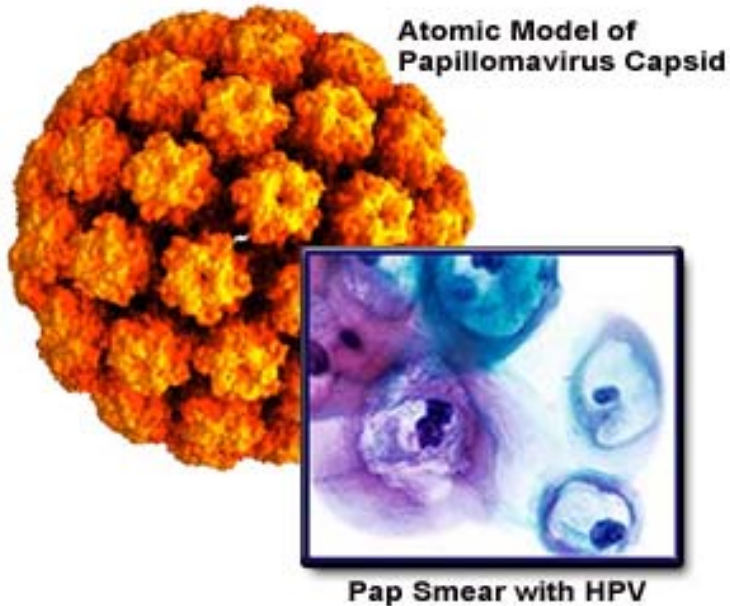
LSIL: typical eosinophilic and basophilic koilocytes associated with some parakeratosis and binucleated cells. (obj. 20x)

HSIL

A **B**
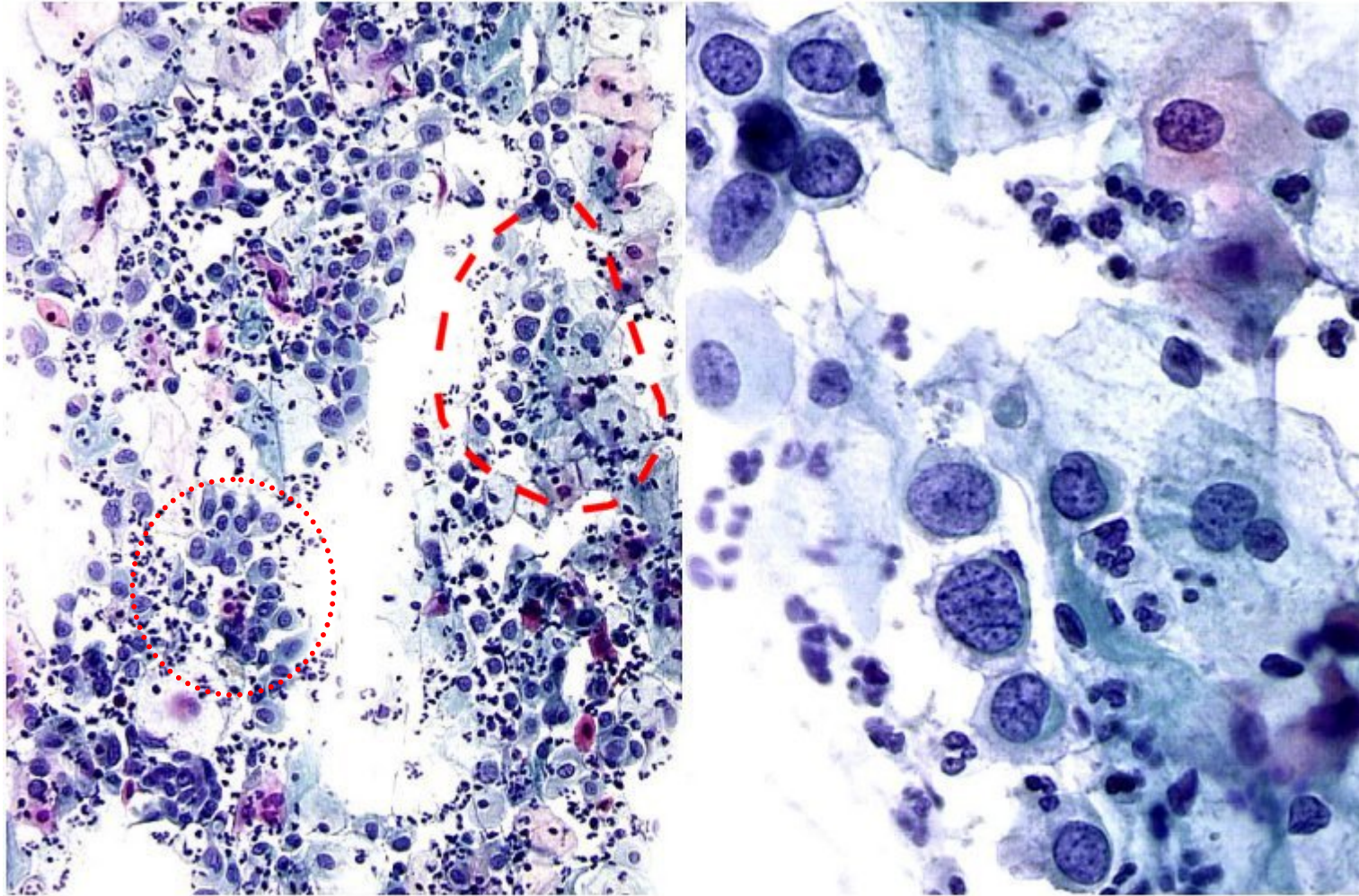
HSIL: inflammatory smear containing many parabasal cells with enlarged Nuclei With irregular chromatin (dotted line). (A: obj. 10x, B: obj. 40x)

