BSP Belgian Society of Pathology

Cervix
ICCR dataset and grading of squamous carcinoma

Claire Bourgain

ICCR data set for cervix carcinoma reporting

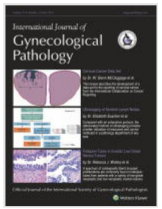
ICCR (international collaboration on cancer reporting)

- Royal colleges of pathologists of Australasia and the United Kingdom
- College of American Pathologists
- Canadian Partnership Against Cancer
- European Society of Pathology

International Society of Gynecological Pathologists

Aim: to develop a standardized evidence-based data set for cervical cancer

- Required and recommended elements in the pathology report
- Address grading, measurement and multifocal tumors



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ICCR cervix required elements

Clinical	Macroscopic	Microscopic
Specimen/s submitted	Specimen dimensions	Tumor dimensions
	Number of tissue pieces	Horizontal extent (2 measurements)
	Tissue piece dimensions	Depth of invasion or thickness
	Cervix	Histologic tumor type
	a. Diameter of ectocervix	Lymphovascular space invasion
	b. Depth of specimen	Coexistent pathology
	Vaginal cuff	Squamous intraepithelial lesion (CIN)
	a. Minimum length	Adenocarcinoma *in situ*/high-grade cervical glandular
	b. Maximum length	intraepithelial neoplasia
	Macroscopic tumor site(s)	Stratified mucin-producing intraepithelial lesion
		Extent of invasion
		Margin status
		Lymph node status
		Pathologically confirmed distant metastases
		Provisional pathologic staging pre-multidisciplinary team meeting
		FIGO 2009
		TNM pN category (UICC 8th edition 2016)

CIN indicates cervical intraepithelial neoplasia; FIGO, International Federation of Obstetricians and Gynaecologists; UICC, Union for International Cancer Control.

Data Set for the Reporting of Carcinomas of the Cervix: Recommendations From the International Collaboration on Cancer Reporting (ICCR).
McCluggage, W; Judge, Meagan; Alvarado-Cabrero, Isabel; Duggan, Maire; Horn, Lars-Christian; Hui, Pei; Ordi, Jaume; Otis, Christopher; Park, Kay; Plante, Marie; Stewart, Colin; Wiredu, Edwin; Rous, Brian; Hirschowitz, Lynn

International Journal of Gynecological Pathology. 37(3):205-228, May 2018.
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TABLE 1 Required Data Items for Pathologic Reporting of Carcinomas of the Cervix

ICCR recommended elements

- Prior treatment
- Lateral measurement of parametria
- Macroscopic appearance of tumor
- Block identification key
- Histological grading of the tumor
- Precursor lesions other than SIL, AIS, SMILE
- Ancillary studies
- Margin distance
- TNM

Carcinoma of the Cervix
Histopathology Reporting Guide

Family/Last name | Date of birth DD – MM – YYYY

Given name(s)

Patient identifiers | Date of request DD – MM – YYYY | Accession/Laboratory number

Elements in **black text** are REQUIRED. Elements in grey text are RECOMMENDED.

PRIOR TREATMENT (Note 1)

Previous procedure performed

- ○ Loop
- ○ Cone
- ○ Trachelectomy (simple or radical)
- ○ Other, *specify*
- ○ Information not provided
- ○ No prior procedure

Previous therapy

- ○ Chemotherapy
- ○ Radiation
- ○ Chemoradiation
- ○ Other, *specify*
- ○ Information not provided
- ○ No prior therapy

SPECIMENS SUBMITTED (select all that apply) (Note 2)

- ☐ Loop excision*
- ☐ Cone biopsy
- ☐ Trachelectomy
  - ○ Simple
  - ○ Radical
  - ○ Type not specified
- ☐ Hysterectomy
  - ○ Simple
  - ○ Radical
  - ○ Part of exenteration
  - ○ Type not specified
- ☐ Left tube
- ☐ Left ovary
- ☐ Left parametrium
- ☐ Vaginal cuff
- ☐ Pelvic exenteration
  - ☐ Urinary bladder
  - ☐ Vagina
  - ☐ Other, *specify*
  - ☐ Rectum
  - ☐ Sigmoid colon
- ☐ Right tube
- ☐ Right ovary
- ☐ Right parametrium
- ○ Not specified
- ☐ Lymphadenectomy specimen/s
  - ☐ Sentinel node/s
    - ☐ Left
    - ☐ Right
  - ☐ Regional nodes: pelvic
    - ☐ Left
    - ☐ Right
  - ☐ Non-regional nodes: inguinal
    - ☐ Left
    - ☐ Right
  - ☐ Non-regional: para-aortic
  - ☐ Other node group, *specify*
- ☐ Other, *specify*

*Loop excision includes – loop electrosurgical excision procedure (LEEP) and large loop excision of the transformation zone (LLETZ)

SPECIMEN DIMENSIONS (Note 3)

Number of tissue pieces*

Tissue piece dimensions* *(Note: Record for each piece)*

mm x mm x mm

mm x mm x mm

mm x mm x mm

Cervix**

DIAMETER OF ECTOCERVIX mm x mm

DEPTH OF SPECIMEN mm

Vaginal cuff***

- ○ Not applicable

MINIMUM LENGTH mm

MAXIMUM LENGTH mm

Left parametrium

- ○ Not applicable

LATERAL EXTENT mm

Right parametrium

- ○ Not applicable

LATERAL EXTENT mm

**Applicable to loop/cone biopsies only*

***Applicable to loop/cone biopsies and trachelectomy specimens only*

****Applicable to trachelectomy and hysterectomy specimens*

MACROSCOPIC APPEARANCE OF TUMOUR(S) (Note 4)

- ○ No macroscopically visible tumour
- ☐ Exophytic/polypoid
- ☐ Flat
- ☐ Ulcerated
- ☐ Circumferential/barrel shaped cervix
- ☐ Other, *specify*

MACROSCOPIC TUMOUR SITE(S) (select all that apply) (Note 5)

- ○ No macroscopically visible tumour
- ○ Indeterminate
- ☐ Ectocervix
  - ☐ Anterior
  - ☐ Posterior
  - ☐ Left lateral
  - ☐ Right lateral
  - ☐ Circumference of cervix
- ☐ Endocervix
  - ☐ Anterior
  - ☐ Posterior
  - ☐ Left lateral
  - ☐ Right lateral
  - ☐ Circumference of cervix
- ☐ Vagina
- ☐ Uterus
  - ☐ Lower uterine segment
  - ☐ Corpus
- ☐ Parametrium
  - ☐ Left
  - ☐ Right
- ☐ Other organs or tissues, *specify*

BLOCK IDENTIFICATION KEY (Note 6)

(List overleaf or separately with an indication of the nature and origin of all tissue blocks)

TUMOUR DIMENSIONS (Note 7)

(If separate tumours specify the dimensions for each tumour)

- ○ Tumour dimensions cannot be determined

Horizontal extent mm x mm At least**

Depth of invasion mm At least**

OR ○ Not assessable

If not assessable record:

Thickness mm

*** It is advisable to include "at least" for the tumour measurements in loop or cone excisions when tumour is present at a resection margin/s. If not applicable, delete "at least".*

HISTOLOGICAL TUMOUR TYPE (Note 8)

HISTOLOGICAL TUMOUR GRADE (Note 9)

- ○ Not graded/applicable
- ○ G1: Well differentiated
- ○ G2: Moderately differentiated
- ○ G3: Poorly differentiated
- ○ GX: Cannot be graded

LYMPHOVASCULAR INVASION (Note 10)

- ○ Not identified
- ○ Indeterminate
- ○ Present

COEXISTENT PATHOLOGY (Note 11)

(Required for loop/cone excisions/trachelectomies only and recommended for other specimens)

Squamous intraepithelial lesion (SIL) (CIN)

- ○ Not identified
- ○ Present

GRADE

- ○ Low-grade SIL (LSIL) (CIN 1)
- ○ High-grade SIL (HSIL) (CIN 2/3)

Adenocarcinoma in-situ (AIS)/High-grade cervical glandular intraepithelial neoplasia (HG CGIN)

- ○ Not identified
- ○ Present

Stratified mucin-producing intraepithelial lesion (SMILE)

- ○ Not identified
- ○ Present

Other possible precursor lesions

- ○ Not identified
- ○ Present
  - ☐ Lobular endocervical glandular hyperplasia
  - ☐ Adenocarcinoma in situ of gastric type
  - ☐ Other, *specify*

EXTENT OF INVASION (Note 12)

- ○ Not applicable

Vagina

- ○ Not involved
- ○ Not applicable
- ○ Involved
  - ☐ Upper two thirds
  - ☐ Lower third

Lower uterine segment

- ○ Not involved
- ○ Not applicable
- ○ Involved

Endometrium

- ○ Not involved
- ○ Not applicable
- ○ Involved

Myometrium

- ○ Not involved
- ○ Not applicable
- ○ Involved

Parametrium

- ○ Not involved
- ○ Not applicable
- ○ Involved
  - ☐ Left
  - ☐ Right

Fallopian tube

- ○ Not involved
- ○ Not applicable
- ○ Involved
  - ☐ Left
  - ☐ Right

Ovary

○ Not involved ○ Not applicable
○ Involved
☐ Left
☐ Right

Bladder

○ Not involved ○ Not applicable
○ Involved

Specify compartment

Rectum

○ Not involved ○ Not applicable
○ Involved

Specify compartment

Other organs or tissues

○ Not involved ○ Not applicable
○ Involved

Specify

PATHOLOGICALLY CONFIRMED DISTANT METASTASES (Note 14)

○ Not identified
○ Present

Specify site(s)

ANCILLARY STUDIES (Note 15)

○ Performed ○ Not performed

⇓

HPV testing, *specify details*

Immunohistochemistry, *specify details*

Other, *specify details*

MARGIN STATUS (Note 13)

For carcinoma

HYSTERECTOMY/TRACHELECTOMY SPECIMEN

Margin	Involved	Not involved	Distance from tumour (mm)	Cannot be assessed
Ectocervical/vaginal cuff				
Endocervical *				
Radial/deep stromal				
Closest lateral	○ Left ○ Right			

LOOP/CONE

Margin	Involved	Not involved	Distance from tumour (mm)	Cannot be assessed
Ectocervical				
Endocervical				
Radial/deep stromal				
Unspecified **				

For preinvasive disease

Margin	HSIL				AIS				SMILE				Margin is not applicable to specimen
	Involved	Not involved	Dist. from margin (mm)	Cannot be assessed	Involved	Not involved	Dist. from margin (mm)	Cannot be assessed	Involved	Not involved	Dist. from margin (mm)	Cannot be assessed	
Ectocervical/vaginal cuff													
Endocervical													
Radial/deep stromal													
Unspecified**													

