

Cervix ICCR dataset and grading of squamous carcinoma

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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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Clinical	Macroscopic	Microscopic
Specimen/s submitted	Specimen dimensions Number of tissue pieces Tissue piece dimensions Cervix a. Diameter of ectocervix b. Depth of specimen Vaginal cuff a. Minimum length b. Maximum length Macroscopic tumor site(s)	Tumor dimensions Horizontal extent (2 measurements) Depth of invasion or thickness Histologic tumor type Lymphovascular space invasion Coexistent pathology Squamous intraepithelial lesion (CIN) Adenocarcinoma <i>in situ</i> /high-grade cervical glandular intraepithelial neoplasia 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)

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

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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

Carcinom	a of the Cervix		
Histopatholo	gy Reporting Guide	MACROSCOPIC TUMOUR SITE(S) (select all that apply) (Note 5) O No macroscopically visible tumour	COEXISTENT PATHOLOGY (Note 11) (Required for loop/cone excisions/trachelectomies only and
Family/Last name	Date of birth DD _ MM _ VVVV	O Indeterminate	Squamous intraenithelial lesion (SIL) (CIN)
		Ectocervix	
Given name(s)			
		Left lateral	
Patient identifiers	Date of request Accession/Laboratory number	Circumference of cervix	GRADE
	DD – MM – YYYY		Low-grade SIL (LSIL) (CIN 1)
Elements in black text are REQUIRED. Elements in grey text	are RECOMMENDED.	Anterior	High-grade SIL (HSIL) (CIN 2/3)
		Left lateral	Adenocarcinoma in-situ (AIS)/High-grade cervical
PRIOR TREATMENT (Note 1) Provinue procedure performed	SPECIMEN DIMENSIONS (Note 3)	Right lateral	glandular intraepithelial neoplasia (HG CGIN)
Information not provide	Number of tissue pieces*		O Not identified
O Cone O No prior procedure		Uterus	O Present
O Trachelectomy (simple or radical)	Tissue piece dimensions* (Note: Record for each piece)	Lower uterine segment Comus	Stratified mucin-producing intraepithelial lesion
Other, specify	mm x mm x mm	Parametrium	(SMILE)
			O Not identified
	mm x mm x mm	Other organs or tissues, specify	Opresent
Previous therapy			Other possible precursor lesions
O Chemotherapy O Information not provide O Radiation O No prior therapy	ed mm x mm x mm		O Not identified
Chemoradiation Other, specify			Present
¥	Cervix**	(List every deaf or constately with an indication of the	Lobular endocervical glandular hyperplasia
	DIAMETER OF ECTOCERVIX mm x mm	nature and origin of all tissue blocks)	 Other, specify
			*
	DEPTH OF SPECIMEN mm	(If separate tumours specify the dimensions for each tumour)	
Cone biopsy	Vilf(***		
Trachelectomy	vaginai cum····	Uniour dimensions cannot be determined	
Simple Radical	Not applicable	Horizontal extent mm x mm At least**	EXTENT OF INVASION (Note 12)
Hysterectomy	MINIMUM LENGTH mm		Not applicable
Simple Radical			Vagina
Part of exenteration Type not specified	maximum Leworn mm	Depth of invasion mm At least**	Not involved Not applicable
Left tube Right tube	Left parametrium		
Left parametrium	O Not applicable	OR Vot assessable	Upper two thirds
Vaginal cuff	LATERAL EXTENT mm	If not assessable record:	Lower third
Pelvic exenteration Uripary bladder Rectum		Thickness mm	Lower uterine segment
Vagina Sigmoid colon	Right parametrium		Not involved Not applicable
Other, specify	O Not applicable	in loop or cone excisions when turnour is present at a resection	
	LATERAL EXTENT mm	margin/s. If not applicable, delete "at least".	Endometrium
	*Applicable to loop/cone biopsies only		Involved Involved Involved
Lymphadenectomy specimen/s Sentinel node/s	**Applicable to loop/cone biopsies and trachelectomy specimens only	HISTOLOGICAL TUMOUR TYPE (Note 8)	Myometrium
Left Right	****Applicable to trachelectomy and hysterectomy specimens		Not involved Not applicable
Regional nodes: pelvic	MACROSCOPIC APPEARANCE OF TUMOUR(S) (Note 4)		◯ Involved
Left I Right Non-regional nodes: inquinal	O No macroscopically visible tumour		Parametrium
Left Right	Exophytic/polypoid	HISTOLOGICAL TUMOUR CRADE (Note 9)	○ Not involved ○ Not applicable
Non-regional: para-aortic	Flat	Not graded/applicable	
Utiler node group, specify		O G1: Well differentiated	Left
	Circumferential/barrel shaped cervix	G2: Moderately differentiated	rugn.
Other specify	Other, specify	G3: Poorly differentiated	Net applicable
V otier, speciny	1	GX: Cannot be graded	O Involved O Not applicable
		LYMPHOVASCULAR INVASION (Note 10)	▼ □ Left
*Loop excision includes - loop electrosurgical excision procedure	2)	○ Not identified ○ Indeterminate ○ Present	Right
(LLET) and large loop excision of the transformation zone (LLET	~/		