HSIL with features suspicious of invasion
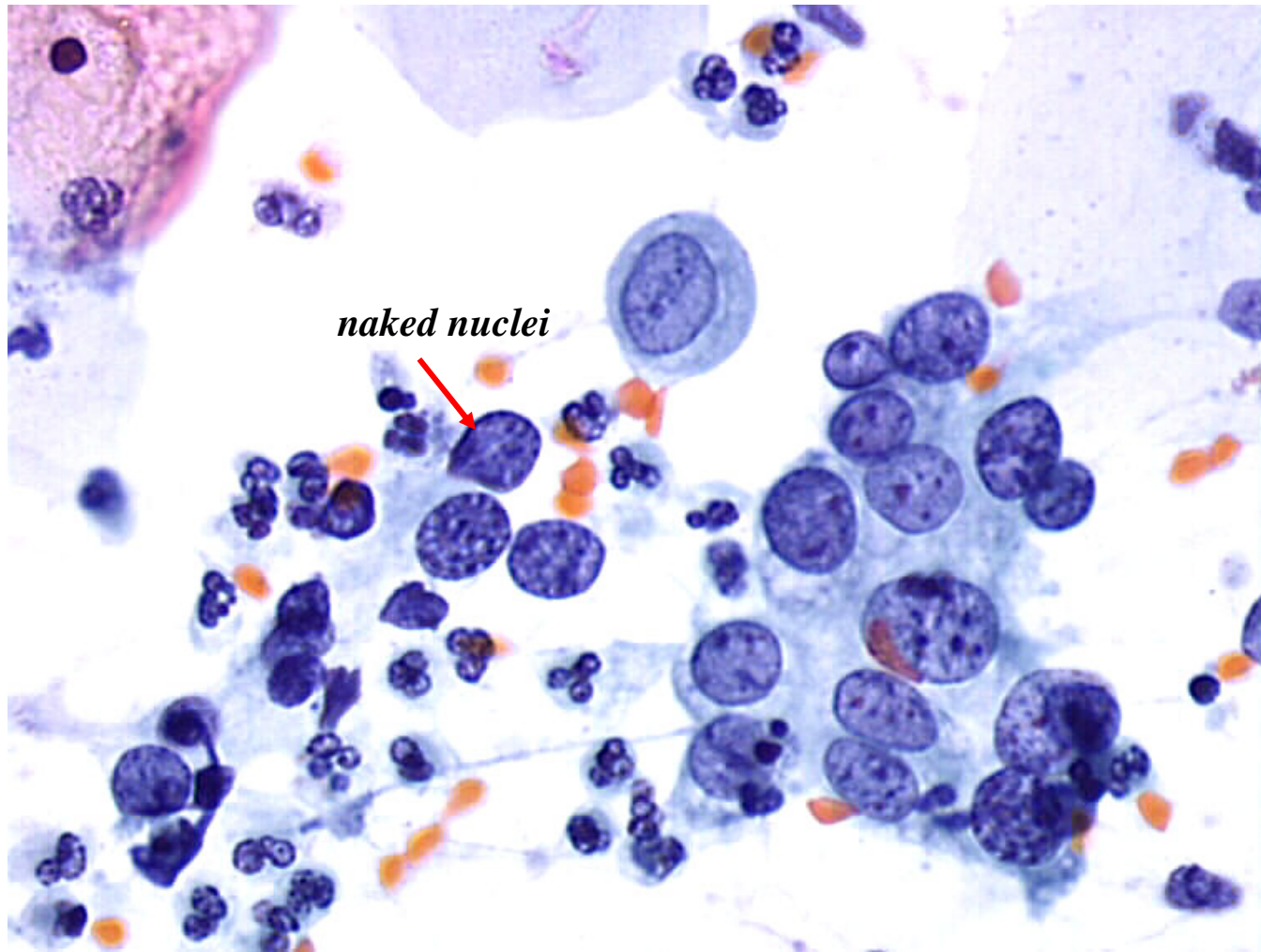
naked nuclei