**This is required only for trachelectomy specimens*
***Use for loop/cone biopsies where it is not possible to say whether the margin is ectocervical or endocervical*

LYMPH NODE STATUS (Note 16)

○ Not submitted

Lymph Node Type	Detail	Number of lymph nodes examined**	Number of positive lymph nodes**
Sentinel node/s	Left		
	Right		
Regional nodes: pelvic	Left		
	Right		
Non-regional nodes: inguinal	Left		
	Right		
Non-regional: para-aortic			
Other node group, *specify:*			

*** If the actual number of lymph nodes examined or the number of positive nodes cannot be determined due, for example, to fragmentation, then this should be indicated in the response.*

PROVISIONAL PATHOLOGICAL STAGING PRE-MDTM (Note 17)

FIGO (2009 edition) (Reproduced with permission)

○ I	Carcinoma is strictly confined to the cervix (extension to the corpus would be disregarded).
○ IA	Invasive cancer identified only by microscopy, with deepest invasion ≤5mm and largest extension ≤7mm.
○ IA1	Measured stromal invasion ≤ 3.0 mm in depth and extension ≤ 7 mm.
○ IA2	Measured stromal invasion >3 mm and <5 mm with an extension ≤7 mm
○ IB	Clinically visible lesions limited to the cervix uteri or preclinical lesions greater than stage IA.
○ IB1	Clinically visible lesions ≤ 4 cm in greatest diameter
○ IB2	Clinically visible lesions > 4 cm in greatest diameter
○ II	Cervical carcinoma extends beyond the uterus, but not to the pelvic wall or to the lower third of the vagina.
○ IIA	Without parametrial invasion
○ IIA1	Clinically visible lesion ≤ 4.0 cm in greatest diameter
○ IIA2	Clinically visible lesion > 4 cm in greatest dimension.
○ IIB	With obvious parametrial invasion
○ III	The tumour extends to the pelvic wall and/or involves lower third of the vagina and/or causes hydronephrosis or non-functioning kidney. On rectal examination, there is no cancer–free space between the tumour and the pelvic wall.
○ IIIA	No extension to the pelvic wall but involvement of the lower third of vagina.
○ IIIB	Extension on to pelvic wall and/or hydronephrosis or non-functioning kidney.
○ IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. A bullous oedema, as such, does not permit a case to be allotted to stage IV.
○ IVA	Spread of growth to adjacent organs.
○ IVB	Spread to distant organs

TNM (UICC 8th edition 2016) (Reproduced with permission)

☐ m - multiple primary tumors ☐ r - recurrent
☐ y - post treatment

Regional lymph nodes(pN)

○	No nodes submitted or found
○ NX	Regional lymph nodes cannot be assessed
○ N0	No regional lymph node metastasis
○ N1	Regional lymph node metastasis

Primary tumour (pT)

○ TX	Primary tumour can not be assessed
○ T0	No evidence of primary tumour
○ Tis	Carcinoma in situ (preinvasive carcinoma)
○ T1[1]	Tumour confined to the cervix
○ T1a[2,3]	Invasive carcinoma diagnosed only by microscopy; stromal invasion with a maximum depth of 5.0 mm measured from the base of the epithelium and a horizontal spread of 7.0 mm or less[4]
○ T1a1	Measured stromal invasion 3.0 mm or less in depth and 7.0 mm or less in horizontal spread
○ T1a2	Measured stromal invasion more than 3.0 mm and not more than 5.0 mm with a horizontal spread 7.0 mm or less
○ T1b	Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a/IA2
○ T1b1	Clinically visible lesion 4.0 cm or less in greatest dimension
○ T1b2	Clinically visible lesion more than 4.0 cm in greatest dimension
○ T2	Tumour invades beyond uterus but not to pelvic wall or to lower third of vagina
○ T2a	Tumour without parametrial invasion
○ T2a1	Clinically visible lesion 4.0 cm or less in greatest dimension
○ T2a2	Clinically visible lesion more than 4.0 cm in greatest dimension
○ T2b	Tumour with parametrial invasion
○ T3	Tumour extends to pelvic wall, involves lower third of vagina, causes hydronephrosis or nonfunctional kidney
○ T3a	Tumour involves lower third of vagina
○ T3b	Tumour extends to pelvic wall, causes hydronephrosis or nonfunctional kidney
○ T4	Tumour invades mucosa of bladder or rectum or extends beyond true pelvis[5]

1 *Extension to the corpus uteri should be disregarded*
2 *The depth of invasion should be taken from the base of the epithelium, either surface or glandular, from which it originates. The depth of invasion is defined as the measurement of the tumour from the epithelial–stromal junction of the adjacent most superficial papillae to the deepest point of invasion.*
3 *All macroscopically visible lesions even with superficial invasion are T1b/IB*
4 *Vascular space involvement, venous or lymphatic, does not affect classification.*
5 *Bullous oedema is not sufficient to classify a tumour as T4.*

Distant metastasis

○ No distant metastasis identified microscopically
○ pM1 – Distant metastasis (includes inguinal lymph nodes and intraperitoneal disease) It excludes metastasis to vagina, pelvic serosa, and adnexa

ICCR cervix required elements

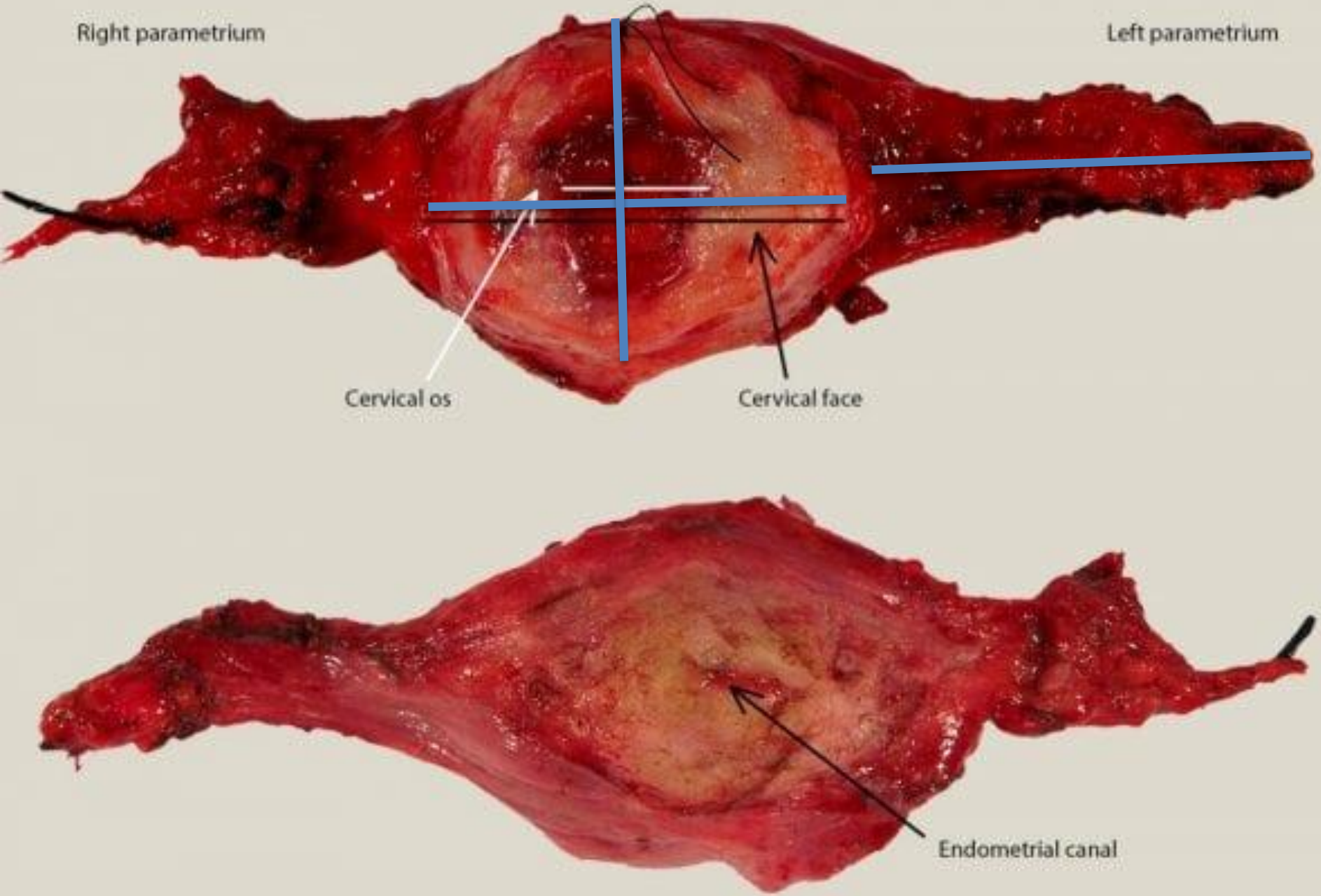
- Specimens submitted
  - Loop or cone excision
  - Simple and radical hysterectomy
  - Simple and radical trachelectomy
  - Pelvic exenteration
  - Lymph nodes and subdivision

