

# Endometrial carcinoma

## Prognostic factors

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# Prevalence

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- Flanders 1997-1999: 670 new cases/year
- 5,3 % of all malignancies in women
- third after breast (35,3 %) and colorectum (13,5 %)
- Increase !!
- 2000-2001 761 new cases/year

# Prognostic factors

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- **Stage**
- Type
- Grade
- Lymphovascular permeation

# Stage

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- Figo
- TNM
- not on biopsy or curettings



# Endometrial Ca: stage

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- FIGO
- TNM
- I: limited to corpus
  - pT1
    - IA: only EM
    - IB: <50% MM
    - IC: ≥50% MM
  - pT1a
  - pT1b
  - pT1c

# Endometrial Ca: stage (2)

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- FIGO
- TNM
- II: in cx but not beyond
  - pT2
- IIA: endocx glands
  - pT2a
- IIB: in stroma cx
  - pT2b

# Endometrial Ca: stage (3)

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- FIGO
- TNM
- III: pelvic extension
  - IIIA: in serosa, adnex or + cytology
  - IIIB: in vagina
  - IIIC: meta in lymph nodes: pelvic, paraAo
  - pT3a
  - pT3b
  - pN1

# Endometrial Ca: stage (4)

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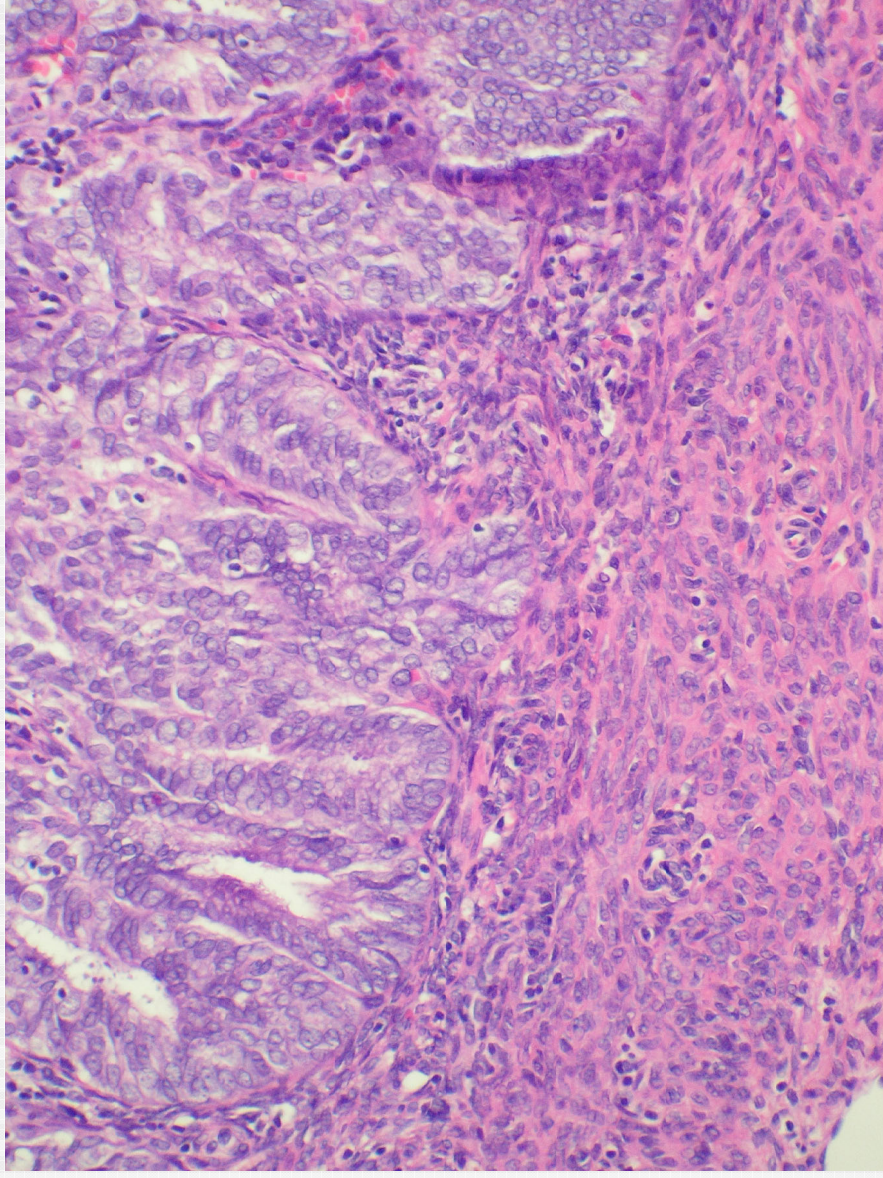
- FIGO
- TNM
- IV: spread beyond pelvis
  - IVA: in **mucosa** of bladder or bowel
  - IVB: distant meta
    - pT4
    - pM1

# Problems with stage I

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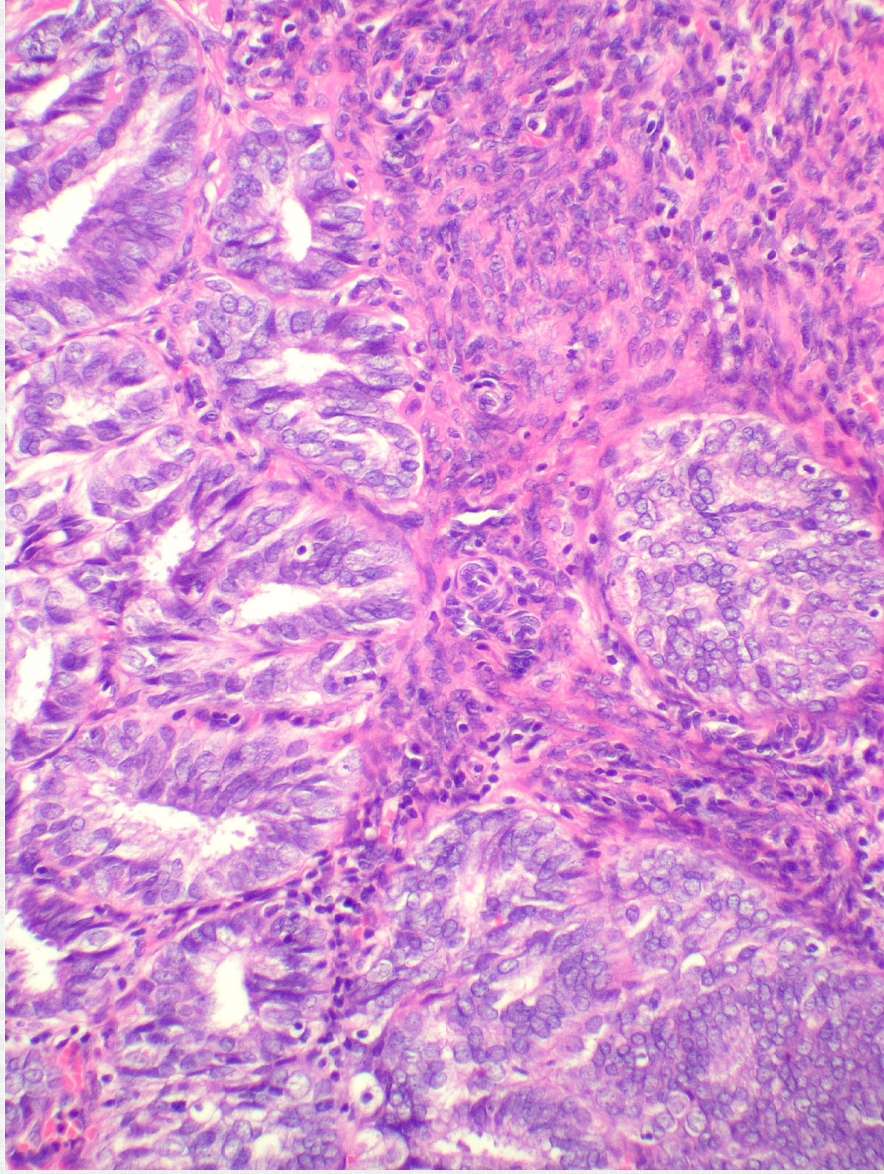
- Irregular border between endometrium and myometrium
- Distinction between IA and IB; and between IB and IC is difficult

pT1a or pT1b ?





**pT1b !**



# Can CD 10 assist ?

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- CD 10 + in endometrial stromal cells
  - Prove of endometriosis
- If + round tumour : stage IA ?