HSIL with features suspicious of invasion: cluster of basal cells with ill-defined cellular limits, enlarged nuclei, irregular chromatin and a thickened nuclear membrane. Some Isolated atypical cells and naked nuclei. Inflammatory background. (obj. 40x)
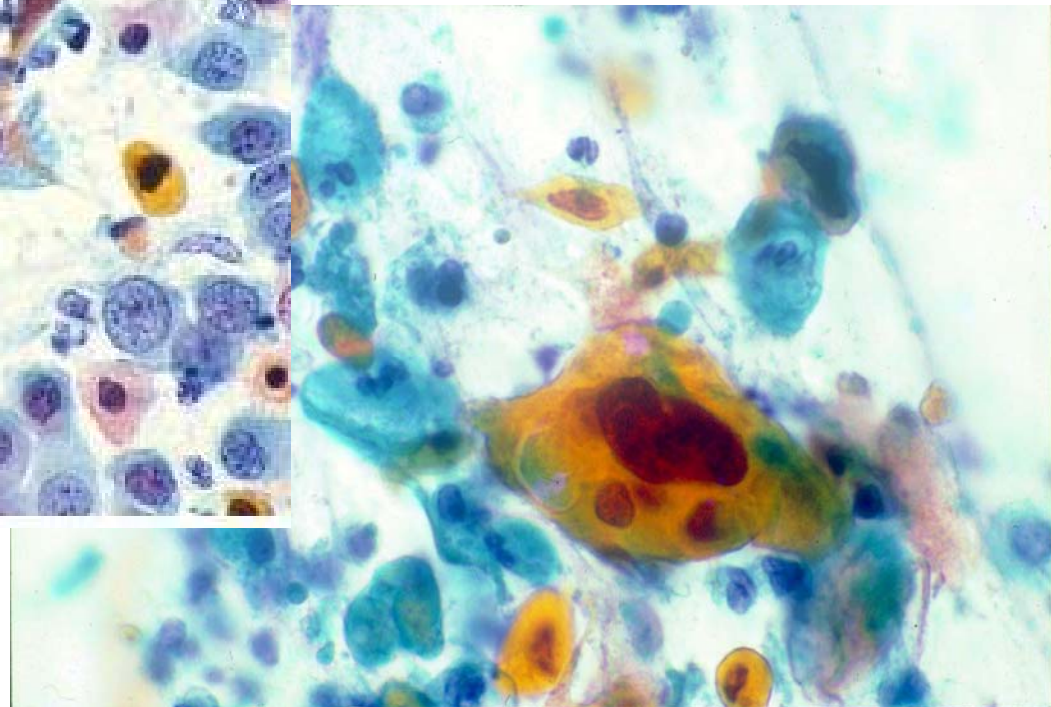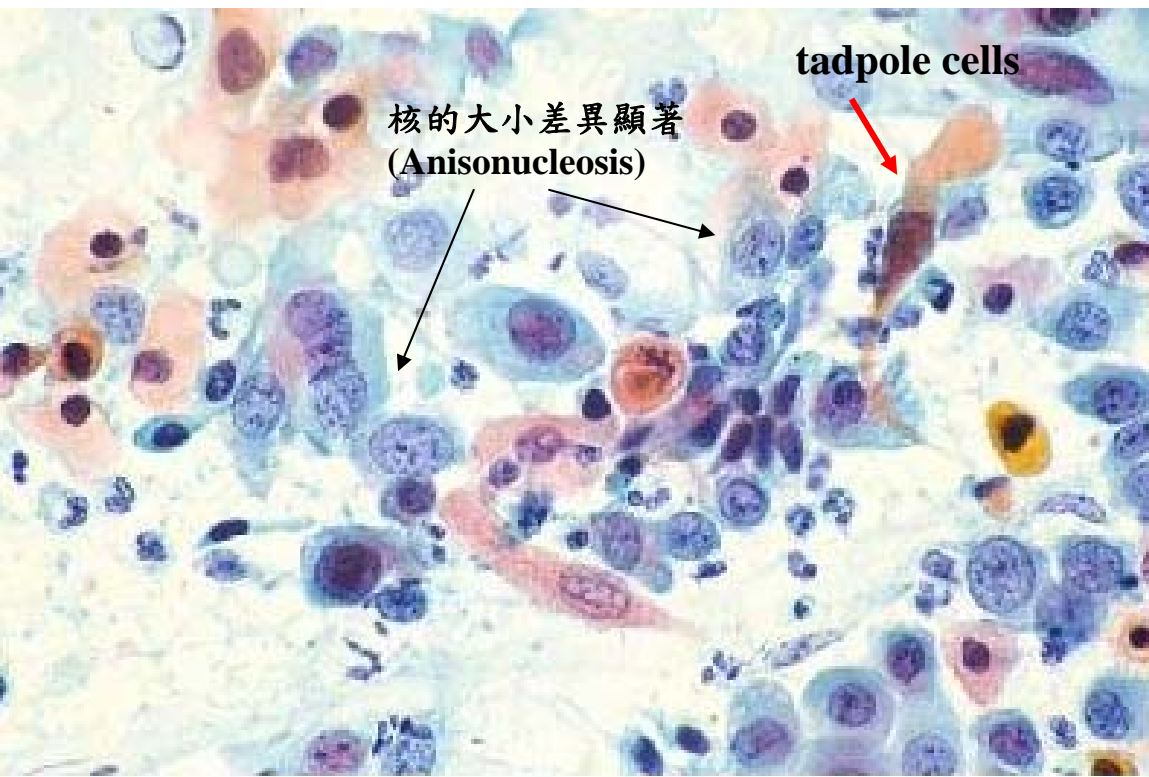
Non- keratinizing Squamous cell carcinoma
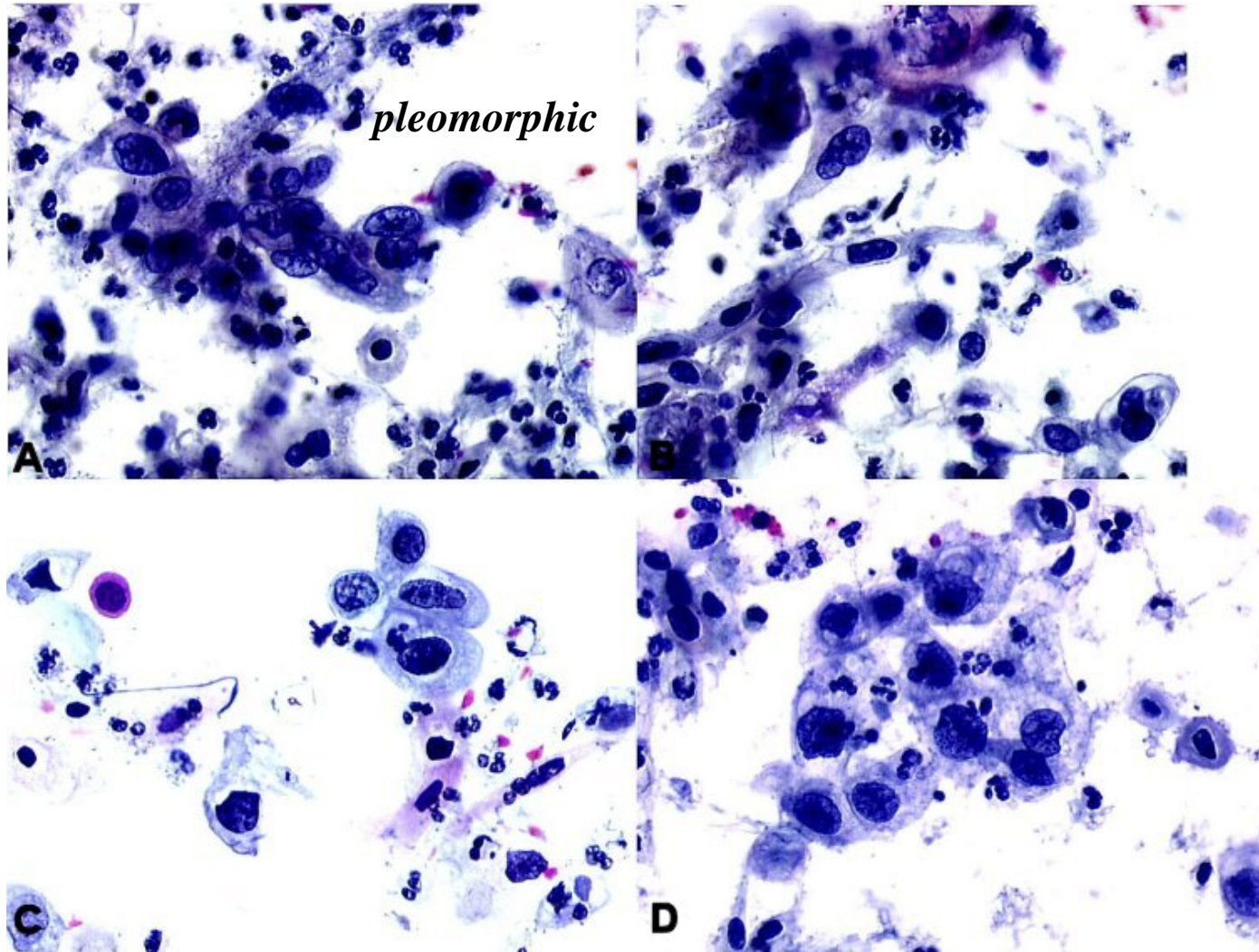
pleomorphic

