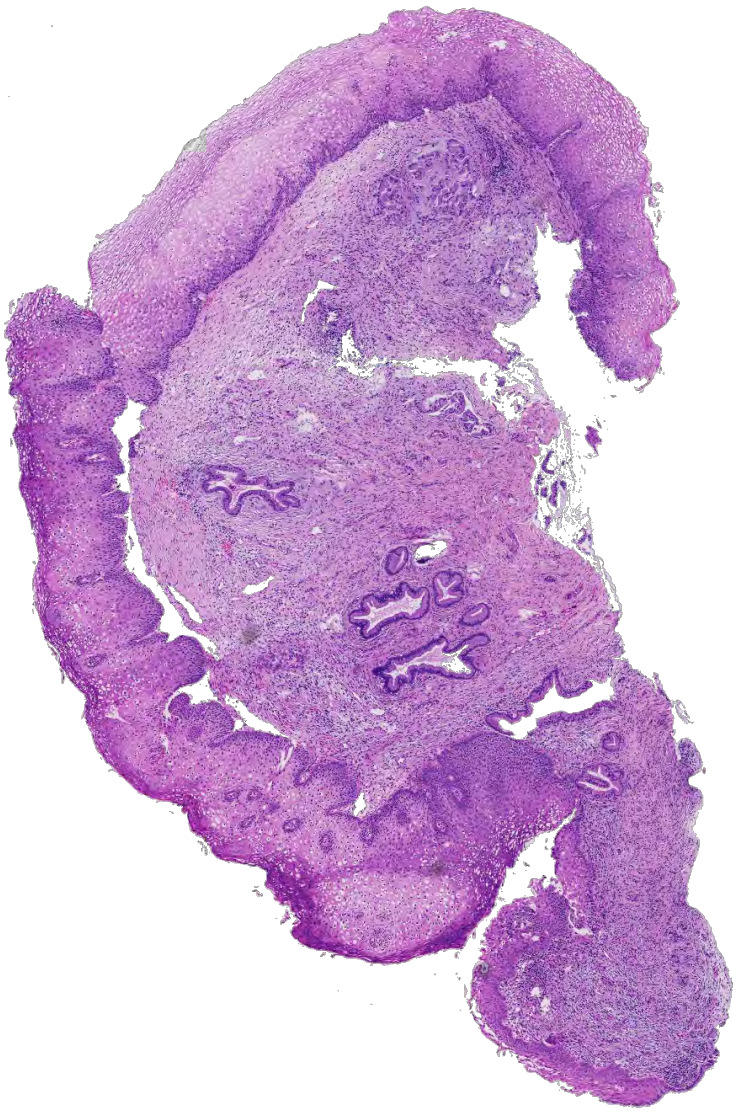
Zora

Državni program zgodnjega odkrivanja
predrakavih sprememb
materničnega vratu

PILOTNA SHEMA ZAGOTAVLJANJA KAKOVOSTI NA PODROČJU CERVIKALNE PATOLOGIJE (SZKP)

Zbornik prispevkov delavnice za patologe in specializante, ki so sodelovali v elektronski shemi zagotavljanja kakovosti



Onkološki inštitut Ljubljana, 27. januar 2018

Prispevke v zborniku uredila: Snježana Frković Grazio

Znanstveni odbor: Snježana Frković Grazio, Margareta Strojan Fležar, Helena Gutnik, Vivijana Snoj, Urška Ivanuš

Organizacijski odbor: Urška Ivanuš, Mojca Florjančič, Tine Jerman, Mojca Kuster, Ana Pogačnik, Blaž Podobnik

PILOTNA SHEMA ZAGOTAVLJANJA KAKOVOSTI NA PODROČJU CERVIKALNE PATOLOGIJE

Delavnica za patologe in specializante, ki so sodelovali v elektronski shemi zagotavljanja kakovosti

27. januar 2018

Onkološki inštitut Ljubljana, predavalnica v stavbi C
Zaloška 2, 1000 Ljubljana

Delavnica poteka pod okriljem Državnega programa ZORA
Znanstveni odbor: Snježana Frković Grazio, Margareta Strojan Fležar, Helena Gutnik, Vivijana Snoj, Urška Ivanuš
Organizacijski odbor: Urška Ivanuš, Mojca Florjančič, Tine Jerman, Mojca Kuster, Ana Pogačnik, Blaž Podobnik