# Limited use of CD 10

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- Carcinoma cells can induce CD 10 + cells round the tumour
- Only CD 10 negativity is helpful: prove of invasion in myometrium

# pT1b or pT1c: often difficult

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- Use arcuate vascular plexus as cut off
- In doubt: use thickness of opposite uterine wall
- Williams: Assessment of uterine wall thickness and position of the vascular plexus in the deep myometrium: Implications for the measurement of depth of myometrial invasion of endometrial Ca

*I J Gynecol Pathol (2006) 25: 59-64*

# Invasion or extension in adenomyosis ?

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- Extension in adenomyosis without invasion does not have the same negative prognosis as deep invasion
- Extension in adenomyosis more often associated with stage IC
- What about invasion originating from adenomyosis ???

# Alternative for subdividing stage I

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- Lindauer: Is there a prognostic difference between depth of myometrial invasion and the tumour-free distance from the uterine serosa in endometrial cancer?  
*Gynecol Oncol* 2003; 91(3): 547-551

TFD but not DOI is predictive of recurrence and is more significant predictor of DOD  
Tumour free distance: 1 cm

- Combination of DOI and TFD ?
- Combined with myometrial thickness?

# Problems with stage II

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- On curettings: only stage II if endometrial carcinoma in a clearly cervical fragment

Do not trust your clinician !!!

- Difficult assessment of stromal invasion

# Are all stage II really stage II ?

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- Reisinger: Preoperative radiation therapy in clinical stage II endometrial carcinoma  
*Gynecol Oncol 1992, 45(2): 174-178*

Survival in Stage IIA is significantly higher than in Stage IIB (86% vs 46%)

# Frequency of stage IIA

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- **Mariani: Endometrial cancer: predictors of peritoneal failure**  
*Gynecol Oncol 2003; 89(2): 236-242*

**Superficial implants in cervix with no or minimal stromal invasion occurs in 40%**

# Etiology of stage IIA

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- Implants are due to settling of tumour on endocervical mucosa following curettage
- Stage II is induced by curettage !!!

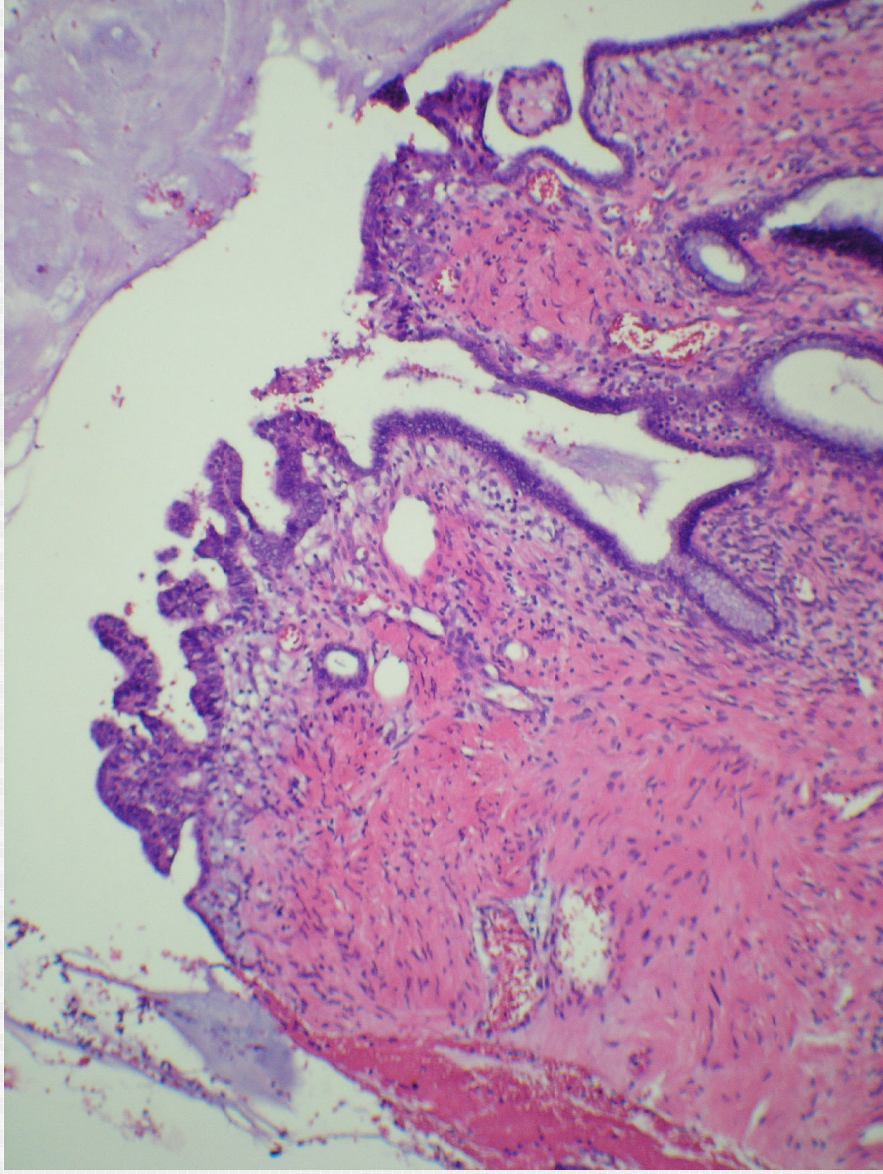


# Therapeutical implication

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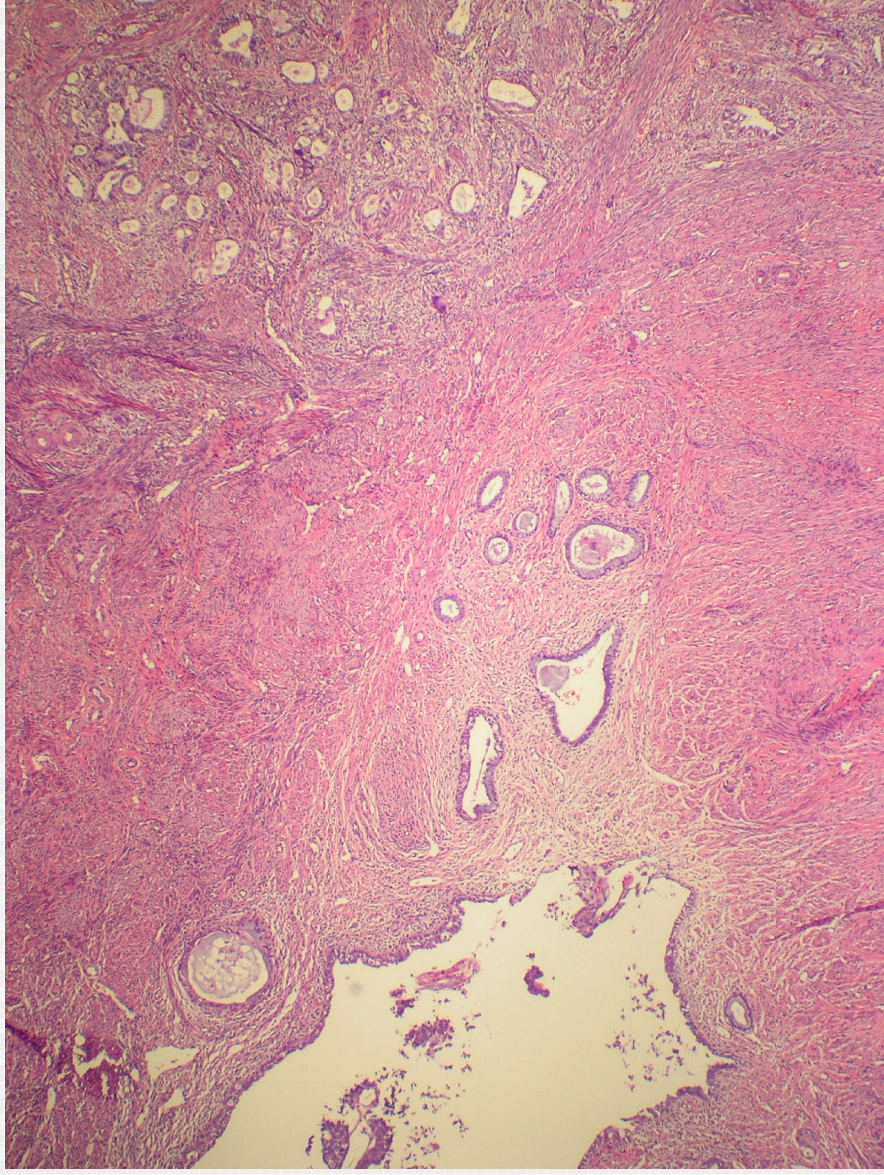
- Stage IIB : radiotherapy
- Stage IIA : no radiotherapy

pT2a ?