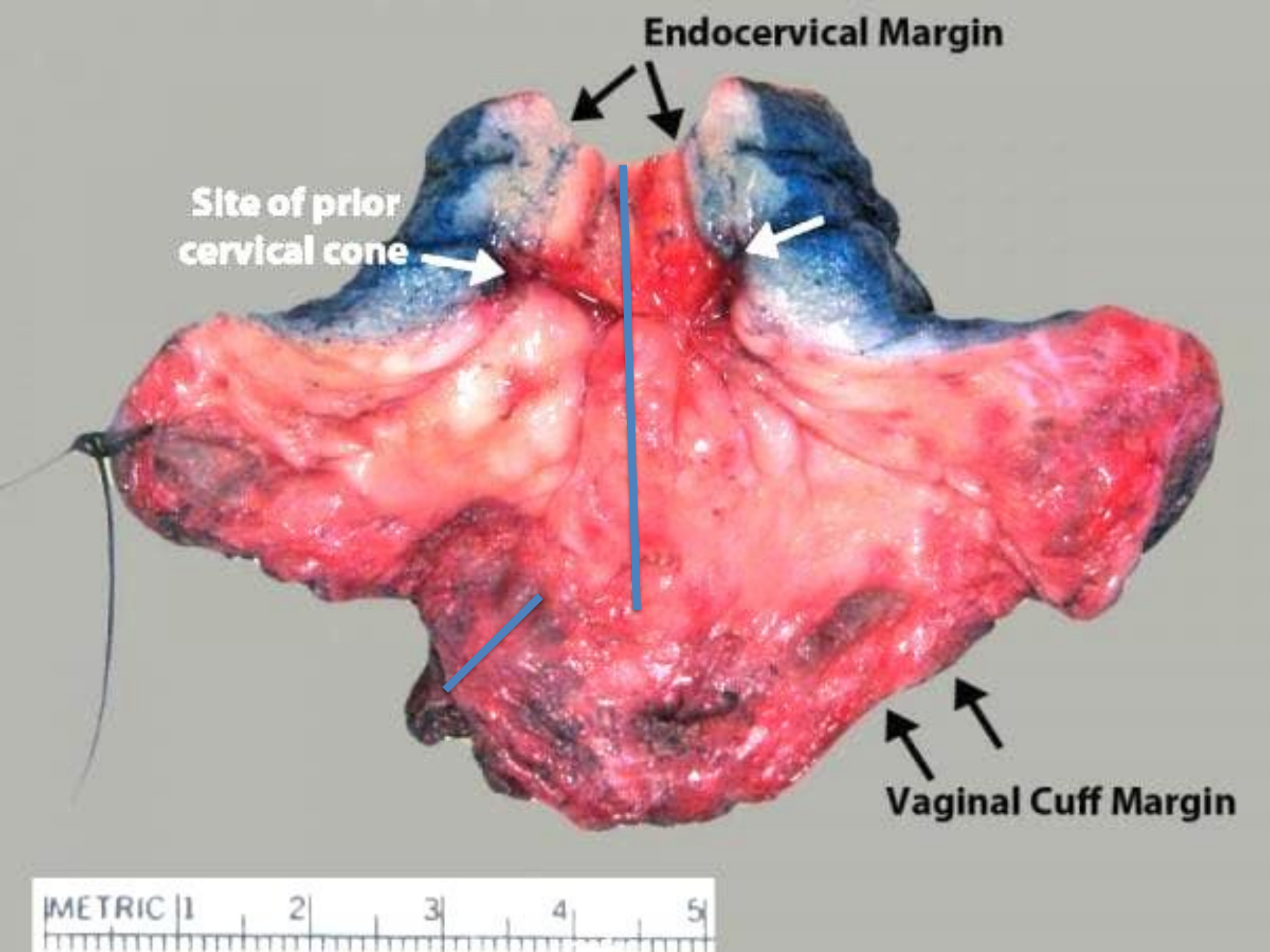
Mention all organs submitted!

Organs may be incomplete or different from the procedure mentioned by the surgeon

ICCR cervix required elements

- Specimen dimensions (metric, mm)
  - Loop or cone excision
    - Ectocervix in 2 dimensions
    - Depth of the specimen
  - Vaginal cuff
    - Craniocaudal length
  - Parametria
    - Length from side of uterus to lateral extend
- Measure all submitted specimens


Right parametrium
Left parametrium
Cervical os
Cervical face
Endometrial canal


Endocervical Margin
Site of prior cervical cone
Vaginal Cuff Margin
METRIC
1
2
3
4
5

ICCR cervix required elements

- Tumor macroscopy
  - Correlation with clinic and radiology
  - If you don't see tumor, sample the entire cervix
  - If you see a tumor, sample representatively
    - Nearest margin
    - Maximal depth of invasion
  - If you see a tumor it is at least stage IB
  - Large blocks may be useful

ICCR cervix required elements

- Tumor site
  - Anatomical location in the cervix
  - Proximity to margins and other structures
    - Vaginal cuff, parametrium, lower uterine segment, corpus …

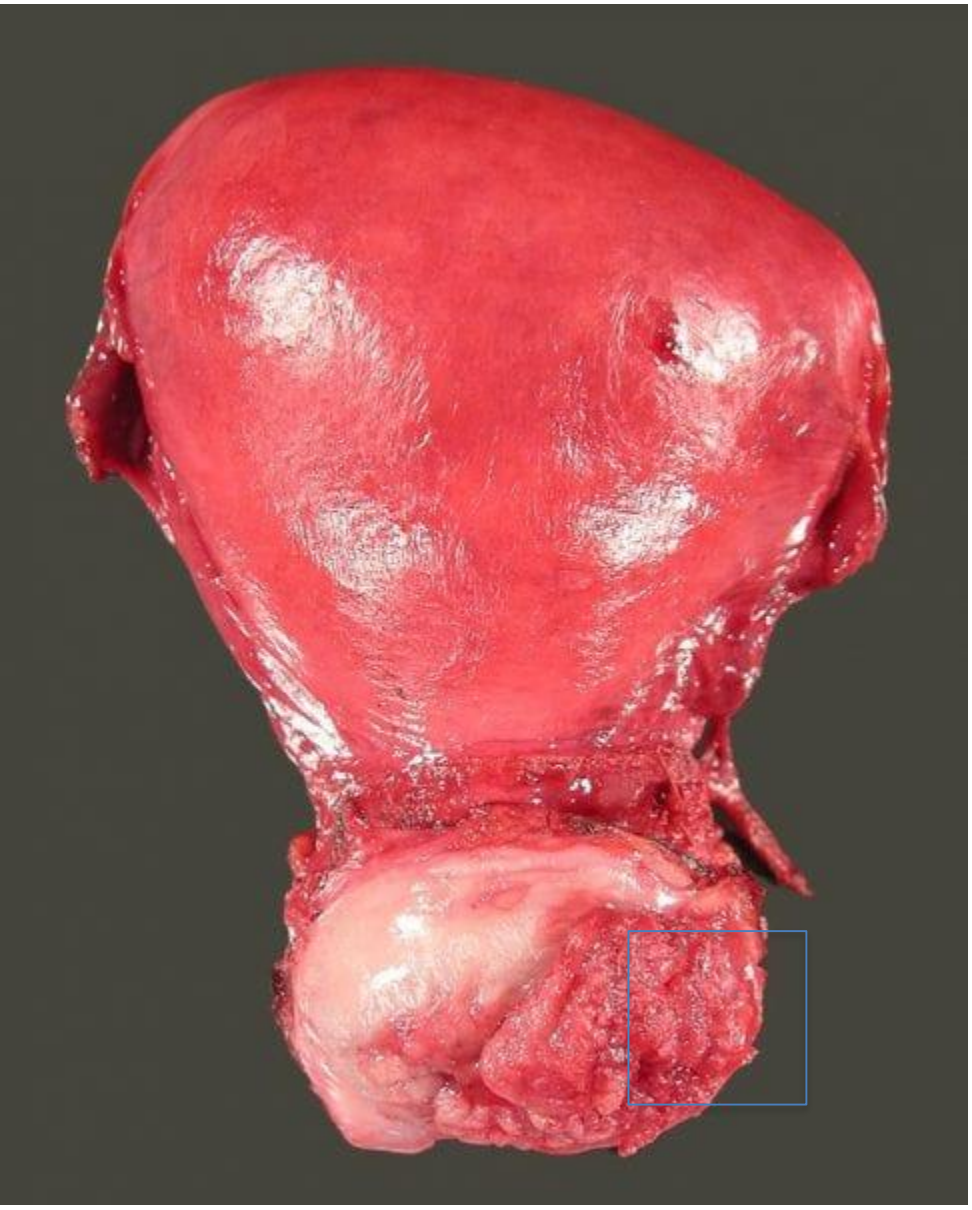
ICCR cervix required elements

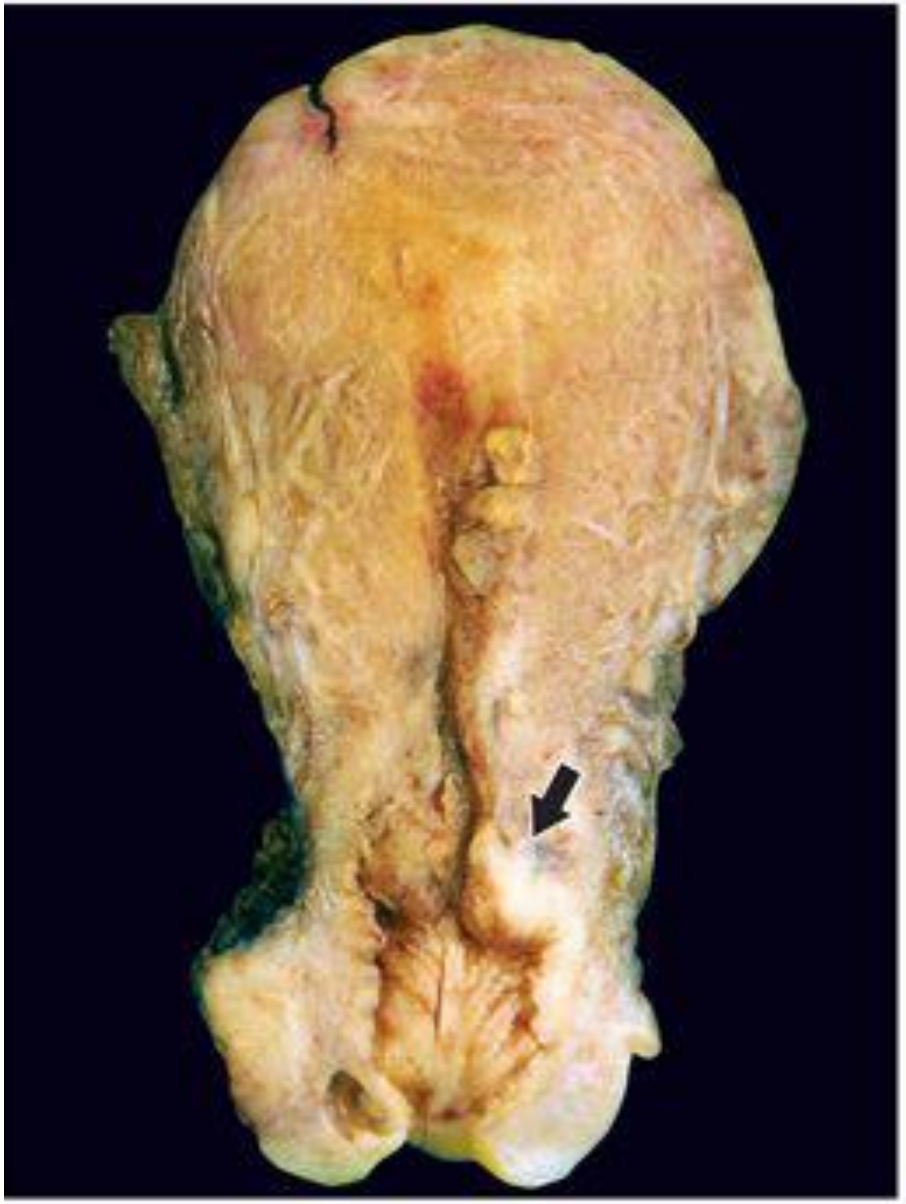
- Tumor dimensions (macroscopy)
  - In large tumors, use macroscopical size
    - Not resected or neo-adjuvant: clinical or radiological size
  - In damaged or fragmented specimens: estimate