PROGRAM

09.00–09.30 Registracija

09.30–09.45 **Novi izzivi v presejanju za raka materničnega vratu – presoja presejalne politike programa ZORA in prenova informacijskega sistema**
Urška Ivanuš

09.45–10.00 **Shema zagotavljanja kakovosti na področju cervikalne patologije (SZKP)**
Snježana Frković Grazio

10.00–11.30 **Prikaz posameznih primerov iz pilotne SZKP: primeri 1–5**
Margareta Strojan Fležar, Snježana Frković Grazio, Vivijana Snoj, Helena Gutnik

11.30–12.00 Odmor s kavo in prigrizkom

12.00–13.30 **Prikaz posameznih primerov iz pilotne SZKP: primeri 6–10**
Helena Gutnik, Snježana Frković Grazio, Vivijana Snoj, Margareta Strojan Fležar

13.30–14.00 **Razprava o obsegu, načinu in pogostosti izvajanja SZKP**
Moderatorice:Snježana Frkovič Grazio, Margareta Strojan Fležar, Urška Ivanuš

Kazalo

Shema zagotavljanja kakovosti v na področju cervikalne patologije v sklopu programa ZORA - izročki predavanj

Shema zagotavljanja kakovosti v na področju cervikalne patologije (SZKP) 1

Prikaz posameznih primerov iz pilotne SZKP: primeri 1–5 5

Prikaz posameznih primerov iz pilotne SZKP: primeri 6–10 47

Priloge:

Smernice

Smernice za standardizacijo postopkov in histopatoloških izvidov na področju ginekološke patologije – cervikalna neoplazija 71

Smernice ICCR 89

Znanstveni članek

The Lower Anogenital Squamous Terminology Standardization Project for HPV-Associated Lesions 125

Prispevki 7. izobraževalnega dneva programa ZORA, 17. maj 2017

Novi izzivi v presejanju za raka materničnega vratu: izhodišča za prenovo presejalne politike DP ZORA 159

Nove funkcionalnosti prenovljenega informacijskega sistema DP ZORA 167

Presejalni register DP ZORA danes 173

Shema zagotavljanja kakovosti v na področju cervikalne patologije v sklopu programa ZORA

- namen je ugotoviti, kakšna je skladnost med patologi pri postavljanju histopatoloških diagnoz na področju ginekološke patologije
- prispevati k standardizaciji diagnostike na področju cervikalne patologije
- k sodelovanju so povabljeni vsi patologi (in specializanti patologije), ki pregledujejo tkivne vzorce maternicnega vratu.

	Število izvidov v 2016 brez histerektomij
Lab 1	1.955
Lab 2	1.869
Lab 3	1.141
Lab 4	694
Lab 5	582
Lab 6	514
Lab 7	453
Lab 8	444
Lab 9	166
Lab 10	142
Lab 11	42

Shema zagotavljanja kakovosti v na področju cervikalne patologije v sklopu programa ZORA

- članice strokovne skupine za histopatologijo (SSP) v programu ZORA so pripravile histološke preparate
- digitalizacija in priprava sheme v elektronski obliki na spletni strani Zore
- zaradi lažje primerljivosti rezultatov smo diagnoze standardizirali v osem osnovnih diagnostičnih kategorij
- z analizo anonimiziranih odgovorov poskusimo ugotoviti, ali se diagnostični kriterij med patologi v Sloveniji razlikujejo
- na ta način pa ugotoviti, na katerih področjih so morda potrebna dodatna izobraževanja in usklajevanje kriterijev

Shema zagotavljanja kakovosti v na področju cervikalne patologije v sklopu programa ZORA

- po zaključku diagnostičnega dela sheme organiziramo delavnico
- v sklopu delavnice bomo:
  - predstavili primere in preliminarne rezultate sheme
  - skupaj pregledali preparate, komentirali razhajanja v diagnozah oz. diagnostičnih kriterijih
  - se pogovorili o diferencialnih diagnozah in uporabi morebitnih dodatnih metod (IHK ipd)
  - dokončno zaključili diagnoze – določimo osnovno diagnostično kategorijo, v primerih, ko je to potrebno, natančnejšo opredelitev
  - se pogovorili o novostih na področju cervikalne patologije