Version 1.0 Carcinoma of the Cervix - published March 2017

A CHARTER M					PATHOLO	GICAI		FIRME	DISTA	NT META	STASES	LYMPH NO	DE STATUS (N	lote 16)					
Not involved	\bigcirc	lot applica	ble			ot ident	tified			(1	Note 14)	O Not s	submitted	Lymph Node Type	Deta	I Num node	ber of lymph s examined**	Number of positive lymph nodes**	
					↓ Pr S	esent	cite(c)							Sentinel node/s	Left				
Right					с, Г	peeny s	Since(S)							Perional padatu palvia	Right				-
					Ļ									Regional hodes: pervic	Pinht	_			-
Not involved	0	lot applica	bla											Non-regional nodes: ingui	inal Left				-
	0	iot applica	DIE											non representation and	Right				-
 Specify comparts 	ment				ANCILLAR	RY STU	JDIES	(Note 15)					Non-regional: para-aortic		_			-
					OP	erforme	ed	0	Not perfo	rmed				Other node group, specify	12				-
						Ť													
Rectum						HPV	testing,	specify	details					** If the actual number of h	moh nodes evemin	ad or the	woher of pacit	lua nadas cannat ha da	termined d
Not involved	0	lot applica	ble											example, to fragmentation	n, then this should	be indica	ed in the respon	nse.	termineu u
												PROVISION	AL PATHOLO	GICAL STAGING PRE-MD	「M (Note 17)				
Specify comparts	ment			- I												Primar	y tumour (p1	Г)	
						Imm	unohisto	ochemist	r <mark>y, spec</mark> i	fy details		FIGO	(2009 edition	(Reproduced with permission)		S TX	Primary tu No ovideo	umour can not be as	sessed
Other organs or ti	issues											0 1	Carcinoma	s strictly confined to the cer	vix (extension	O Tis	Carcinoma	a in situ (preinvasive	e carcinom
Not involved	0	lot applica	ble										Invasive ca	is would be disregarded). Incer identified only by micro	scopy, with	Q 111	Tumour co	onfined to the cervix	: La alta basa
												0.1	deepest inv	asion ≤5mm and largest ext	ension	O Ha	stromal in	vasion with a maxin	num depth
Specify				- I		Othe	er, speci	fy details					Measured s	romal invasion ≤ 3.0 mm in	depth and		measured horizontal	from the base of the spread of 7.0 mm of	e epitheliu or less4
												0 103	extension ≤	7 mm.	<5 mm with	() T1a	1 Measured	stromal invasion 3.0	0 mm or le
													an extensio	n ≤7 mm		() T1a	2 Measured	stromal invasion mo	ore than 3
												O IB	Clinically vis	sible lesions limited to the ce	rvix uteri or		not more	than 5.0 mm with a	horizonta
													preclinical l	sions greater than stage IA			mm or le	55	
													preclinical le Clinically vi	esions greater than stage IA sible lesions ≤ 4 cm in great	est diameter	() т16	mm or le Clinically	ss visible lesion confine	d to the c
N STATUS (Note 13)												Clinically vis	esions greater than stage IA sible lesions ≤ 4 cm in great sible lesions > 4 cm in great	est diameter est diameter	○ Т1Ь	mm or le Clinically microscop 1 Clinically	ss visible lesion confine vic lesion greater tha visible lesion 4.0 cm	ed to the c in T1a/IA2 or less in
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Page 4 of 4

- 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

- 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



Endocervical Margin

Site of prior cervical cone

Vaginal Cuff Margin



- 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

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

- 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



- 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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DOI: 10.1002/ijgo.12749								
FIGO COMMITTEE REPORT WILEY								
Revised FIGO staging for carcinoma of the cervix uteri *								
Neerja Bhatla ¹ Seija Grenman Alexander B. C	.* Jonathan S. B ⁵ Kanishka Karu Nawaiye ⁹ Jaime	erek ² Mauricio C unaratne ⁶ Sean T. Prat ¹⁰ Rengaswa	uello Fredes ³ Lynette A. Denny ⁴ Kehoe ⁷ Ikuo Konishi ⁸ amy 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

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

- 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

- 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

2

3

4

Stendhal et al grading system, 1980

- Tumor cell population •
- **Tumor-host reaction** ٠
- Score from 8-24 points ٠
- **Time-consuming** ٠
- Not widely accepted

	Parameters used for malignancy point grading. Tumour cell population									
Para-		Points								
meter number		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						

Para-		Points		
number		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

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ORIGINAL ARTICLE - CLINICAL ONCOLOGY



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

Lars-Christian Horn¹ · Anne Katrin Höhn¹ · Bettina Hentschel² · Uta Fischer^{1,3} · Karl Bilek³ · Christine E. Brambs⁴

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

The Journal of Pathology: Clinical Research J Path: Clin Res April 2018; 4: 93–102 Published online 24 January 2018 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/cjp2.95



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

Moritz Jesinghaus^{1,2†}, Johanna Strehl^{3†}, Melanie Boxberg¹, Frido Brühl¹, Adrian Wenzel¹, Björn Konukiewitz¹, Anna M Schlitter^{1,2}, Katja Steiger¹, Arne Warth⁴, Andreas Schnelzer⁵, Marion Kiechle⁵, Matthias W Beckmann⁶, Aurelia Noske¹, Arndt Hartmann³, Grit Mehlhorn⁶, Martin C Koch^{6‡} and Wilko Weichert^{1,2‡}*

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 $- \ge 15 \text{ buds}/10 \text{HPF}$



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

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 Tota	al 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 mm² 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



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Pathologist