Determine stage

- Stage IB differentiation FIGO 2019 revision
  - ≥ 5mm and < 2cm: IB1
  - 2-4cm: IB2
  - ≥4cm: IB3

Determine choice of therapy





ICCR cervix required elements

- Tumor dimensions (microscopy)
  - In small tumors, use microscopical size

  Determine stage
  - Stage IA ICCR-FIGO 2009 edition
    - FIGO 2019 revision: lateral extension is removed
    - <3mm depth: Stage IA1
    - ≥3mm and <5mm depth: Stage IA2
  - Stage IB

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FIGO COMMITTEE REPORT

WILEY GYNECOLOGY OBSTETRICS FIGO

Revised FIGO staging for carcinoma of the cervix uteri☆

Neerja Bhatla[1,*] | Jonathan S. Berek[2] | Mauricio Cuello Fredes[3] | Lynette A. Denny[4] | Seija Grenman[5] | Kanishka Karunaratne[6] | Sean T. Kehoe[7] | Ikuo Konishi[8] | Alexander B. Olawaiye[9] | Jaime Prat[10] | Rengaswamy Sankaranarayanan[11,12]

Multifocal carcinoma

- Especially in early invasive carcinoma
- 12-25% of carcinoma
- How to handle?
  - Measure each focus separately
  - >2mm apart (?)
  - Determine the FIGO on the focus with deepest invasion
  - Upstage to IB1?
  - Multidisciplinary approach

ICCR cervix required elements

- Histological type
- According to the WHO 2014 classification
  - Squamous carcinoma
  - Adenocarcinoma (! Gastric type)
  - Adenosquamous carcinoma
  - (Serous carcinoma)
  - (Endometrioid carcinoma)
  - Neuro-endocrine carcinoma
  - Carcinosarcoma

ICCR cervix required elements

- Lymphovascular invasion
- Coexistent precursor pathology
  - SIL
  - AIS
  - SMILE
- Extend of invasion
  - Not applicable
  - Vagina, LUS, endometrium,myometrium, parametrium, fallopian tube, ovary, bladder, rectum,…
- Pathologically proven distant metastasis

ICCR cervix required elements

- Margin status (both invasive and precursor)
  - Ectocervical/vaginal cuff
  - Endocervical
  - Deep stromal
  - Closest lateral
- Lymph node status
  - Sentinel node
  - Regional (pelvic) nodes: Stage IIIC1
  - Non-regional (para-aortic) nodes: Stage IIIC2
  - Retroperitoneal nodes: Stage IIIC

ICCR cervix recommended element

- Tumor grading
  - No universally accepted grading system
  - Variability among studies
  - Prognostic element?

Grading of SCC

- 1893 Von Hanseman
  - ‘anaplasia’
- 1912 Scottlaender & Kermauner
  - Mature, semi-mature and immature
- 1920 Brothers & 1976 Goellner
  - High, moderate and poor (scale 1-4)
- 1926 Böhm &Zweifel
  - Modified by keratinization and tumor-host relation
- 1957 Reagan & 1975 Poulson (WHO)
  - Large non-keratinizing, large keratinizing, small cell
- Prediction of patient outcome?? Subjective??

Grading system for squamous carcinoma

Stendhal et al grading system, 1980

- Tumor cell population
- Tumor-host reaction

- Score from 8-24 points
- Time-consuming
- Not widely accepted

Parameters used for malignancy point grading. Tumour cell population

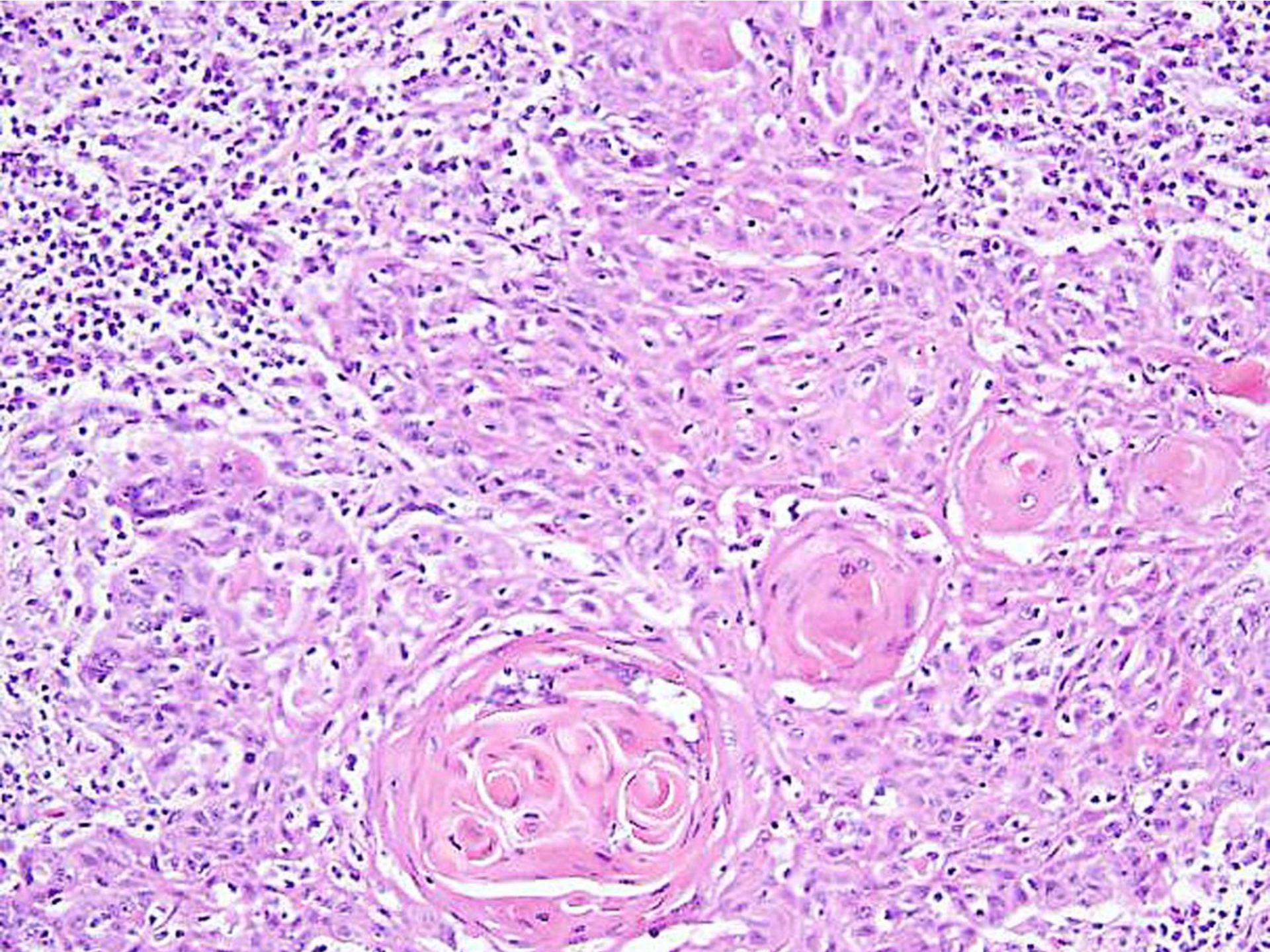
Parameter number		Points 1	2	3
1	Structure	Exophytic, papillary and solid	Small cords and groups of cells	Marked cellular dissociation
2	Differentiation into cell type	Large cell, no keratinization	Large cell keratinized	Small cell, no keratinization
3	Nuclear polymorphism	>75 per cent mature nuclei, few enlarged nuclei	75 to 25 per cent mature nuclei, moderate number of enlarged nuclei	<75 per cent mature nuclei, numerous irregular or anaplastic enlarged nuclei
4	Mitoses	Single 0–1	Moderate number 0–5	Numerous 0–>5

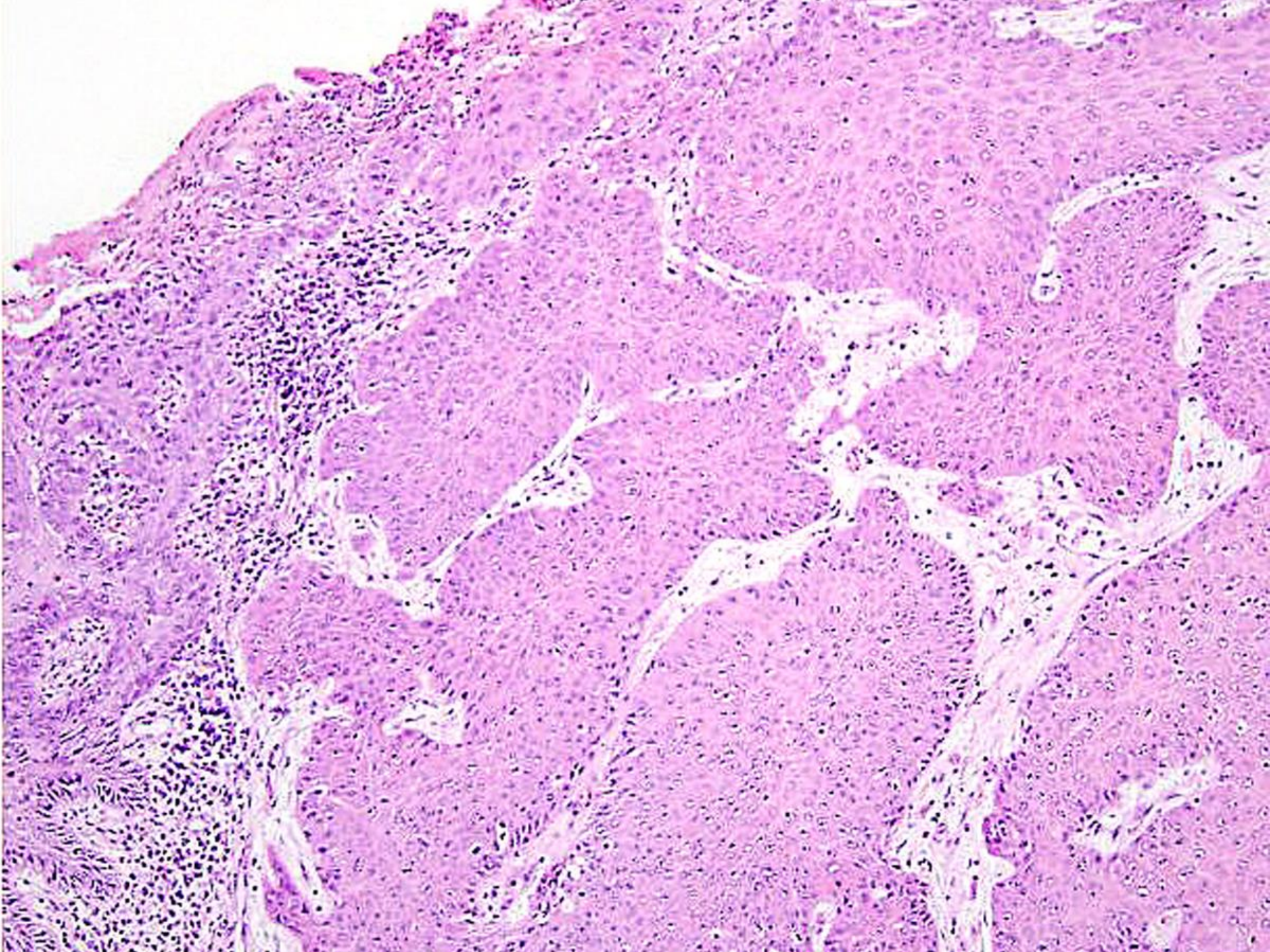
Parameters used for malignancy point grading. Tumour-host relationship