Shema zagotavljanja kakovosti v na področju cervikalne patologije v sklopu programa ZORA

- po delavnici bo RZ v sodelovanju s članicami SSP pripravil e-poročilo o rezultatih SZKP, upoštevajoč morebitne dopolnitve in sklepe s skupne delavnice
- anonimizirano e-poročilo objavimo na spletni strani DP ZORA
- posameznemu sodelujočemu bo na voljo personalizirano poročilo
- po pripravi zaključnega poročila se bo na spletni strani SZKP ob vsakem primeru aktivirala tudi zaključna diagnoza

Shema zagotavljanja kakovosti na področju cervikalne patologije

Povabljeno:
- 29 specialistov patologov (25 aktivno dela)
-18 specializantov patologije

Sodelovalo:
-23 patologov
-7 specializantov

Diagnostične kategorije

- PIL-NS
- PIL-VS / CIN 2
- PIL-VS / CIN 3
- AIS
- invazivni ploščatocelični karcinom
- invazivni adenokarcinom cerviksa
- drugo benigno
- drugo maligno

»Diagnoza« (obvezno polje pri vseh – ena kategorija)

»Natančnejša opredelitev« (obvezno le pri kategorijah 5,6,7,8)

1. PIL-NS
2. PIL-VS / CIN 2
3. PIL-VS / CIN 3
4. AIS
5. invazivni ploščatocelični karcinom
6. invazivni adenokarcinom
7. drugo benigno
8. drugo maligno

»Natančnejša opredelitev«

- invazivni ploščatocelični karcinom
  - histološki tip, gradus
- invazivni adenokarcinom (primarni cerviksa)
  - histološki tip, gradus
- drugo benigno
  - natančnejša diagnoza (npr. mikroglandularna hiperplazija, mezonefrična hiperplazija, atrofija ...)*
- drugo maligno
  - natančnejša diagnoza (npr. infiltracija cerviksa s kolorektalnim adenokarcinomom, maligni melanom...)*

* *pri drugo maligno ali drugo benigno - v to polje naj bi vpisali le eno (najbolj verjetno) natančnejšo diagnozo, ostale pa pod diferencialno diagnozo*

»Diferencialna diagnoza« (ni obvezno polje)

- največkrat izpolnimo le pri istih diagnostičnih kategorijah, pri katerih je obvezno izpolniti polje natančnejša opredelitev
- tudi pri ostalih diagnostičnih kategorijah, pri katerih ne bomo povsem prepričani v diagnozo
- v teh primerih naj bi bilo večinoma izpolnjeno tudi polje "komentar"

»Komentar« (ni obvezno polje)

- komentar glede primernosti in/ali tehnične kakovosti izbranega histološkega preparata
- potrebe po dodatnih metodah (IHK, HK...) in kako bi rezultati opravljenih dodatnih preiskav lahko vplivali na vašo diagnozo

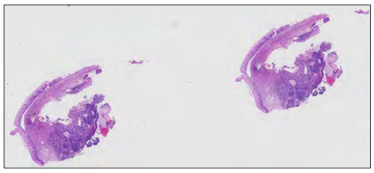
Končne pripombe / pohvale / predlogi

(le 1/3 sodelujočih)

☺ Hvala za poslane poučne primere .Odlična aplikacija. Lepi preparati.
☺ Hvala za vaš trud in zanimive in koristne primere. Se veselim povratnih informacij in delavnice. Lep pozdrav
☺ Hvale vredna ideja za ugotovitev skladnosti in razlik med subjektivnimi detajli pri diagnostiki.
☺ Odlično
☺ Pohvala organizatorju !
☺ User friendly, hitro odzivno, enostavno za uporabo, koristno.
☺ Veselim se sodelovanja in možnosti izboljšanja mojega dela.hvala lepa.
☺ Vsem iskrena hvala.
☹ / ☺ Zanimivi primeri. Pohvala za nabor! Kvaliteta preparatov ni optimalna: debele rezine, premočno izražena bazofilija jeder, ni mogoče ocenjevati kvalitete jeder, preveč izrazit kontrat med eozinofilno in bazofilno komponento tkivnih vzorcev. Osebno imel težave pri shranjevanju in odpiranju primerov.
☺ Zelo dobrodošlo! Hvala!!!
☹ / ☺ Zelo zanimivo. Pohvale! Malenkost težav z načinom gledanja, je le drugače kot mikroskop.