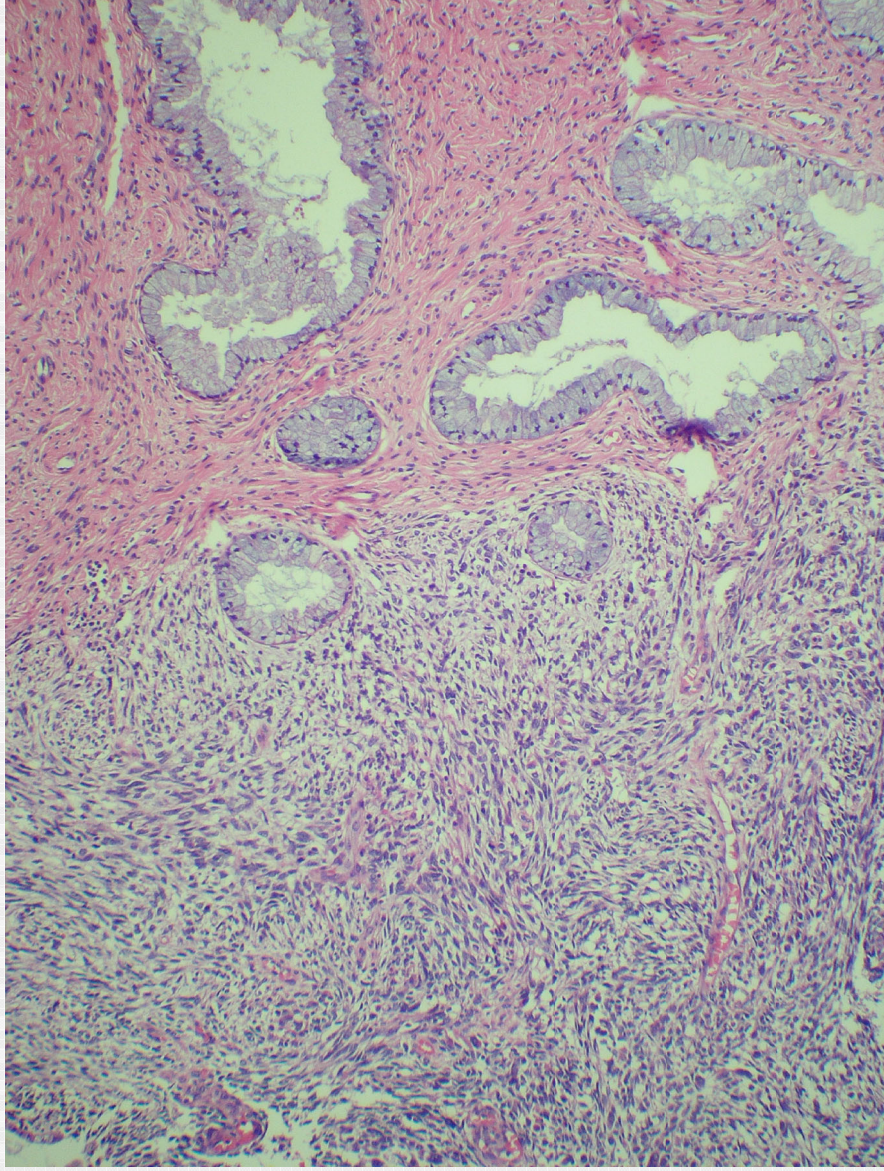


# Continuous extension in cervix





pT2b



# Remarks on stage III

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- Extension to adnex does not have to be continuous
- Para-aortic nodes have worse prognosis than pelvic nodes
- Specimen for cytologic examination should be obtained at the start of the operation

# Adnexal and endometrial involvement in cancer

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- 3 possible scenarios:
  - 1) Primary endometrial
  - 2) Primary ovarian
  - 3) 2 concurrent malignancies

# Primary endometrial metastatic to adnex

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- Deeply invasive type 1 Ca
- Lymphovascular spread
- Often bilateral adnexal involvement
- Often small separate nodules in adnexes

# Primary ovarian metastatic to endometrium

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- Rare
- Only if small, discrete plaques of tumour in an otherwise normal endometrium



## 2 synchronous primaries

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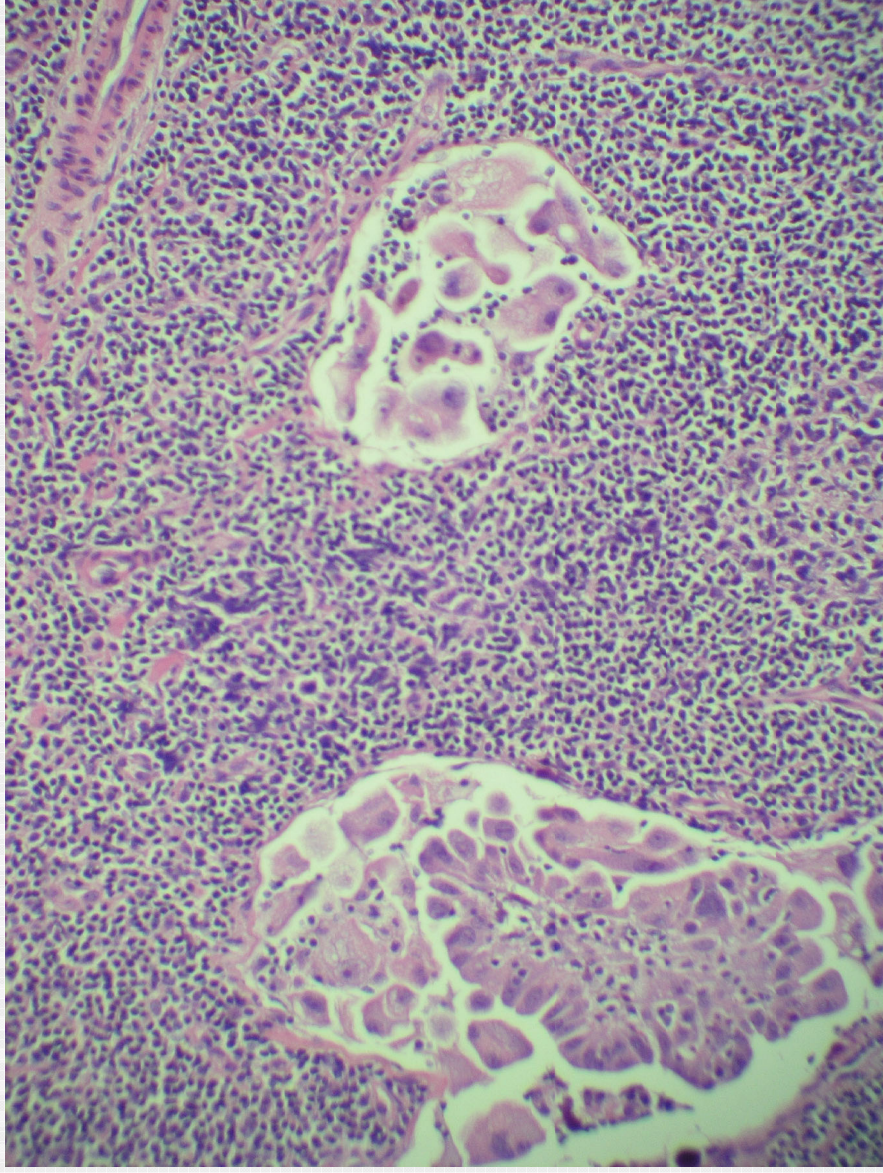
- Younger patients
- If both are endometrioid: good prognosis
- Presumed to arise from endometriosis
  - ➔ high stage cancers can be separate primaries with excellent prognosis

# Frequency of lymph node metastasis

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- Inner third MM 5 %
- Middle third MM 23 %
- Outer third MM 33 %
  
- Grade 1 inner third None
- Grade 1 outer third 25 %

# pN1 stage IIIA



# Lymph node metastasis: predicting prognosis

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- High metastatic ratio: worse
- Extranodal extension: worse
- Desmoplasia in + nodes: worse

Yasunaga: Endometrial carcinoma with lymph node involvement: novel histopathologic factors for predicting prognosis

*I J Gynecol Pathol 2003, 22(4): 341-346*

# IHC on lymph nodes?

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- Gonzalez: CK staining of resected lymph nodes may improve the sensitivity of surgical staging for endometrial cancer

*Gynecol Oncol 2003; 91(3): 518-525*

Using CK the detection of tumour cells is increased: 12,5% (2/16) have micrometastasis, 50% of them will DOD



# Are they important?

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- Yabushita: Occult lymph node metastases detected by CK IHC predict recurrence in node-negative endometrial cancer  
*Gynecol Oncol 2001; 13(1): 38-41*