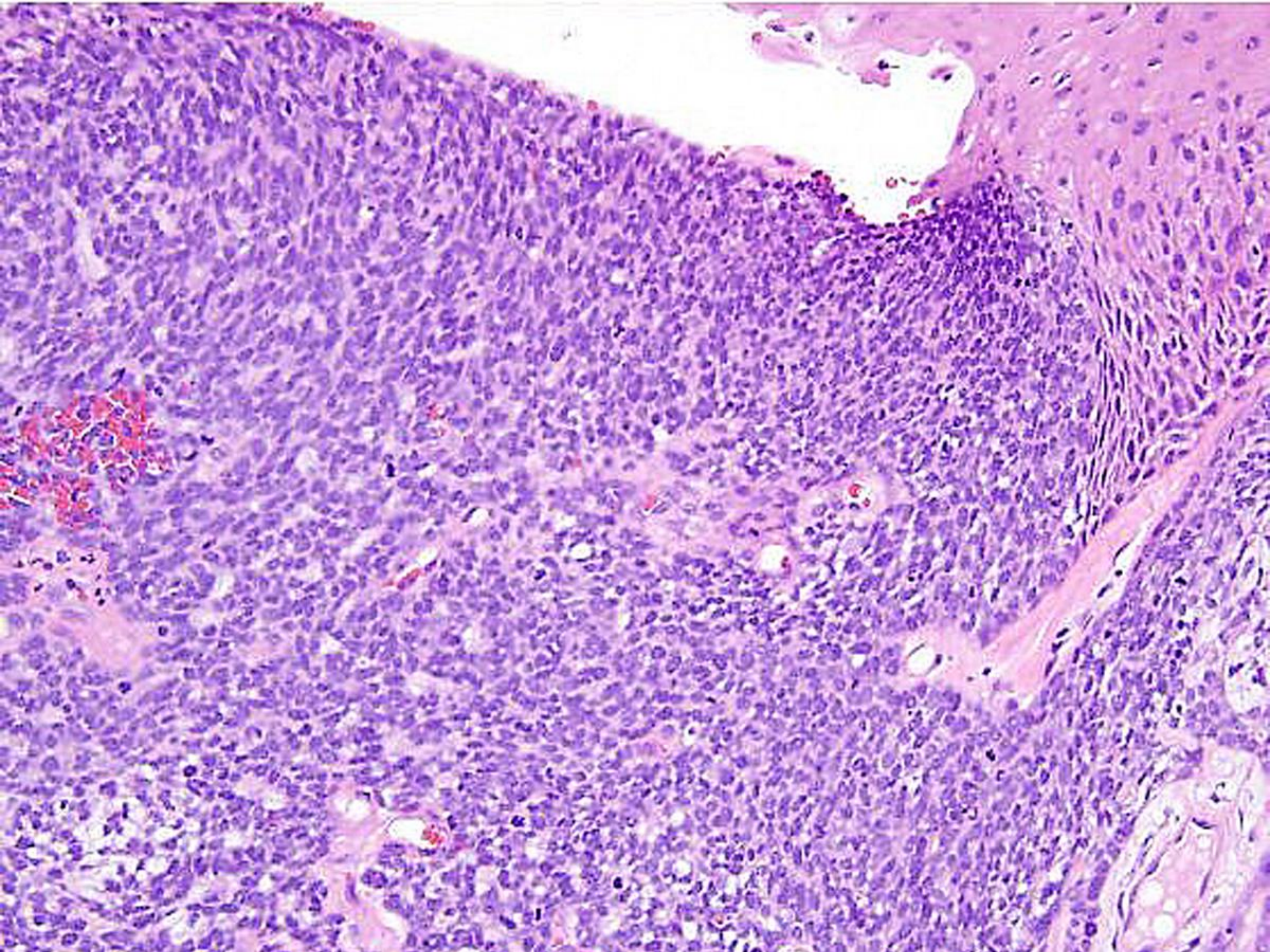
Parameter number		Points 1	2	3
5	Mode of invasion	Well defined borderline	Cords, less marked borderline	Groups of cells or diffuse growth
6	Stage of invasion	(Min. stroma inv.) or microcarcinoma	Nodular into submucosa and connective tissue	Massive; amongst muscles, and vessels
7	Vascular invasion	None	Possible	Well established within the lumina of lymph or blood vessels
8	Cellular response (plasmolymphocytic)	Marked (continuous rim)	Moderate (several large patches)	Slight or none (few small patches or no cells)

WHO 2014 grading

- Grade 1
  - Intercellular bridges, keratinization, pearls
  - Uniform cells, not pleiomorphic, low mitosis
- Grade 2
  - Individual cell keratinization, moderate pleiomorphism, more mitosis
- Grade 3
  - No keratinization, marked pleiomorphism, scant cytoplasm, numerous mitosis, necrosis







Prognosis and grading

- 233 SCC stage IB cervix carcinoma with surgery
- WHO grading (keratinization)
- Relation between grade and overall survival
- Relation between grade and tumor-free survival
- Relation between G3 tumor and node involvement

Journal of Cancer Research and Clinical Oncology (2019) 145:457–462
https://doi.org/10.1007/s00432-018-2793-3

ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Prognostic relevance of low-grade versus high-grade FIGO IB1 squamous cell uterine cervical carcinomas

Lars-Christian Horn[1] · Anne Katrin Höhn[1] · Bettina Hentschel[2] · Uta Fischer[1,3] · Karl Bilek[3] · Christine E. Brambs[4]

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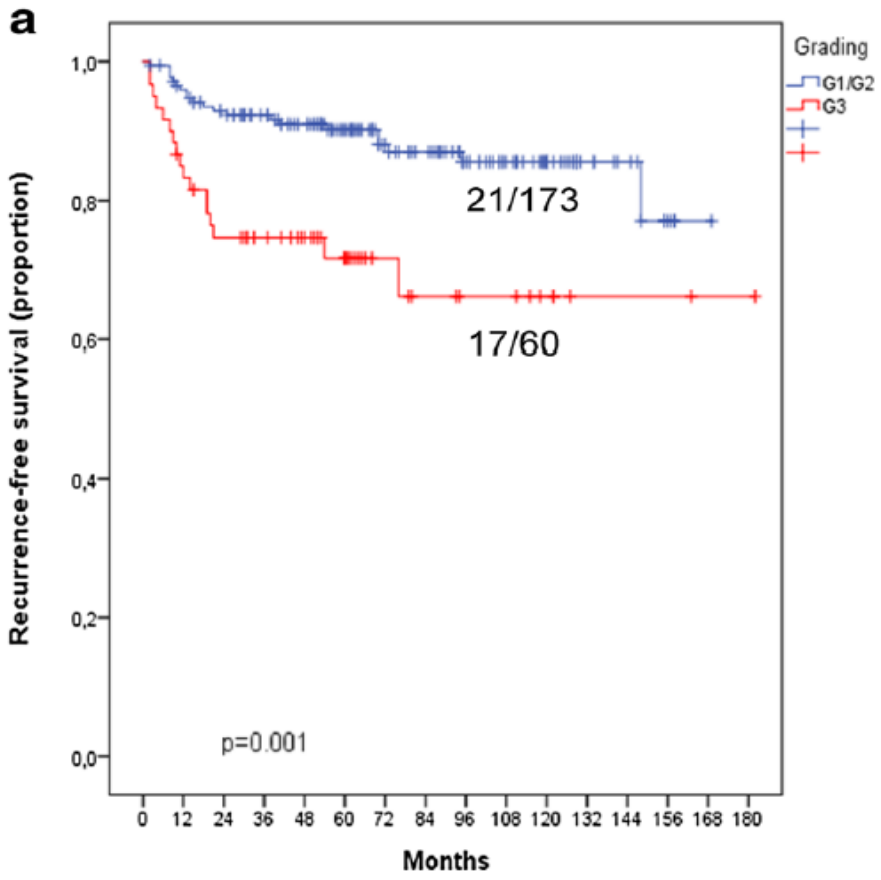
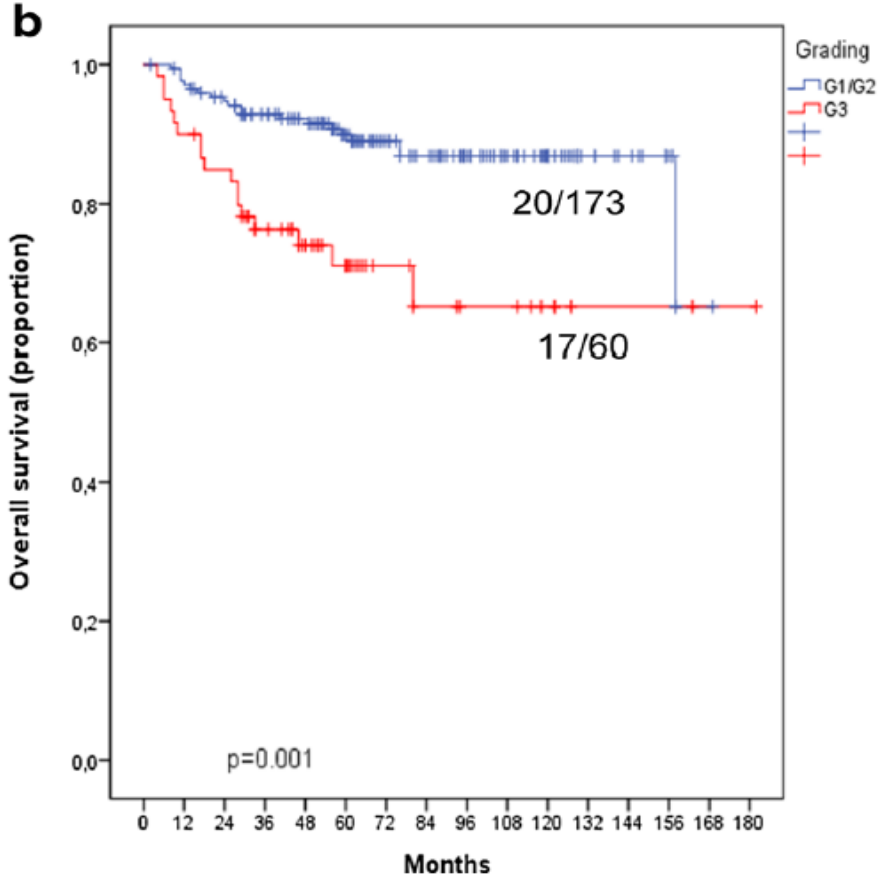
Prognosis and grading





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Criticism on WHO grading of SCC

- Highly subjective, not quantified
- Most cancers are HPV-induced and display a basaloid poorly differentiated pattern
- Small biopsies – heterogeneity?