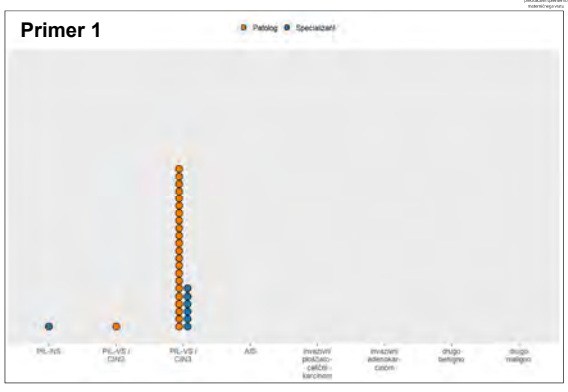
Primer 1

- 35 let stara ženska
- Izvid BMV: APC-VS.
- biopsija porcije



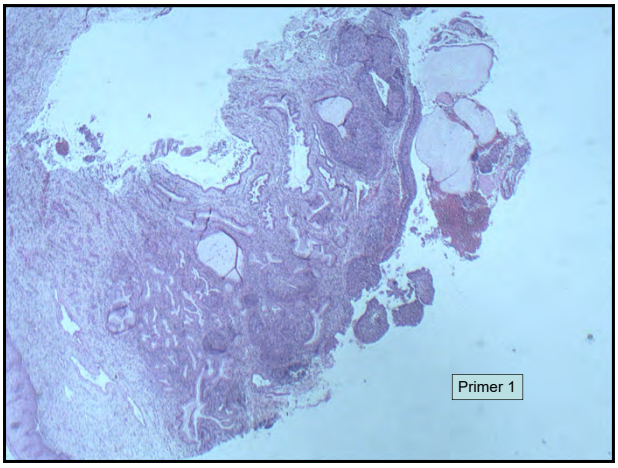
Primer 1

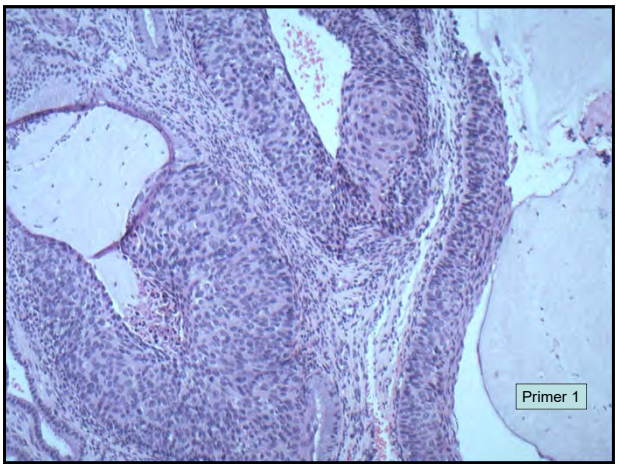
Ploščatocelična intraepitelijska lezija visoke stopnje (PIL-VS / CIN3)



Primer 1

- specialisti
  22/23 PIL-VS / CIN 3
  1/23 PIL-VS / CIN 2
- specializanti
  6/7 PIL-VS / CIN3 - 1x ? invazivna komponenta
  1/7 PIL-NS - dif.dg.CIN2/CIN3 (? p16)





Ploščatocelične intraepitelijske lezije

Klasifikacija, kriteriji ocenjevanja, diferencialna diagnoza in pomen bioloških označevalcev

Helena Gutnik
Margareta Strojan Fležar

CAP in ASCCP - LAST

- **The Lower Anogenital Squamous Terminology Standardization Project for HPV-Associated Lesions:** background and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology

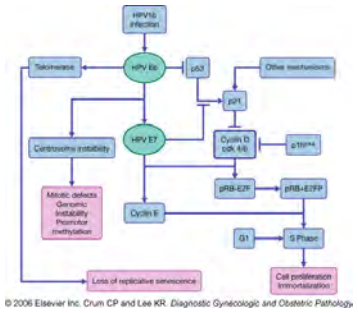
- ***Arch Pathol Lab Med* 2012;136:1-32.**

J Low Genit Tract Dis 2012 Jul;16(3):205-42.
Int J Gynecol Pathol 2013 Jan;32(1):76-115.