Invasive squamous cell carcinoma: loose clusters of pleomorphic poorly differentiated malignant cells. Inflammatory and necrotic background. (A, B, C and D: obj. 40x)

Keratinizing Squamous cell carcinoma
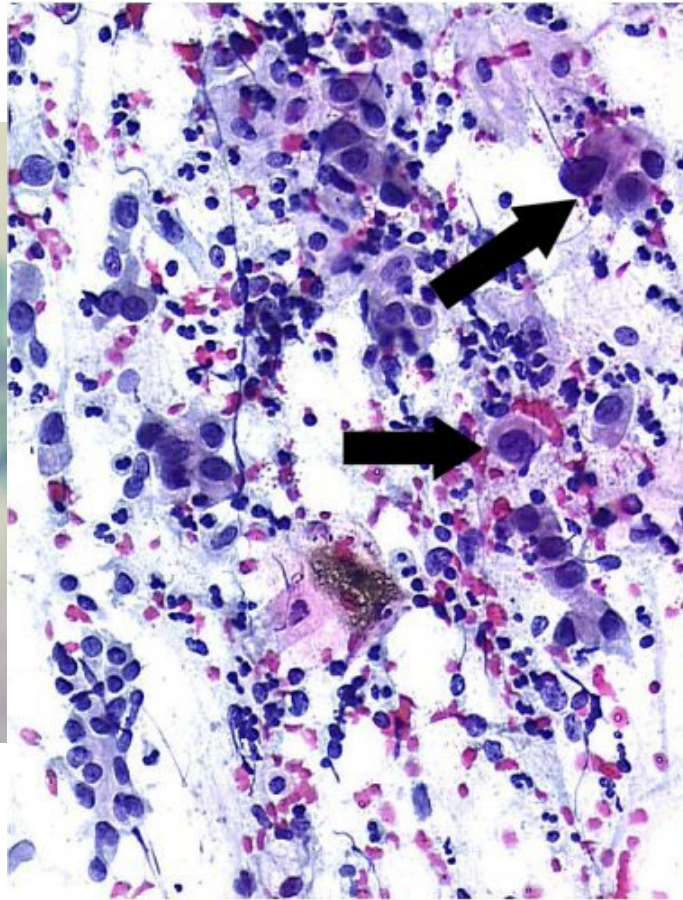

核的大小差異顯著
(Anisonucleosis)