- Grading is not mandatory in AP reports
- Grading is not included in treatment choices

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ORIGINAL ARTICLE

Introducing a novel highly prognostic grading scheme based on tumour budding and cell nest size for squamous cell carcinoma of the uterine cervix

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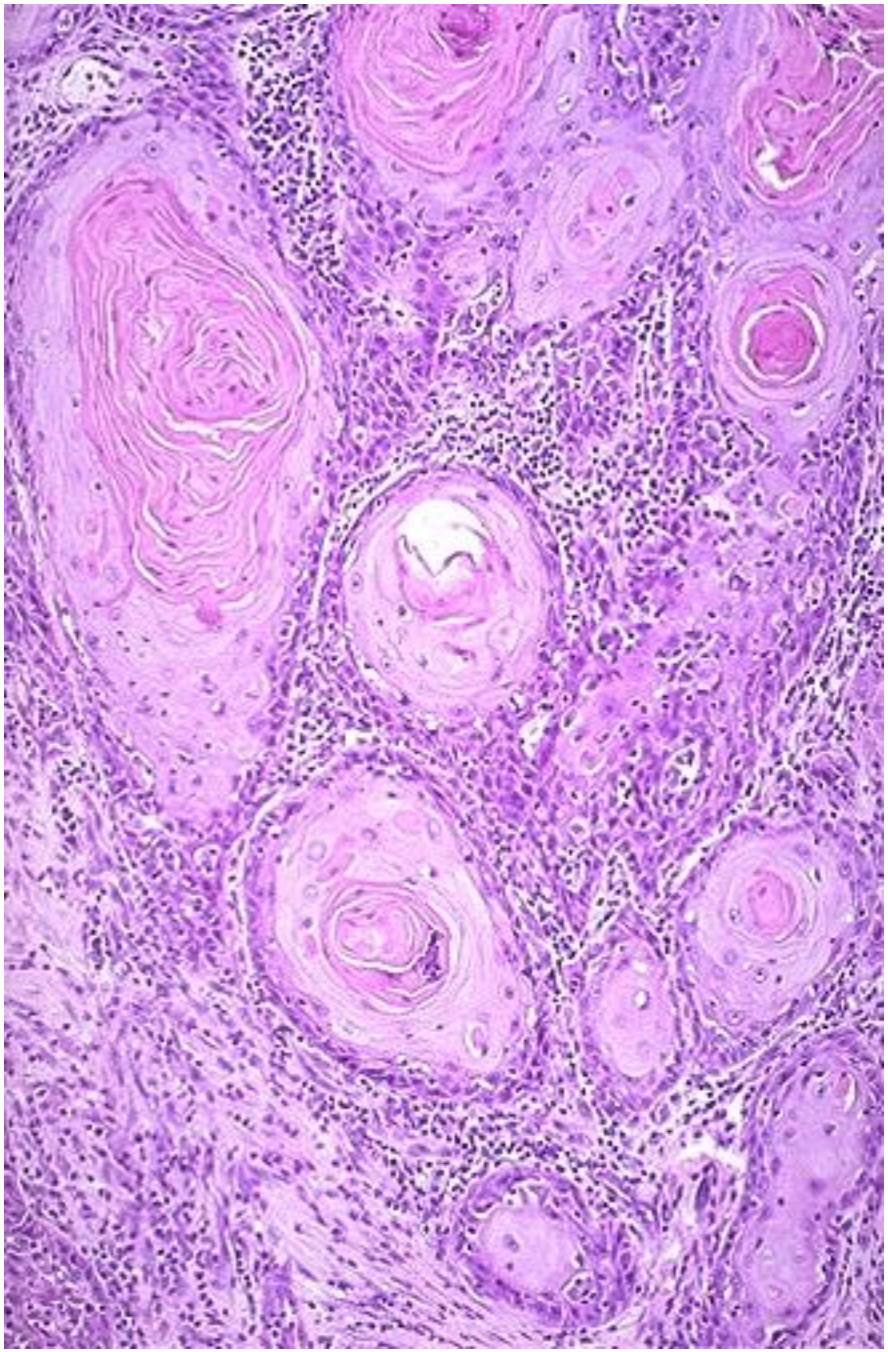
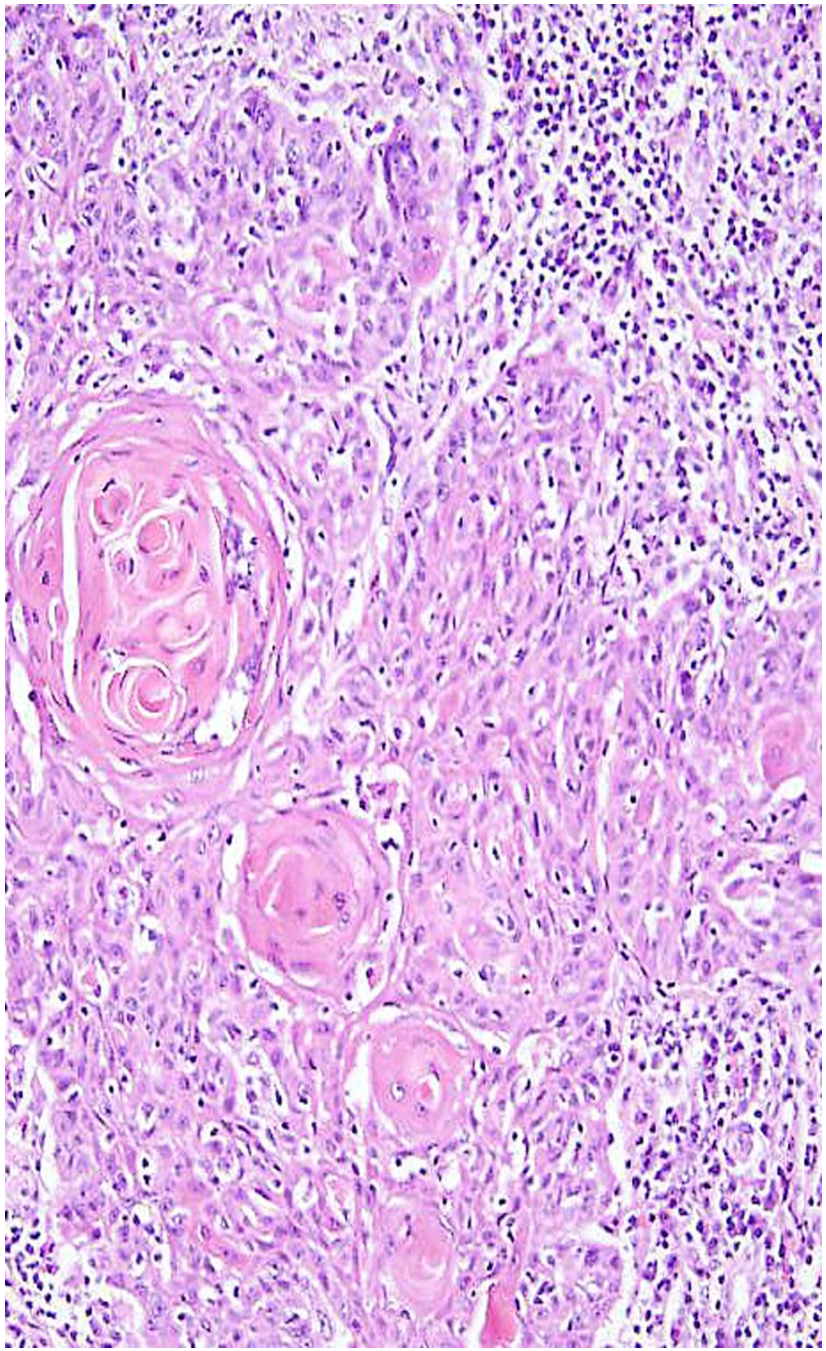
New grading proposal

- Based on prognosis in oral and oesophagal SCC
- Tumor budding
- Tumor nest size

- Measure capacity of cellular dissociation

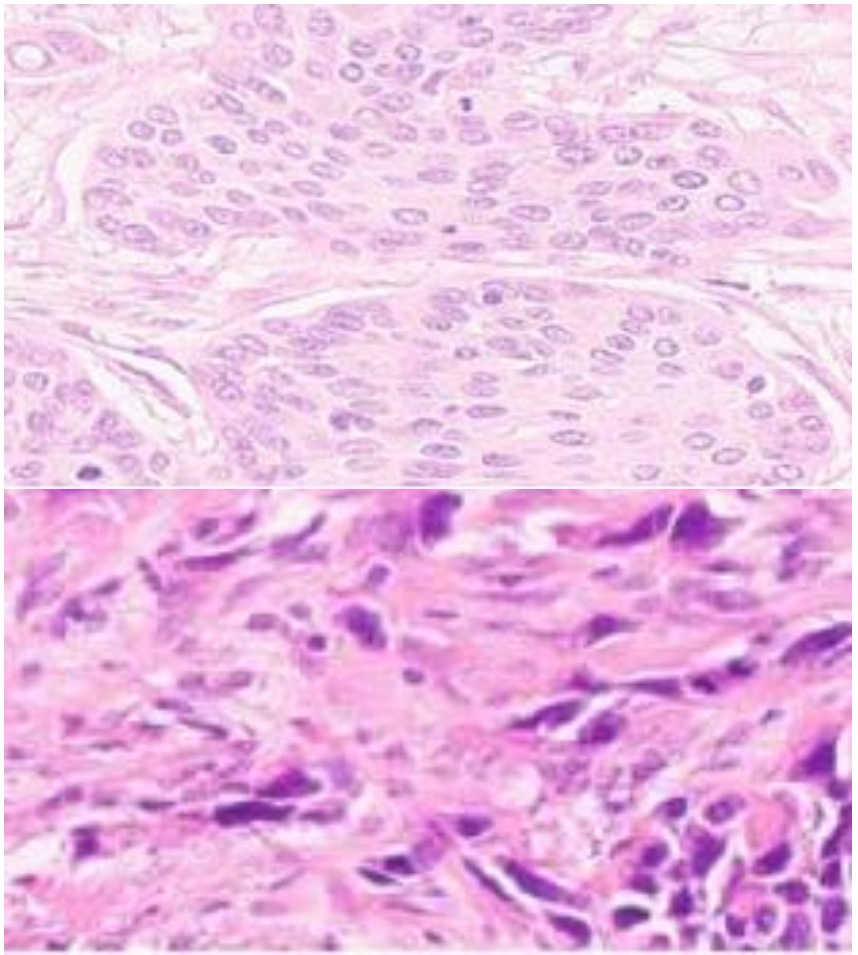




Tumor budding

- Small tumor complexes of <5 neoplastic cells growing into the surrounding stroma