HPV

- Kritičen pomen za nastanek rakov sp. anogenitalnega trakta (lower anogenital tract – LAT)
- Interakcija HPV – ploščati epitelij
- **2. prekanceroze** – ekspresija virusnih genov poruši kontrolo diferenciacije epitelija
- ↑ ekspresija virusnih onkogenov→celična proliferacija →klonalna ekspanzija nediferenciranih celic
- Klinika: stalno +test HPV, vztrajajoče kolpo spremembe, napredujejo
- Znatno tveganje za mlg transformacijo
- **Morfološko enake spremembe ne glede na spol ali mesto lezije**

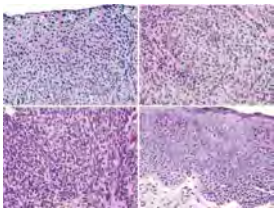
Molekularne osnove cervikalne neoplazije



© 2006 Elsevier Inc. Crum CP and Lee KR. *Diagnostic Gynecologic and Obstetric Pathology*

Terminologija?

- **Morfološko in biološko enake spremembe ne glede na spol ali mesto lezije**
- Različna terminologija s HPV povezanih sprememb v SAT
- Ginekologija, ginekološka patologija
- Dermatologija, dermatopatologija
- Gastropatologija?



Ploščatocelične (skvamozne) intraepitelijske lezije (PIL / SIL)

- Poenotena histopatološka nomenklatura
- Isti diagnostični izrazi za vse preinvazivne skvamozne lezije SAT (angl. LAT)
- **2-stopenjska nomenklatura za neinvazivne s HPV povezane proliferacije ploščatega epitelija v SAT, nadaljna klasifikacija po –IN terminologiji**
- PIL-NS (“LSIL”) in PIL-VS (“HSIL”), subklasifikacija –IN, (cito PIL-NS; PIL-VS)

Ploščatocelične (skvamozne) intraepitelijske lezije (PIL / SIL)

cerviks	CIN
vagina	VaIN
vulva	VIN
anus	AIN
perianus	PAIN
penis	PeIN

WHO klasifikacija (2014)

- Prevzela 2-stopenjsko nomenklauturo za ploščatocelične prekanceroze materničnega vratu (tudi nožnice in vulve):
  - **PIL-NS** (CIN 1, koilocitoza)
  - **-PIL-VS** (CIN 2 in CIN 3)

Benign squamous cell lesions
- Condyloma acuminatum
- Squamous papilloma 8052/0
- Fibroepithelial polyp

WHO – Ploščatocelični tumorji materničnega vratu

Squamous cell carcinoma, not otherwise specified	8070/3
Keratinizing	8071/3
Non-keratinizing	8072/3
Basaloid	8083/3
Verrucous	8051/3
Warty	8051/3
Papillary	8052/3
Lymphoepithelioma-like	8082/3
Squamotransitional	8120/3

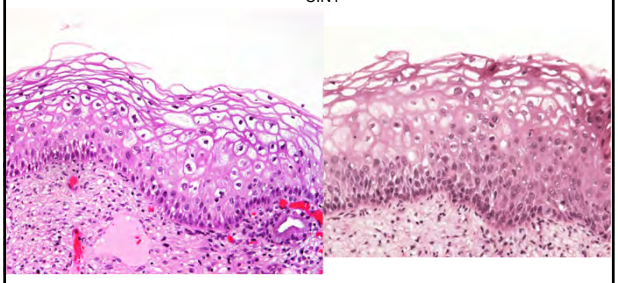
Superficially invasive squamous cell carcinoma – SISCCA (globina do 3 mm, horizontalno do 7 mm, FIGO st. IA1)

Ploščatocelične (skvamozne) intraepitelijske lezije (PIL / SIL)

- Kriteriji morfološke ocene PIL-NS:
  Proliferacija ploščatih ali metaplastičnih celic z **abnormnimi jedrnimi značilnostmi** (jedra in jedrno/CTPL razmerje, nepravilnosti jedrnih membran); **CTPL v spodnji 1/3 epitelija ne dozoreva**, dozorev. se začne v srednji tretjini proti površini; **mitoze so omejene na spodnjo 1/3 epitelija**
  in/ali
  prisoten je citopatski efekt HPV