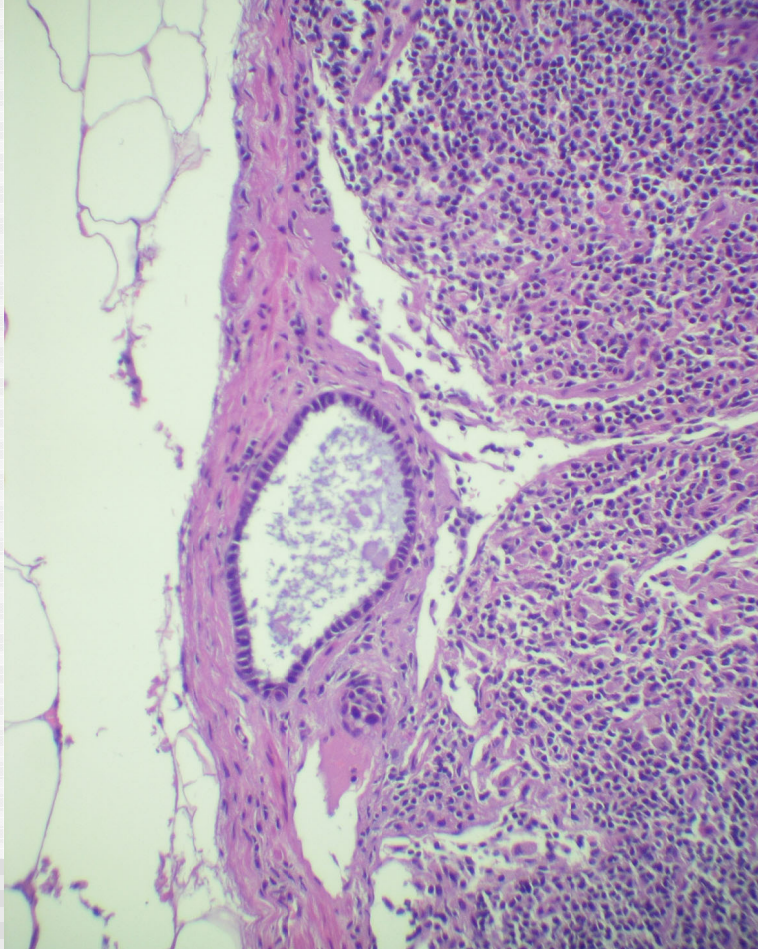
Stage I with no nodal involvement : 0/22  
recurrence vs 5/14 with CK + cells  
Related to lymphovascular permeation

# Should we do it?

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- Not (yet) recommended on routine basis
- If you consider it:
  - type II Ca or grade 3 type I
  - deeply invasive
  - lymphovascular permeation

# Müllerian inclusions

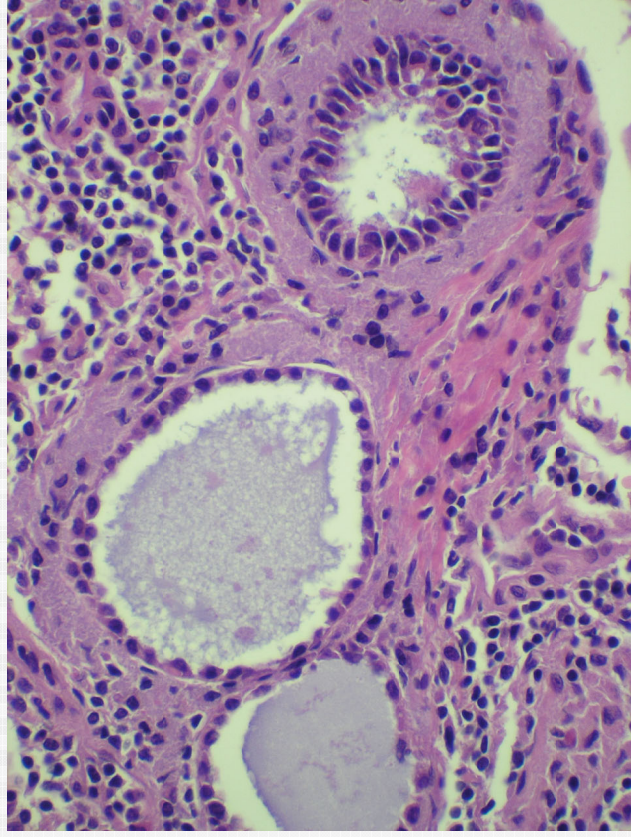


- Glands  $\neq$  metastasis
- Difficult on frozen sections
- Often in capsule



# Müllerian inclusions: diagnosis

- Flat or cuboidal cells
- No atypia
- Compare with tumour



# Stage III by cytology

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- If stage III only because of + cytology:  
prognosis does not equal that of other  
stage III
- + cytology remains stage III, but other  
therapy

# Importance of + cytology

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- Kadar: Positive peritoneal cytology is an adverse risk factor in endometrial carcinoma only if there is other evidence of extrauterine disease

*Gynecol Oncol* 1992, 46: 145-149

- Tebeu: Impact of peritoneal cytology on survival of endometrial cancer patients treated with surgery and radiotherapy

*Br J Cancer* 2003 89(11): 2023-2026

# Recent evidence

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- **Slomowitz: Heterogeneity of stage IIIA endometrial carcinomas: implications for adjuvant therapy**

*Int J Gynecol Cancer 2005, 15(3): 510-516*

- **Fadare: Upstaging based solely on positive peritoneal washing does not affect outcome in endometrial cancer**

*Mod Pathol 2005, 18: 673-680*

# Prognostic factors

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- Stage
- **Type**
- Grade
- Lymphovascular permeation

# Type

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- WHO
- Type 1: estrogen-related :  
    endometrioid Ca, mucinous Ca
- Type 2: serous or clear cell Ca
- Carcinosarcoma
- Undifferentiated carcinoma
- Endometrial stromal sarcoma



# Type 1      Type 2

Prototype	Endometrioid	USC, CC
Age	50-60	60-70
Obesity	Common	Uncommon
Estrogenic stimuli	Common	Uncommon
Endometrium	Hyperplastic	Atrophic
Spread	Lymph nodes	Peritoneum

# Prognostic factors

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- Stage
- Type
- **Grade**
- Lymphovascular permeation



# Endometrioid Ca: grading

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- Mostly based on architectural grade
- Nuclei only important if grade 3

# Architectural grade

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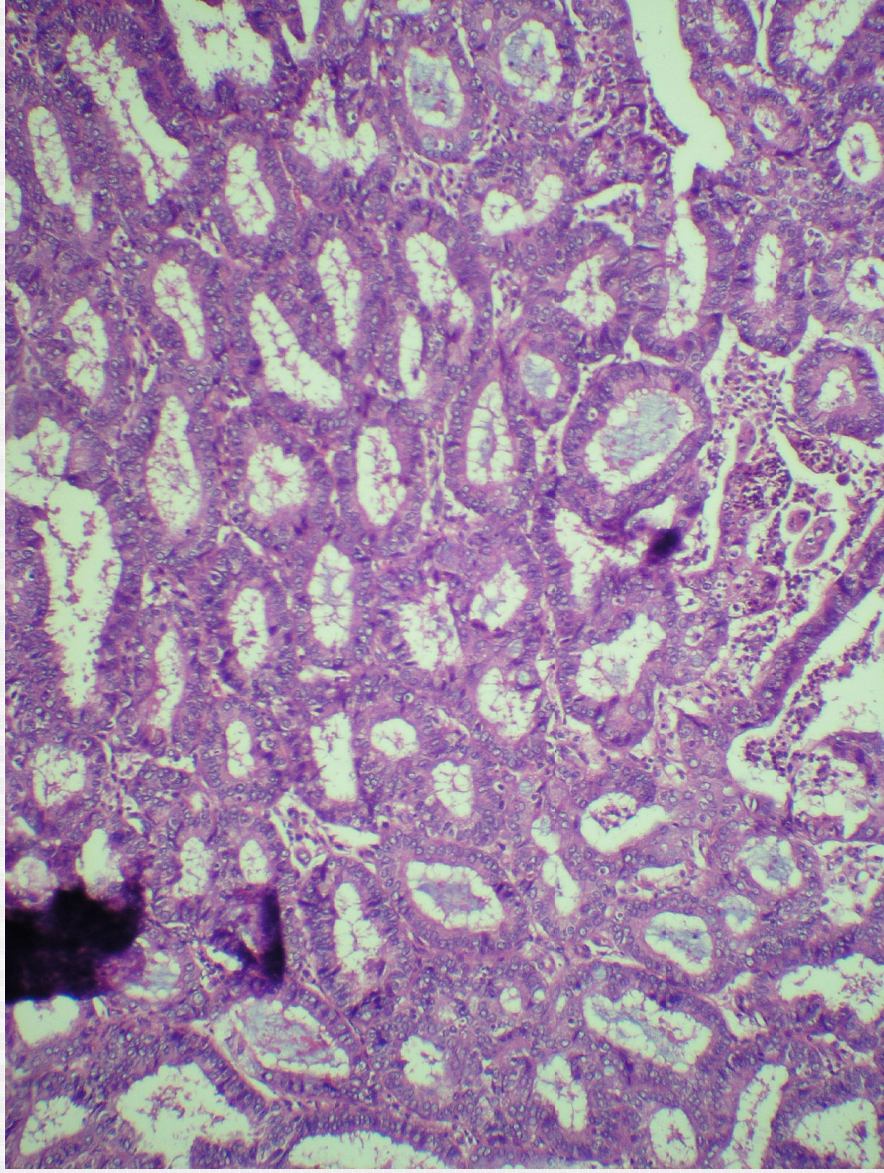
- Depends on the extent of solid zones in comparison to the glands
- Do not consider squamous zones !!