tadpole cells

Dysplastic squamous cells with anisocytosis and anisonucleosis including keratinization and tadpole cells are diagnostic of invasive squamous cell carcinoma.
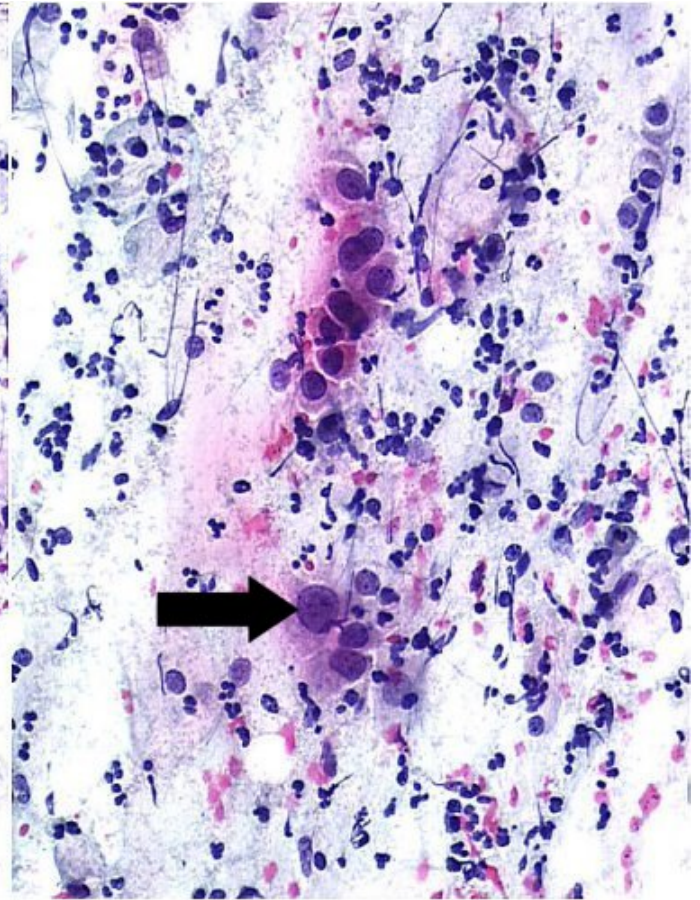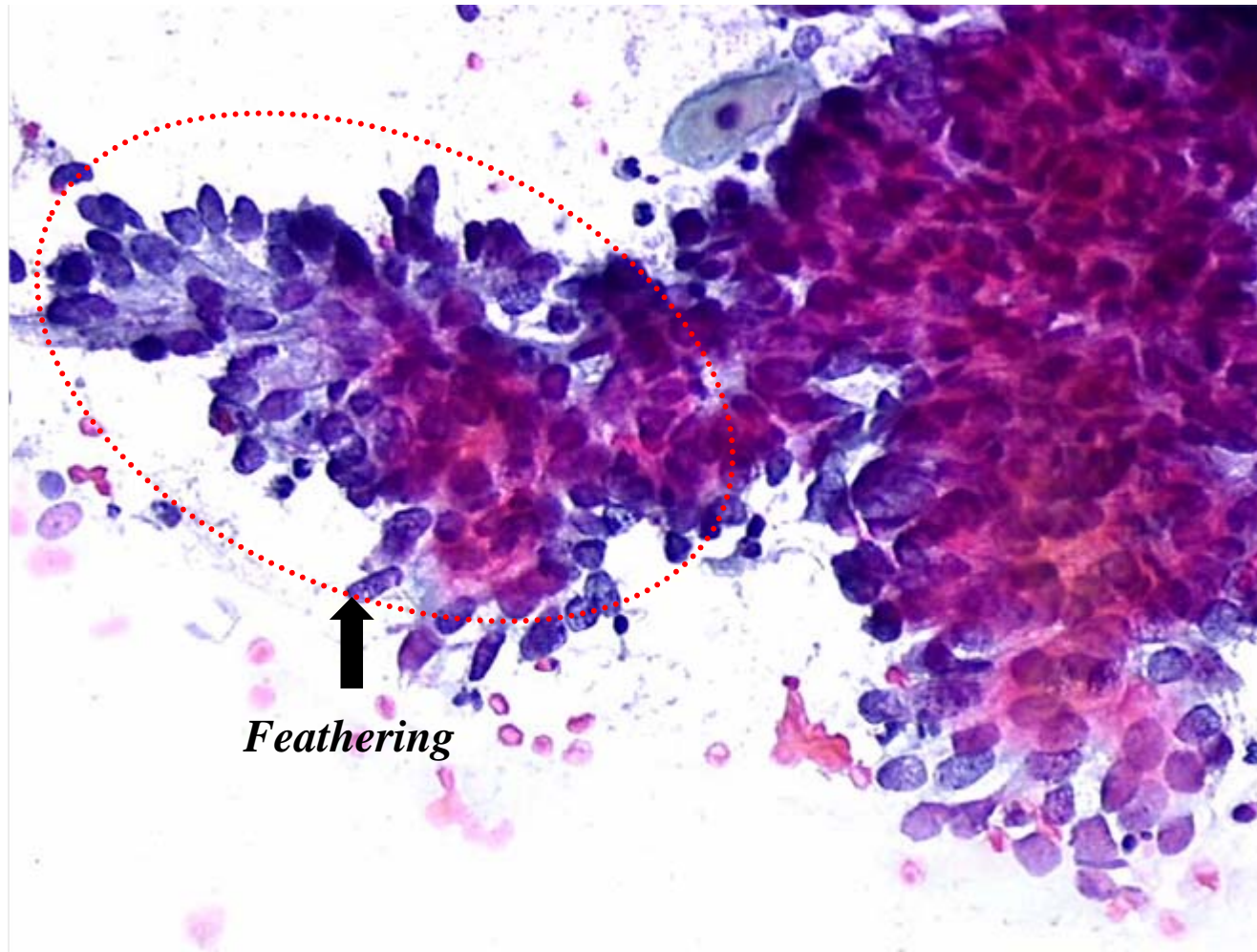
Atypia of glandular cells (AGC)
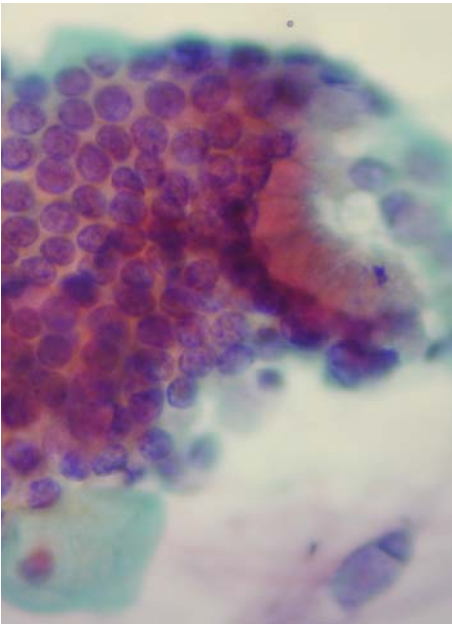
Normal