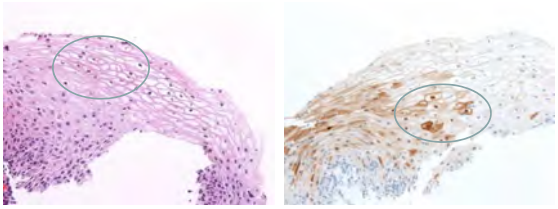
Ploščatocelične (skvamozne) intraepitelijske lezije (PIL / SIL)

CIN1



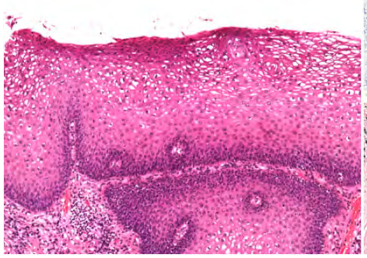
Ploščatocelične (skvamozne) intraepitelijske lezije (PIL / SIL)

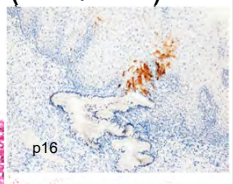
KOILOCITOZA

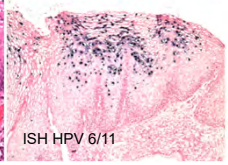


Ploščatocelične (skvamozne) intraepitelijske lezije (PIL / SIL)

DD: Ploščatocelični kondilom





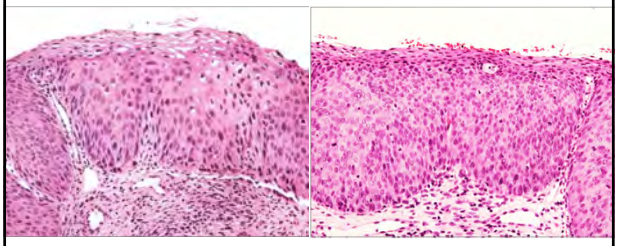


Ploščatocelične (skvamozne) intraepitelijske lezije (PIL / SIL)

- Kriteriji morfološke ocene PIL-VS:
  Proliferacija ploščatih ali metaplastičnih celic z **abnormnimi jedrnimi značilnostmi** (jedra in jedrno/CTPL razmerje, nepravilnosti j. membran); **CTPL ne dozoreva**, ali le nakazano dozorev. v srednji in zgornji 1/3; **mitoze v celotni debelini epitelija lahko prisoten citopatski efekt HPV**
- Razlika med CIN2 IN CIN3: pri CIN2 ohranjeno dozorevanje v povrhnjem delu, pogostejši citopatski efekt HPV,mitoze niso v zgornji 1/3; „metaplastični tip PIL-VS“, ponavadi ocenjen kot CIN2, pomen bioloških označevalcev!

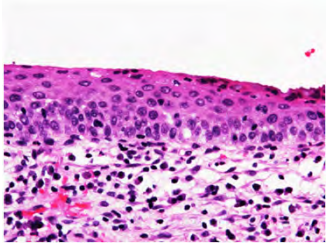
Ploščatocelične (skvamozne) intraepitelijske lezije (PIL / SIL)

CIN2 CIN3



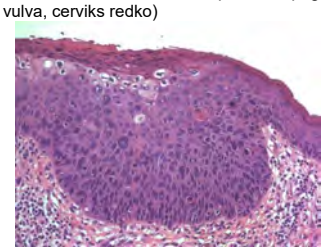
Ploščatocelične (skvamozne) intraepitelijske lezije (PIL / SIL)

- Variante PIL-VS:
- Tanek PIL (manj kot 10 slojev celic + proliferacija atip. bazaloidnih celic + mitoze nad bazalnim slojem)



Ploščatocelične (skvamozne) intraepitelijske lezije (PIL / SIL)

- Variante PIL-VS:
- Poroženevajoči PIL (vsi kriteriji PIL-VS + poroženevanje na površini + diskeratotične celice + eozinofilna citoplazma – pogosteje analna sluznica in vulva, cerviks redko)