# Architectural grade

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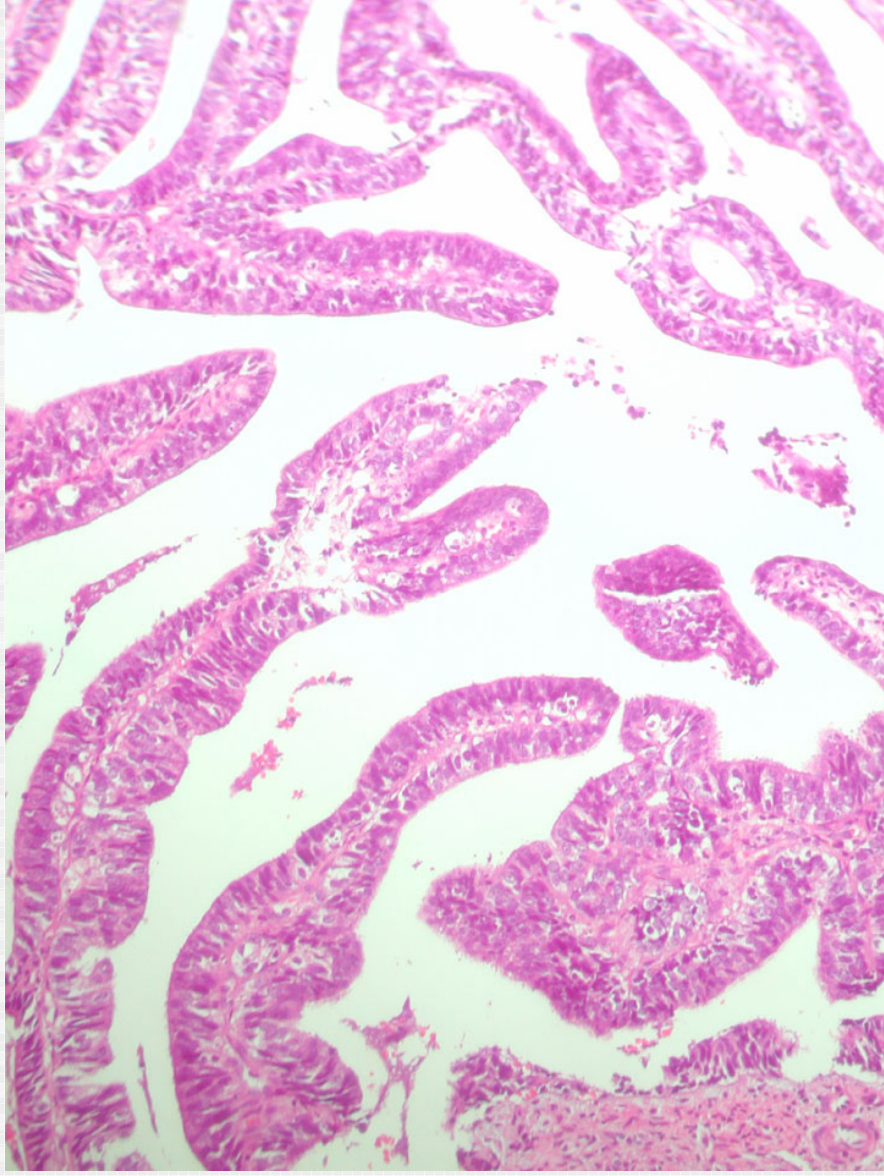
- Grade 1: Max 5 % solid
- Grade 2: 6-50 % solid
- Grade 3: > 50 % solid

# Architectural grade 1

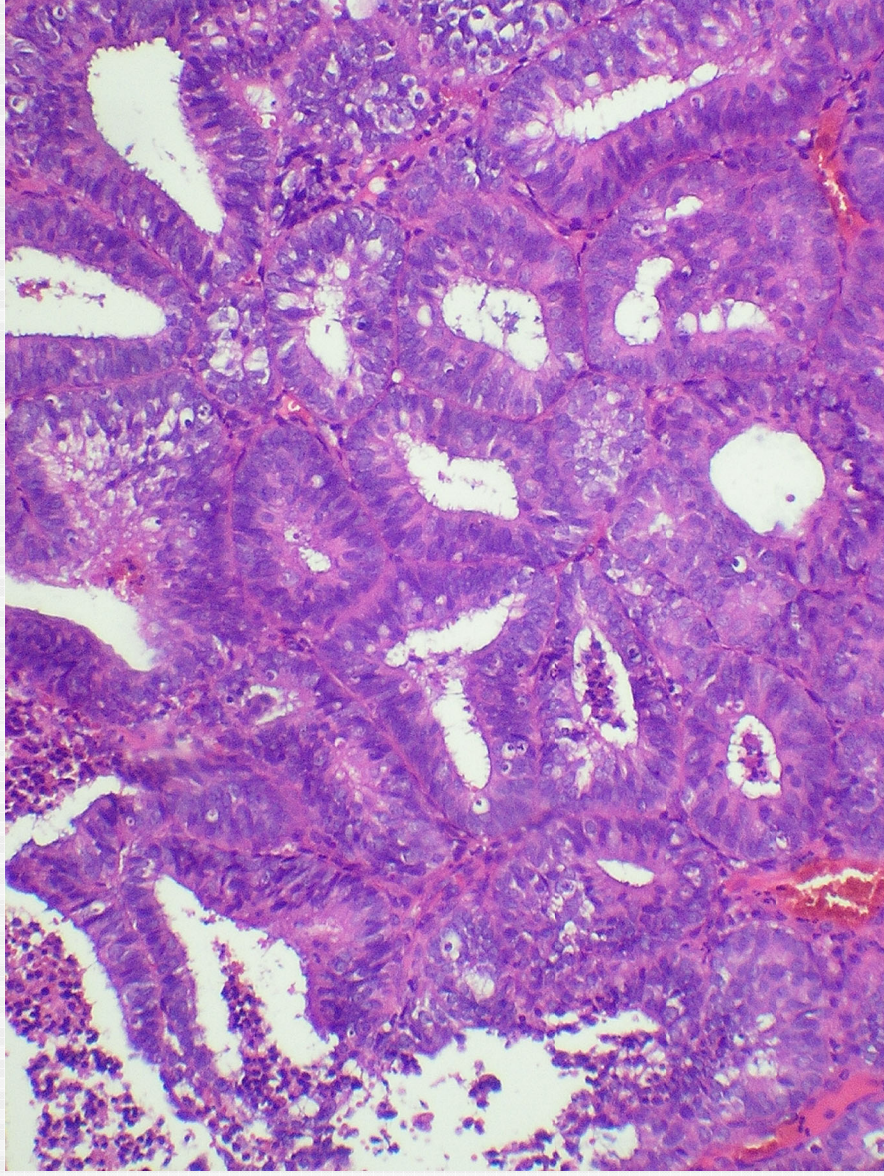




Papillae = glands !