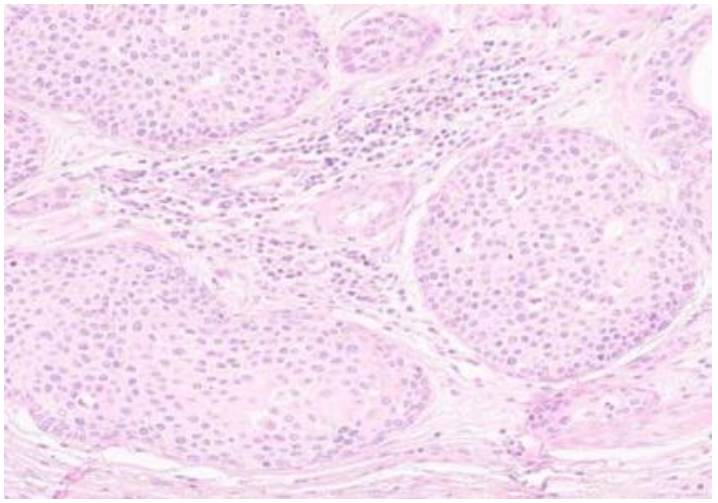
- Low budding
  - 1-14 buds/10HPF
- High budding
  - ≥ 15 buds/10HPF

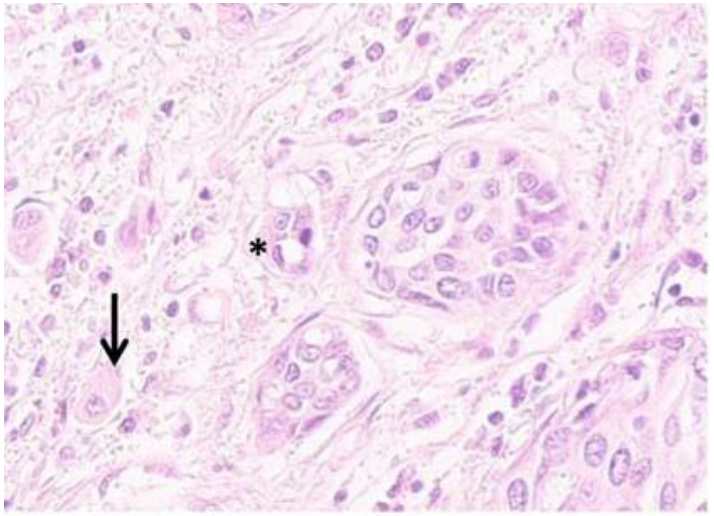


Tumor cell nest size

- Large: >15 cells
- Intermediate: 5-15 cells
- Small: 2-4 cells
- Single cell invasion

Report the smallest indentifiable cell nest

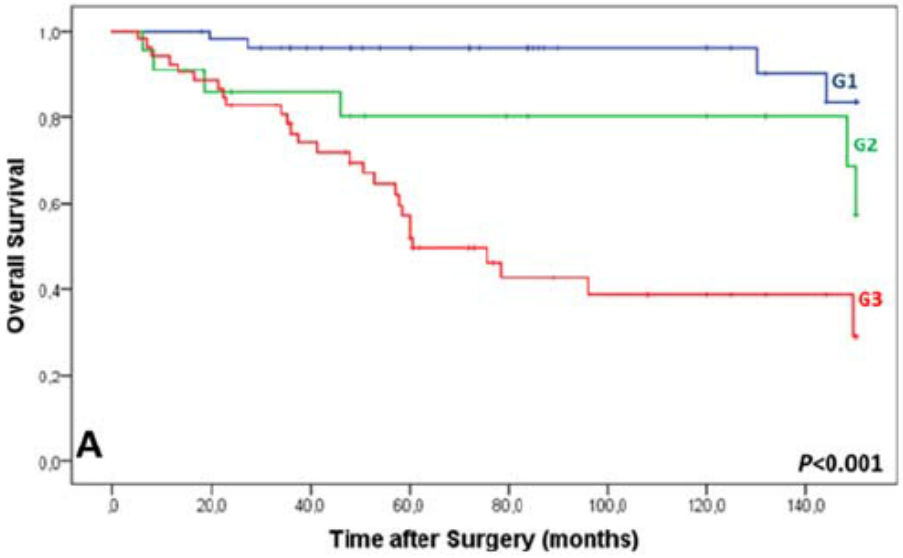


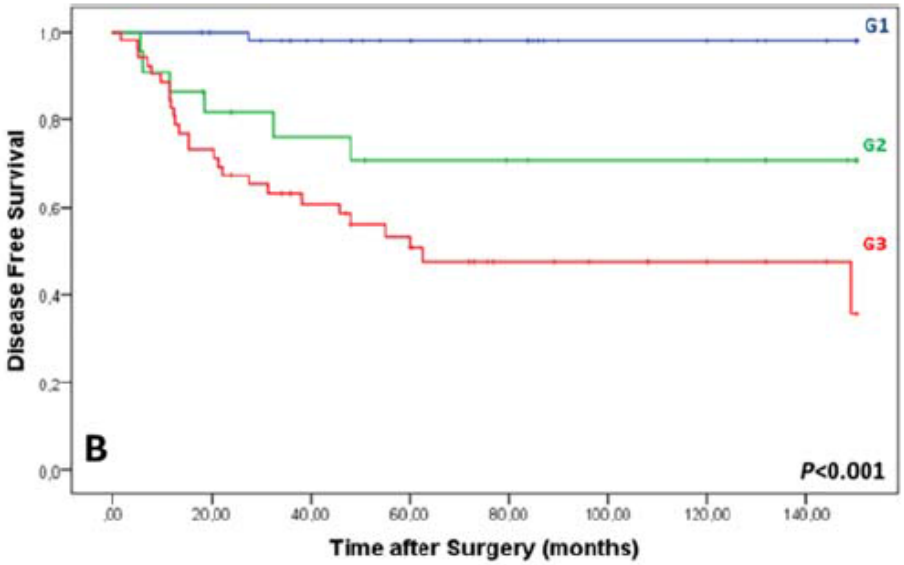


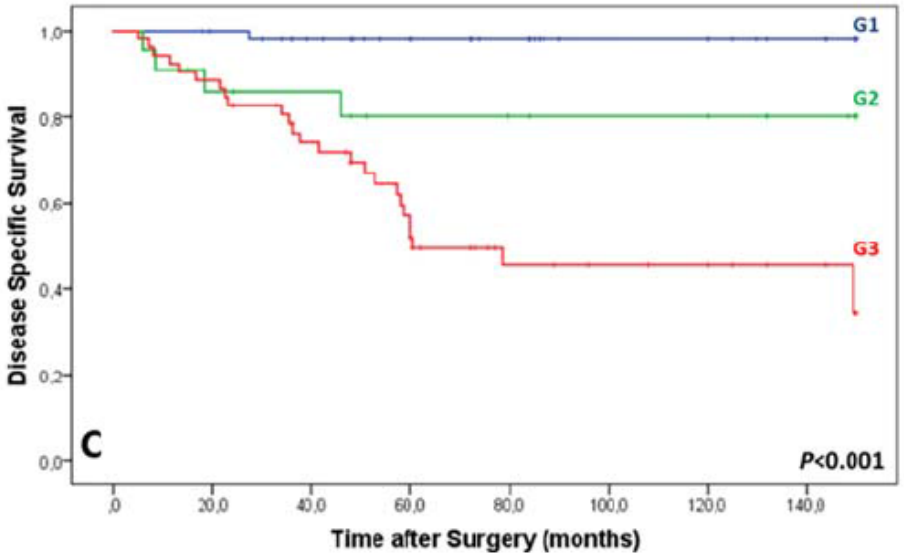
New grading proposal

Grading proposal for SCC of the uterine cervix	
Tumour budding activity/10 HPF	
No budding	1
$<$ 15 budding foci	2
$\geq$ 15 budding foci	3
Smallest cell nest size within the tumour core	
$>$ 15 cells	1
5–15 cells	2
2–4 cells	3
Single cell invasion	4
Tumour grading	Total score
Well differentiated (G1)	2–3
Moderately differentiated (G2)	4–5
Poorly differentiated (G3)	6–7

Prognosis with new grading







Methods of tumor budding assessment

- Scan HE slide for area of maximal budding
- Perform cytokeratin on that area
- 10 fields of 0,95 mm^2 objective 20
- Maximum bud count/HPF determines grade
- LTB: 0-4 buds
- HTB: >5 buds

RESEARCH ARTICLE

High-Grade Tumor Budding Stratifies Early-Stage Cervical Cancer with Recurrence Risk