Biološki označevalci

- **P16**
- Ki-67, ProExC
- **enako* priporočilo za vse lokalizacije za vse spremembe povezane s HPV v spodnjem anogenitalnem traktu**

- *priporočila niso za spremembe, ki niso povezane s HPV – npr. diferenciran VIN

Biološki označevalci

- **p16**
- Priporočilo za uporabo:
- DD: predrakave spremembe PIL-VS (-IN2 ali –IN3) in **posnemovalci** (nezrela ploščatocelična metaplazija, atrofija, tranzicioncelularna metaplazija, reparativne/vnetne spremembe, tangencialno rezanje)
- za razrešitev primerov, sumljivih za predrakave spr (-IN 2 ali – IN3), če se **ocena različnih patologov ne ujema**
- -IN 2 v HE: **biološko dvoumne, med morfološko sliko HPV infekcije (spr nizke stopnje) in predrakavimi spremembami** (močna difuzna pozitivna reakcija v "bloku" = predrakava sprememba; negativna ali neenakomerna/lisasata = spr nizke stopnje ali patologija, ki ni povezana s HPV)

Biološki označevalci

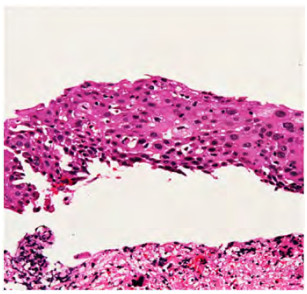
- p16
- Priporočilo za uporabo:
- p16 naj se **ne uporablja rutinsko** v histopatološki diagnostiki, če je morfološka slika jasna
- IZJEMA: p16 naj se uporablja v histopatološki diagnostiki, če je morfološka slika ≤ -IN 1, vendar obstaja **znatno tveganje za spregledano spremembo visoke stopnje**
- definirano kot prejšnja CITOLOŠKA OCENA: PIL-VS, APC-VS, APC-N/HPV16+, AŽC-N

Biološki označevalci

- p16
- Priporočilo za uporabo:
- DD: predrakave spremembe PIL-VS (-IN2 ali –IN3) in **posnemovalci**
- Nezrela ploščatocelična metaplazija
- Atrofija, tranziciocelularna metaplazija
- Reparativne spremembe
- Tangencialno rezanje

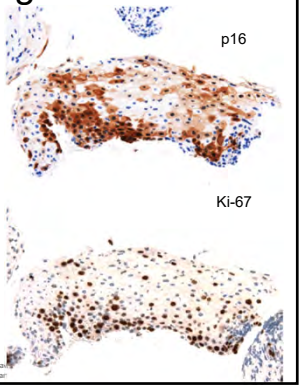
Diferencialna diagnoza PIL/SIL

Ploščatocelična metaplazija

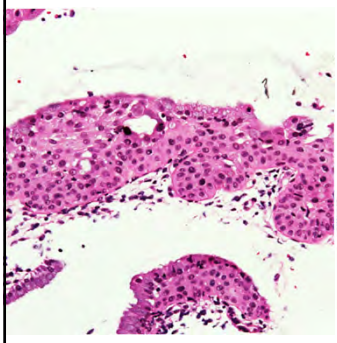


p16

Ki-67



Diferencialna diagnoza PIL/SIL



Ploščatocelična metaplazija

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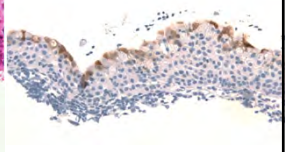
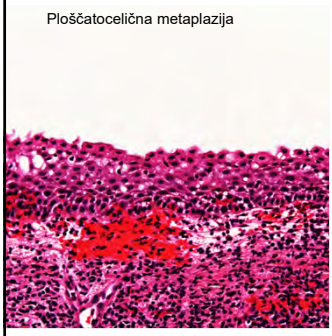


Diferencialna diagnoza PIL/SIL

Ploščatocelična metaplazija



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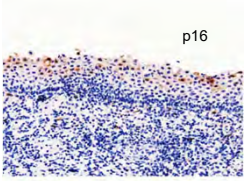