Inflammatory and bloody smear containing atypical glandular cells preserving their columnar shape with enlarged nuclei (arrows). AGC. (A and B: obj. 20x)
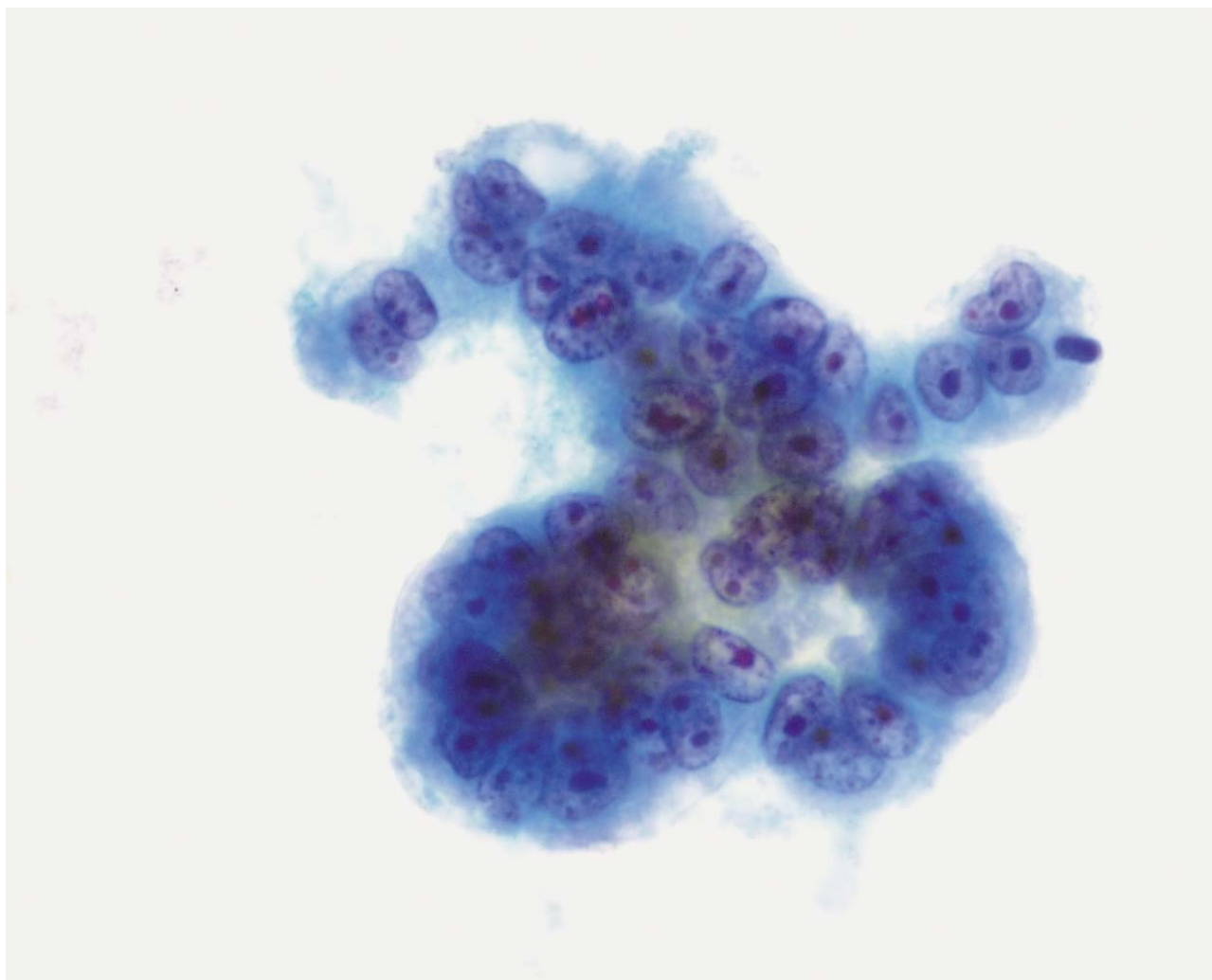
Adenocarcinoma in situ (AIS)