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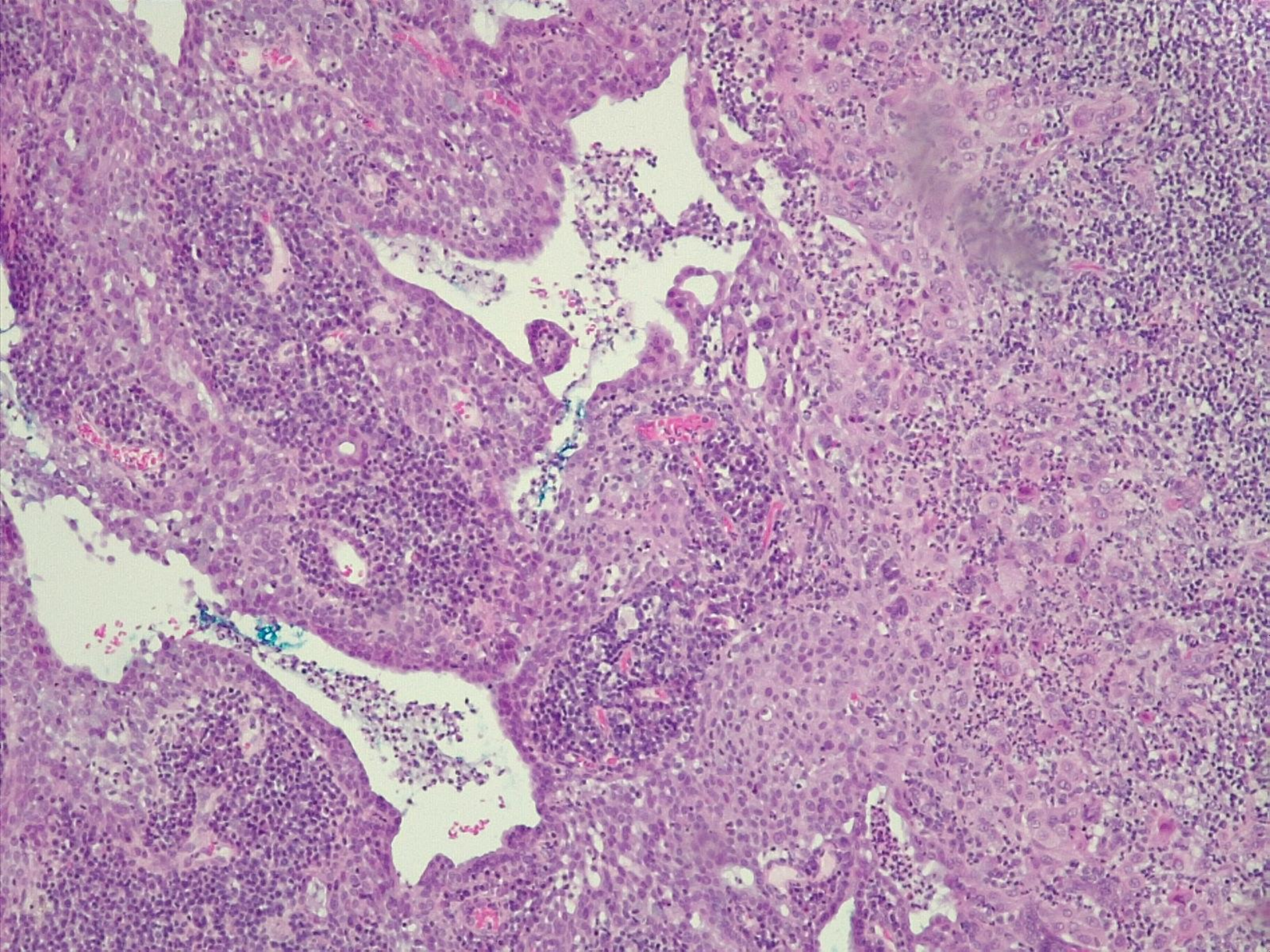

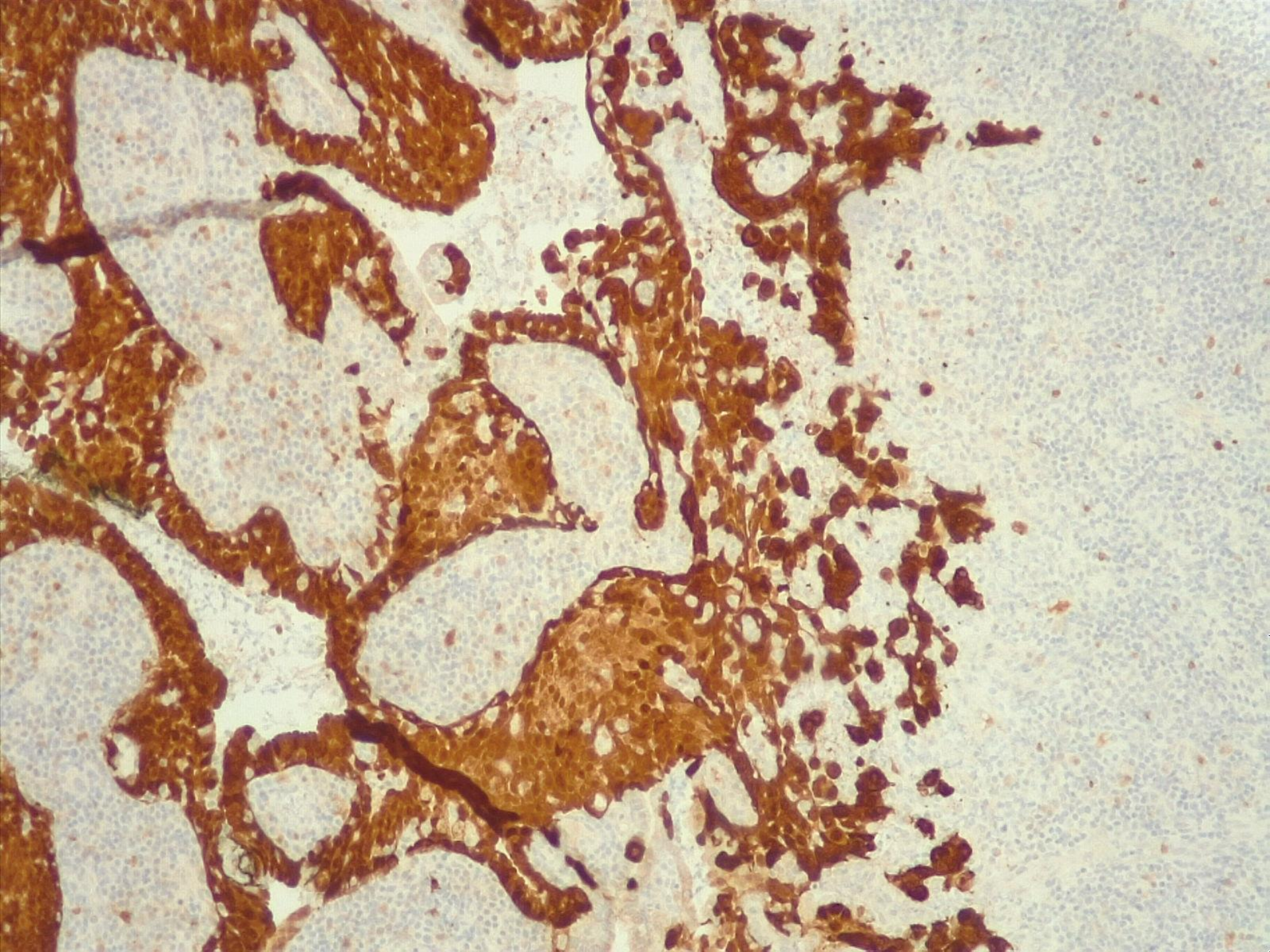

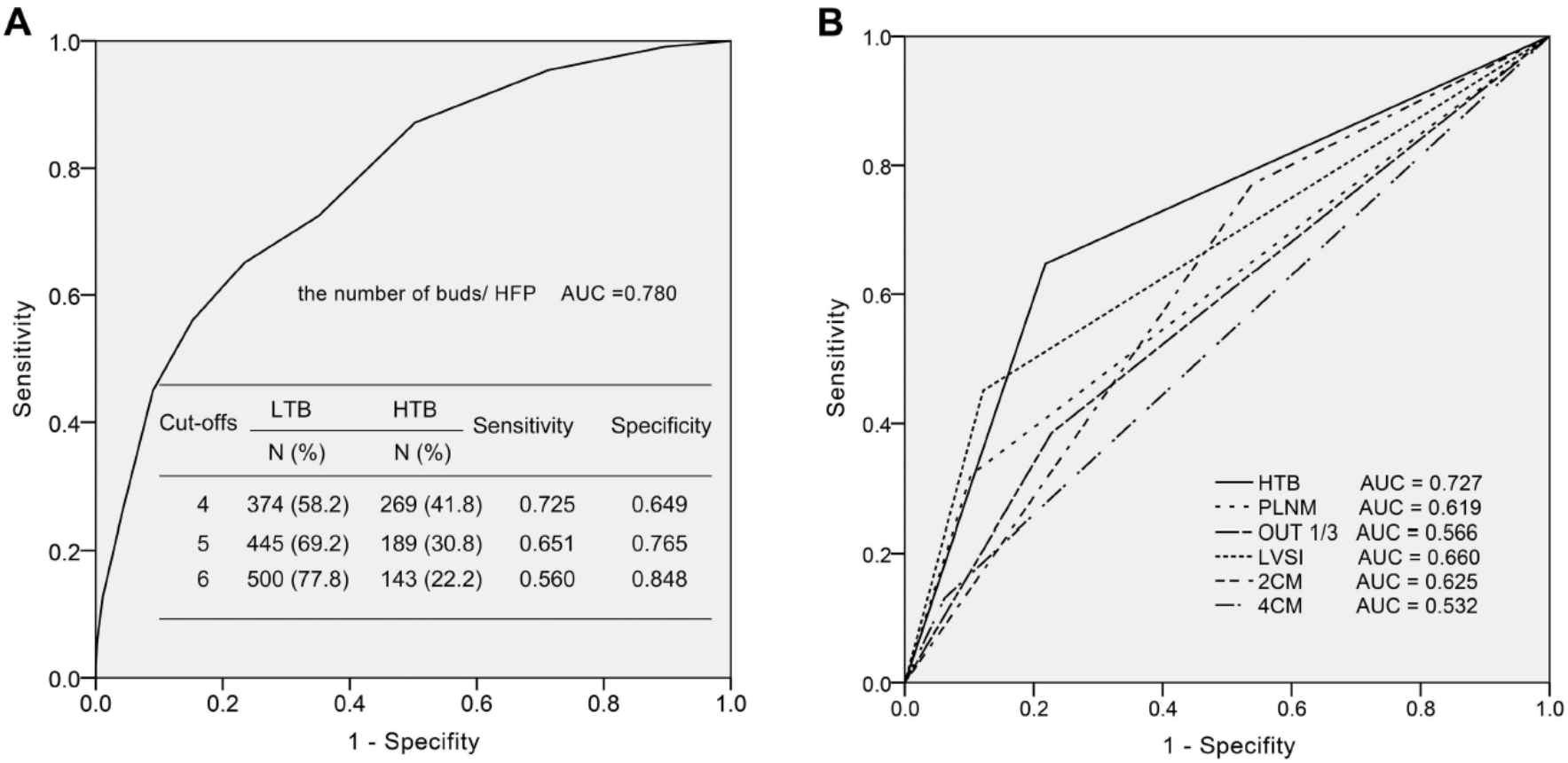

Fig 3. Receive operating characteristic (ROC) curves for the accuracy of disease recurrence. A, ROC curve aiding the selection of the cut-off value for low-grade budding (LTB) and high-grade budding (HTB). A value of 5 buds was selected because of its high sensitivity and specificity. B, ROC curves using various clinicopathological risk factors. HTB exhibited higher areas under the curve (AUC = 0.727) than the other classic clinicopathological risk factors. Abbreviations: OUT 1/3, stromal invasion of the outer 1/3; 2CM, tumor size $\geq$ 2 cm; 4CM, tumor size $\geq$ 4 cm.

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Future studies

- Validation of the new grading in larger cohorts
- Reproducibility testing
- Correlation with other tumor characteristics

THE Budding

Pathologist