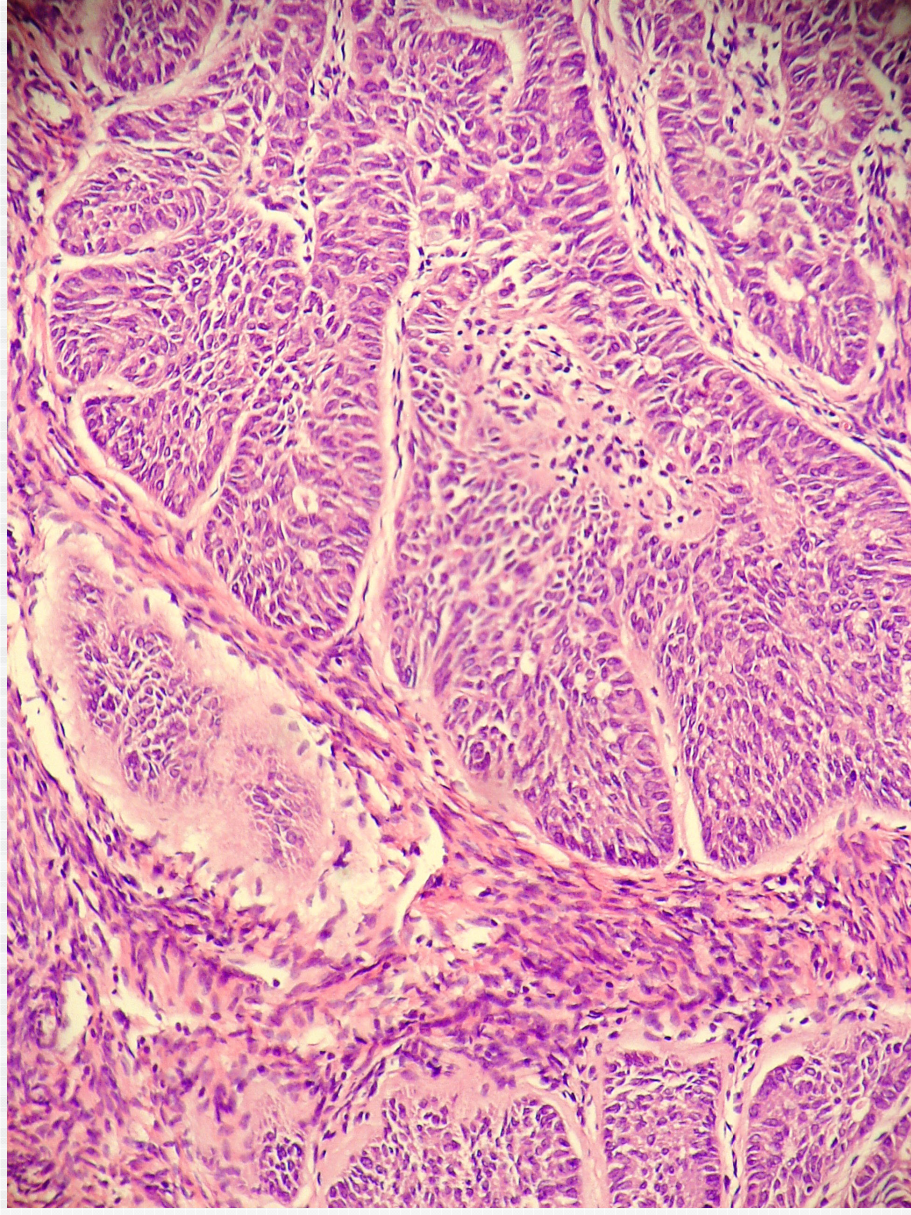


# Architectural grade 2





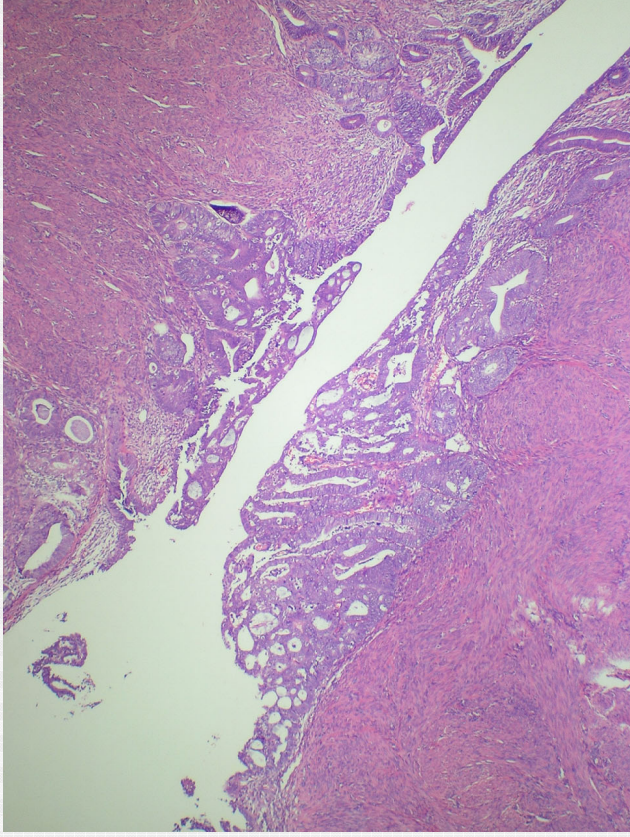
# Architectural grade 3



# Do not forget the tumour in the curettage !!!

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- If little amount of tumour in the hysterectomy: grading should be performed together with the material of the curettage





# Cytological grade

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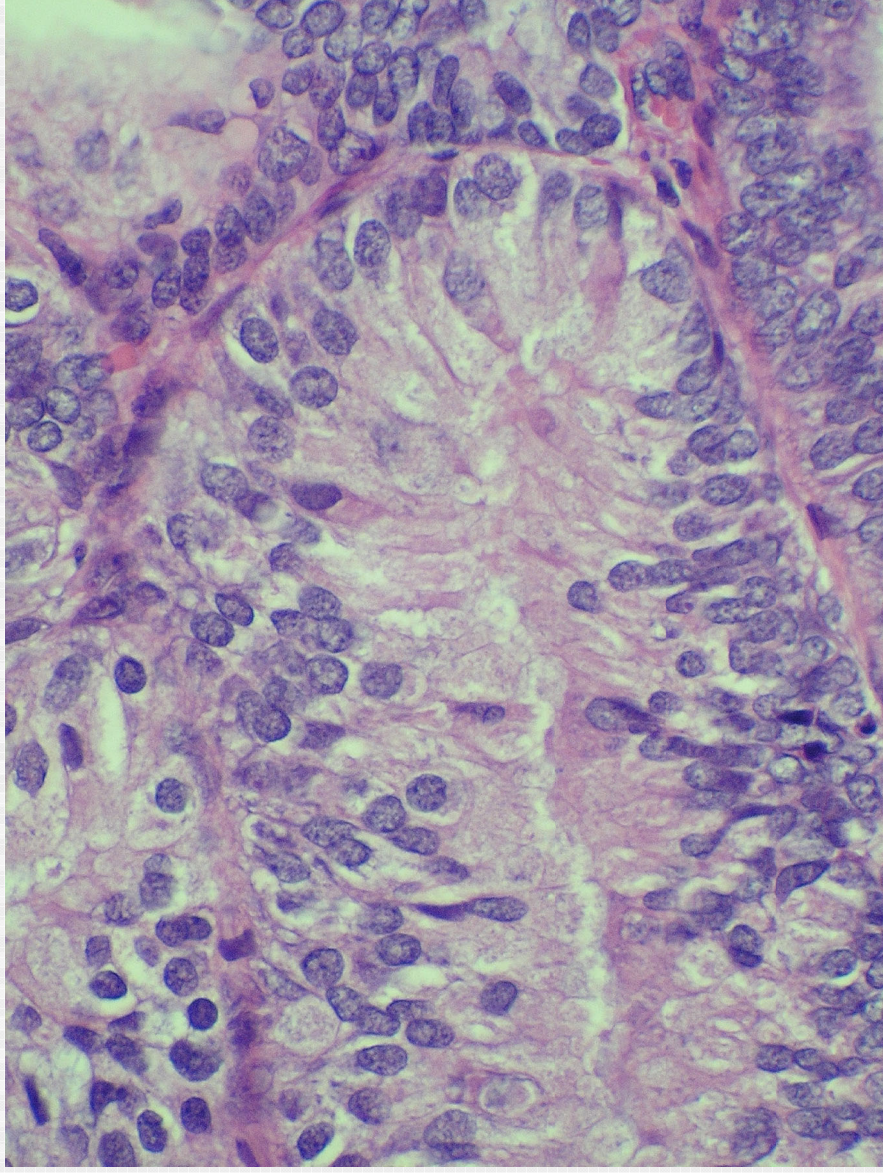
- Nuclei grade 1:
  - oval
  - slightly enlarged
  - fine dispersed chromatin
- Nuclei grade 3:
  - strongly pleomorphic
  - strongly enlarged
  - unregular coarse chromatin
  - prominent eosinophilic nucleoli