Feathering

Endocervical adenocarcinoma in situ (AIS): atypical columnar endocervical cells, with enlarged, elongated and hyperchromatic nuclei. Typical feathering and palisading. (obj. 20x) 原位腺癌
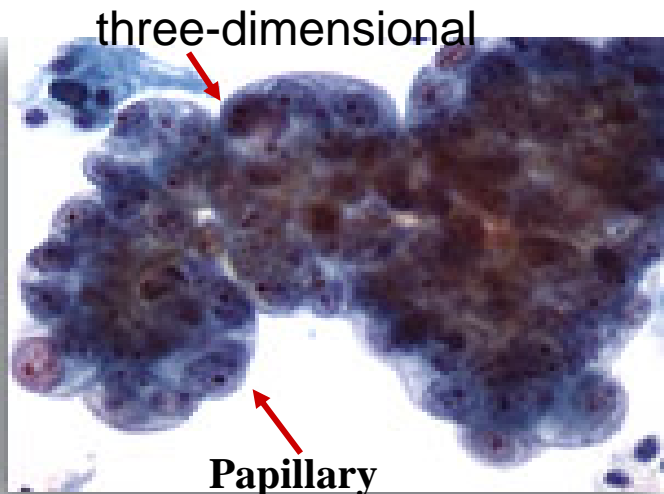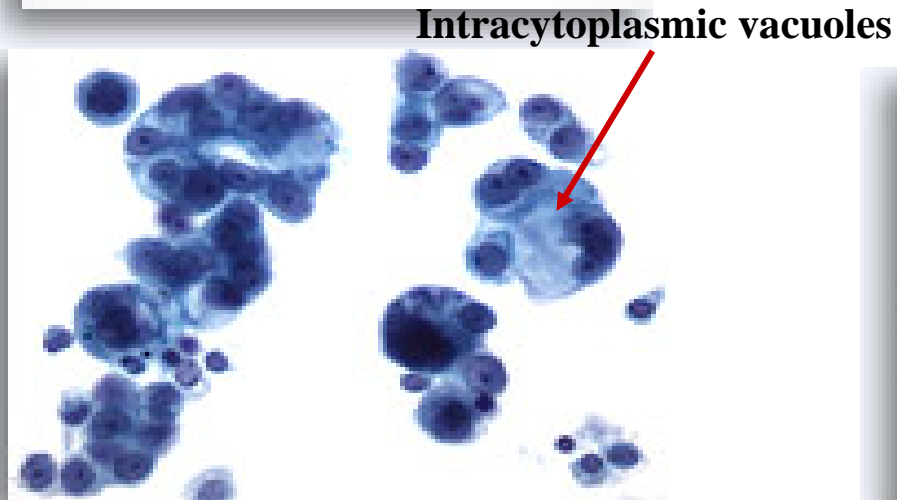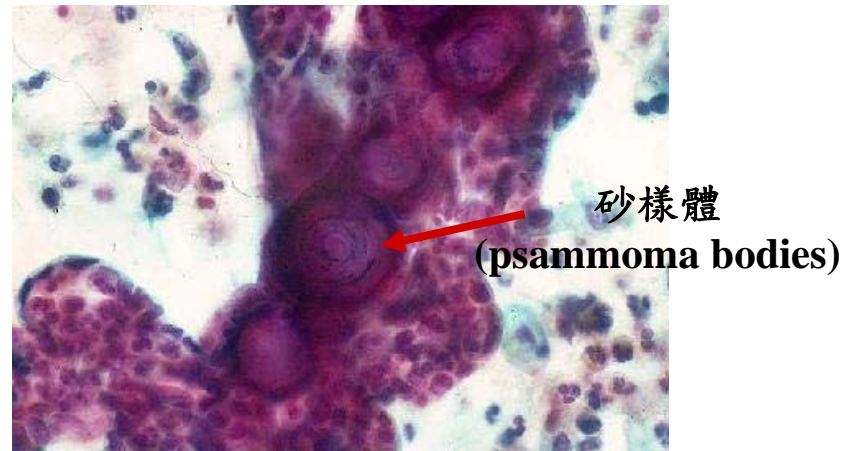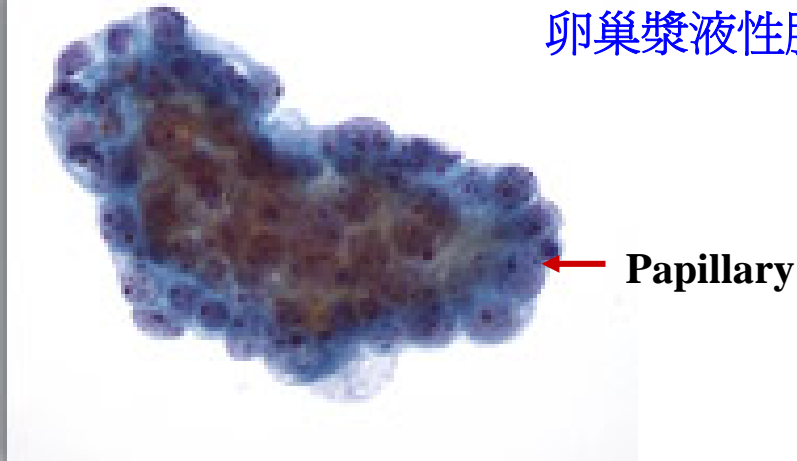
Endocervical adenocarcinoma

Malignant cells with columnar shapes, enlarged nuclei, irregular chromatin distribution, and nucleoli.

Extrauterine Adenocarcinoma
(Metastatic <u>Serous</u> ovarian adenocarcinoma)

卵巢漿液性腺癌

Papillary

砂樣體
(psammoma bodies)

Intracytoplasmic vacuoles

three-dimensional

Papillary

Though three-dimensional, the malignant nature of these ovarian cancer cells is easily appreciated when comparing their size to lymphocytes in the background.

早期發現

早期治療

六分鐘 護一生

6

The end