# Cytological grade

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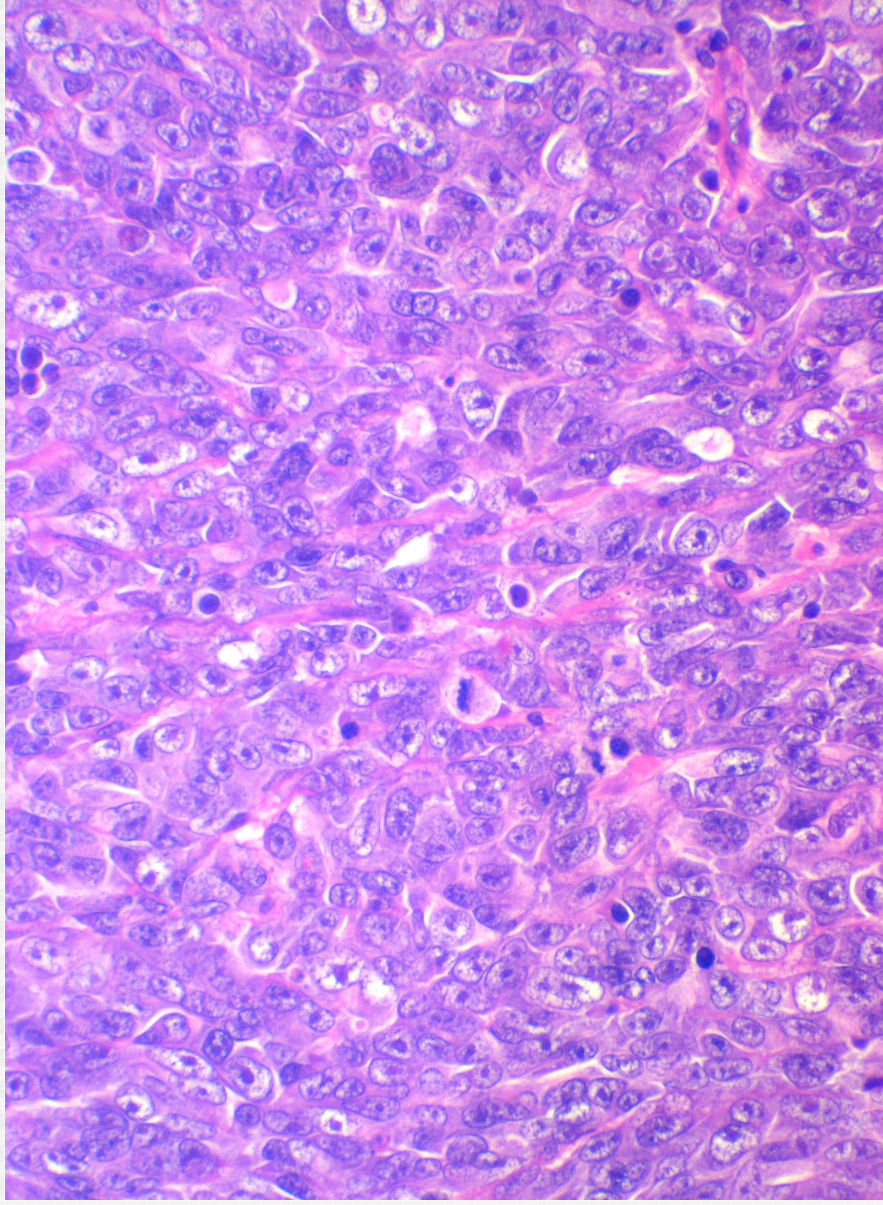
- Nuclei grade 2: between 1 and 3
- Number of mitosis not important

# Nuclear grade 1



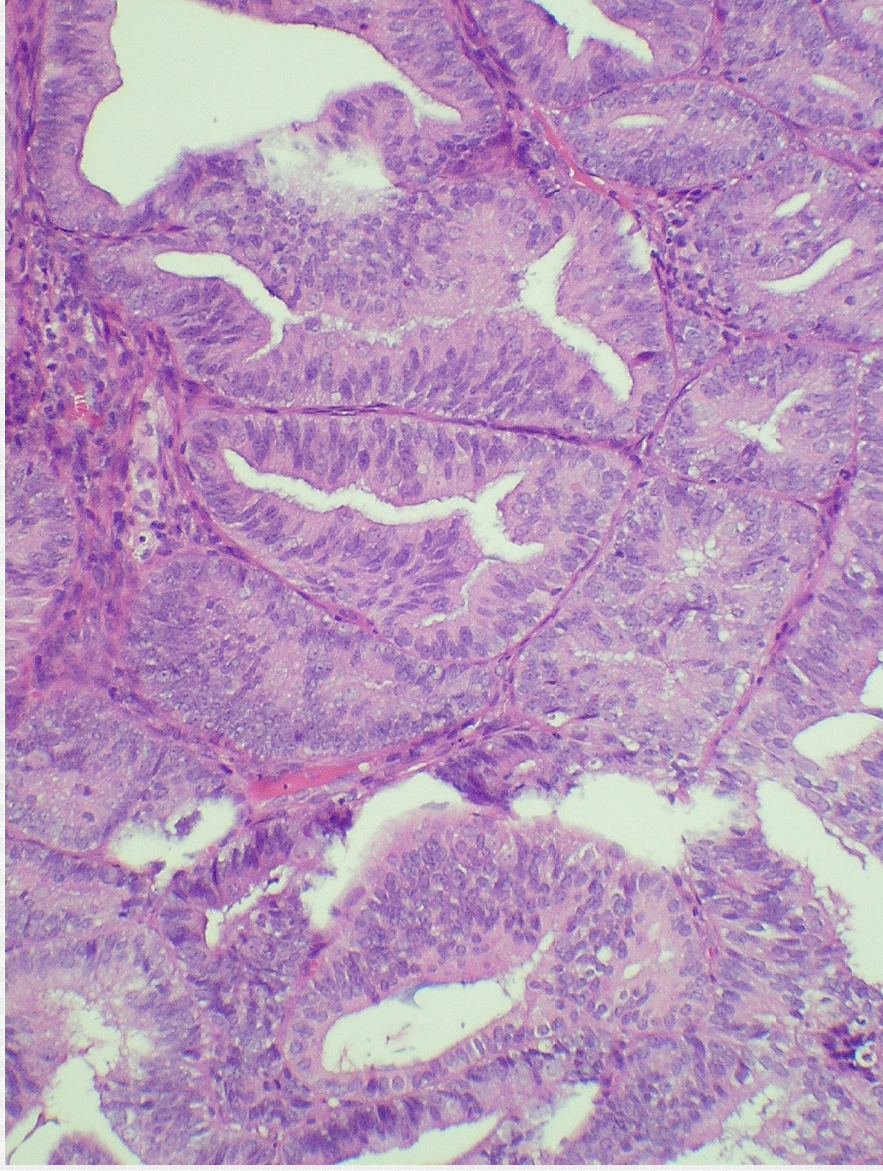


# Nuclear grade 3





# Nuclear grade 2



# Determination of grade

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- Architectural grade primordial
- Cytologic grade 3 augments  
architecturale grade 1 or 2 by 1
- If really discordant: think of
  - Serous Ca
  - Clear cell Ca

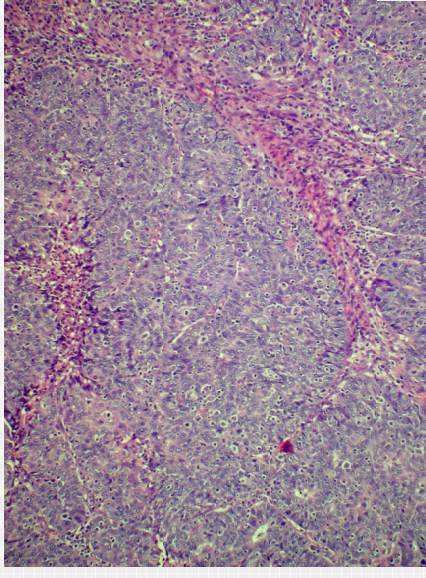
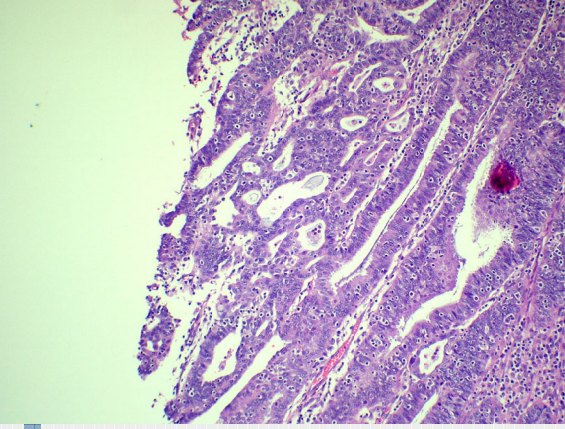
# Examples

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- Arch 1 + Cyt 1 or 2
  - → **Grade 1**
- Arch 2 + Cyt 1 or 2
  - → **Grade 2**
- Arch 1 + Cyto 3
  - → **Grade 2**
- Arch 2 + Cyt 3
  - → **Grade 3**



# Grade can be very heterogenic



- 1 tumour with zones grade 1 and zones grade 3

# Grading

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- Heterogeneity in grade very often
- Reason for discordance between curettage and hysterectomy
- Grade 1 remains grade 1 in 45%



# Grade 1 + undifferentiated Ca

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- Silva: Association of low-grade endometrioid Ca of the uterus and ovary with undifferentiated Ca: a new type of dedifferentiated Ca?

*I J Gynecol Pathol (2006) 25: 52-58*

- Indicates aggressive behavior
- In asynchronous cases: can explain absence of second primary

# Grading mucinous carcinoma

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- No rules !!!
- By convention : rules of endometrioid
- Most are grade 1

Grading type II Ca

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**Always Grade 3!**

# Is grading reproducible ?

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- Architectural grading: kappa 0.70
- Nuclear grading: kappa 0.55
- Combined FIGO grading: kappa 0.65

# Other systems

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- Lax: A binary architectural grading system for uterine endometrial endometrioid Ca has superior reproducibility compared with FIGO grading and identifies subsets of advance-stage tumors with favorable and unfavorable prognosis  
*Am J Surg Pathol (2000) 24: 1201-1208*
- Alkushi: Description of a novel system for grading of endometrial Ca and comparison with existing grading systems  
*Am J Surg Pathol (2005) 29: 295-304*



# Lax (2000)

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- > 50% solid growth (squamous and non-squamous)
- Tumour cell necrosis
- Diffusely infiltrative pattern of invasion (versus pushing)
- $\geq 2/3$  features : high-grade
- $\leq 1/3$  features : low-grade
- Only for endometrioid type

# Alkushi (2005)

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- Predominantly papillary or solid growth
- Mitotic index  $\geq 6/10$  HPF
- Severe nuclear atypia
- $\geq 2/3$  features : high-grade
- $\leq 1/3$  features : low-grade
- For all types of tumour

# Comparison of the 3 systems

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- Alkushi: most prognostic power when applied to **all tumours** (regardless of cell type)
- FIGO: superior when only **endometrioid** type is considered
- Binary system with combining FIGO grade 1 and 2 is most prognostically system

# Prognostic factors

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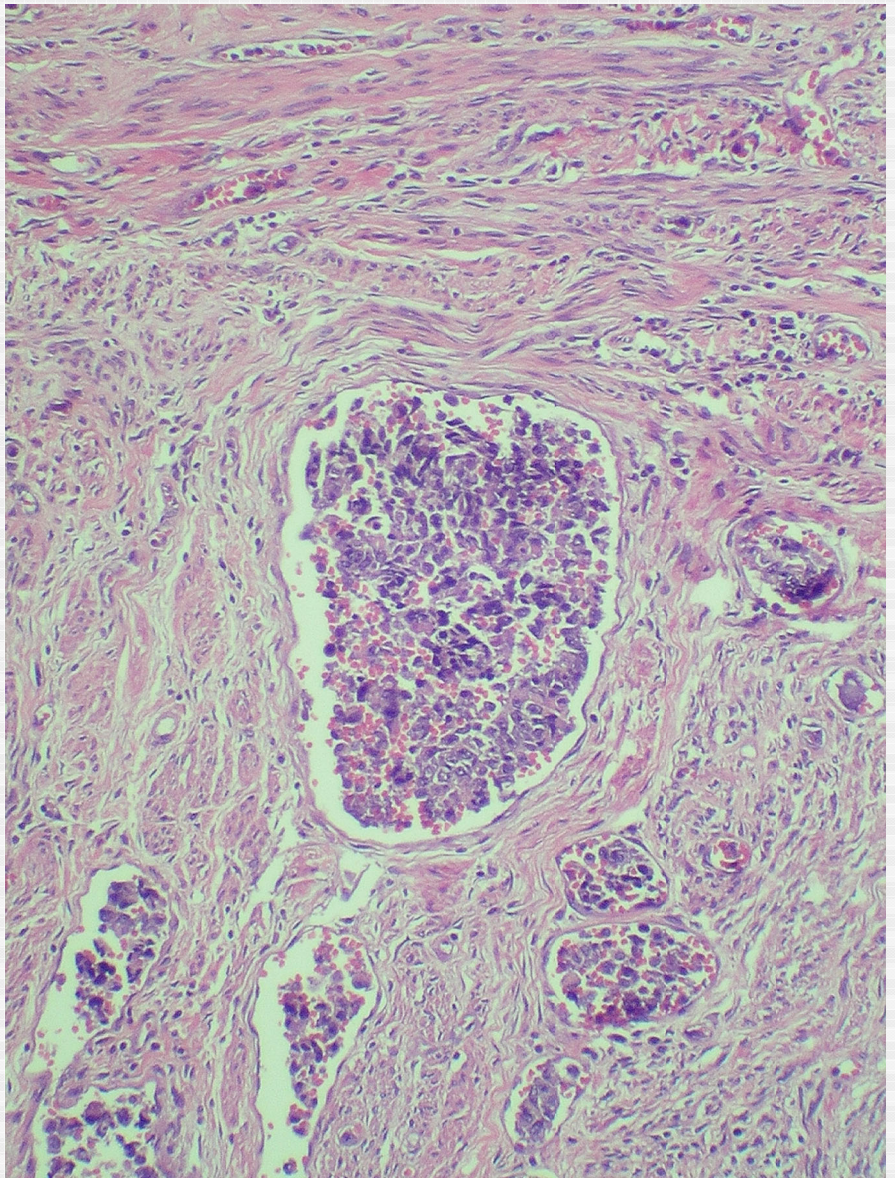
- Stage
- Type
- Grade
- **Lymphovascular permeation**

# Lymphovascular permeation

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- Not on biopsy or curettings
- Cave retraction !!!
- Typical feature of type II Ca





# Vascular invasion as a prognostic marker

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- Definite vascular invasion is a independent prognostic factor

# Other prognostic factors

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- Age :  $\geq 70$  y
- MELF
- K-Ras
- Ploidy
- ER, PR
- MSI: 5y survival 20% better
- PTEN
- Angiogenesis
- Proliferation: Ki67
- $\beta$ Catenin: + in subset of less-aggressive tumours
- bcl2
- C-Erb-B2
- P53
- cyclinA
- CA 125

# Age

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- Prognosis worse if  $\geq 70$  years, even if treated in similar fashion
- Intrinsically more aggressive in older patients
- Alektiar: Is endometrial Ca intrinsically more aggressive in elderly patients?

*Cancer (2003) 98: 2368-77*

# MELF

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- Microcystic
- Elongated
- Fragmented
- Higher incidence of lymphatic invasion



# K-ras

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- Oncogene
- Mutations in 10-15 %
- Little if any significance

# Ploidy

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- Ploidy is strong predictor of outcome
- Stage 1:
  - Diploid: 94 % progression-free survival
  - Aneuploid: 64 %

# ER, PR

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- Type 1 Ca: mostly +
- Type 2 Ca: -
- Conflicting results
- Not independent risk factor:  
correlated with stage and grade

# MSI in EmCa

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- Related with HNPCC
- 20-30 %
- In mucinous Ca, not in USC



# Angiogenesis

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- Tumour > 1mm needs new vessels
- VEGF in high concentration in neoplastic cells
- High microvessel counts are significant predictor of decreased survival

# Proliferation markers: Ki67

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- Ki67 is expressed in all non-resting nuclei
- High expression is significant independent prognosticator

# bcl-2

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- bcl-2 inhibits apoptosis
- Normally highly expressed in proliferative phase, downregulation in secretory phase
- Simple hyperplasia: high level persists
- Diminishes progressively in atypical hyperplasia and with increasing grade in Ca
- Expression is significantly related to probability of lymph node metastasis or tumour recurrence

# c-Erb-B2 (Neu-oncogen)

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- Amplification occurs in 20-40 %
- Associated with aggressive cell types:  
clear cell
- Associated depth of invasion, grade



p53

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- Overexpression related to higher grade, aggressive type (USC), higher stage

# CA 125

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- Preoperative serum level correlates significantly with survival
- $\leq 13$  U/ml versus  $> 13$  U/ml

# Endometrial carcinoma: conclusion on prognosis

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- Classical factors most important
- New markers and genetic factors will have impact on therapy