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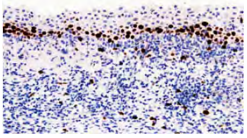
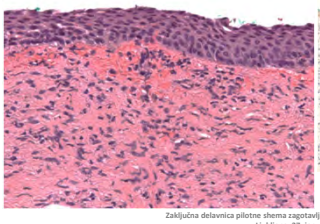


Diferencialna diagnoza PIL/SIL

Atrofija ploščatega epitelija



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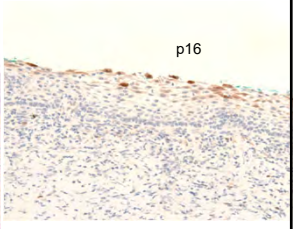
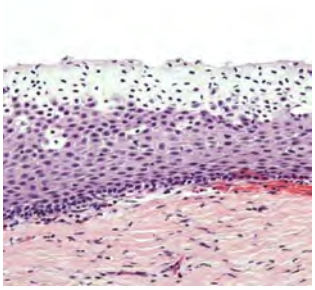


Diferencialna diagnoza PIL/SIL

Atrofija ploščatega epitelija



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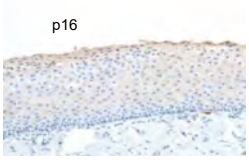

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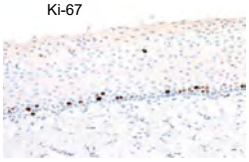
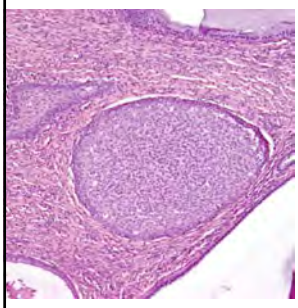
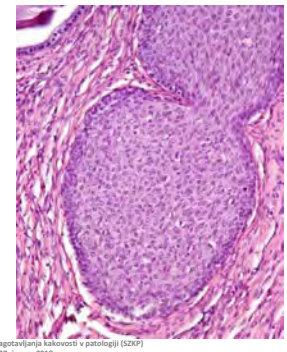


Diferencialna diagnoza PIL/SIL

Tranziciocelularna metaplazija

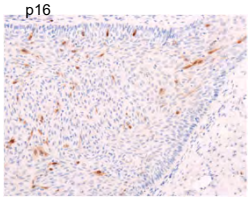




Diferencialna diagnoza PIL/SIL

Tranziciocelularna metaplazija

p16



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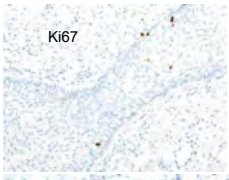

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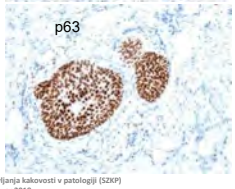
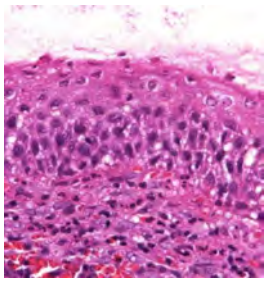
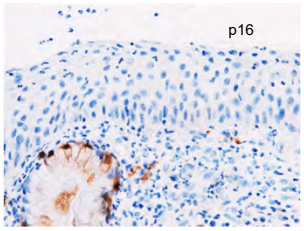


Diferencialna diagnoza PIL/SIL

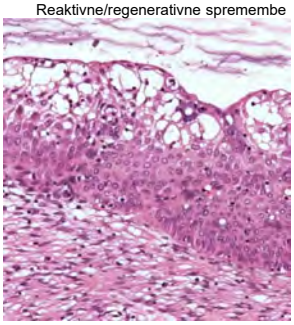
Reaktivne/regenerativne spremembe

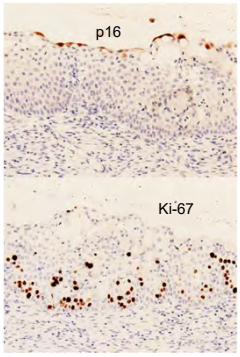




Diferencialna diagnoza PIL/SIL

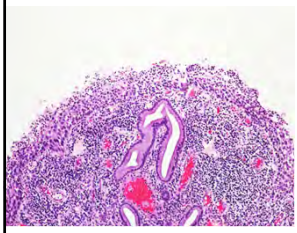
Reaktivne/regenerativne spremembe

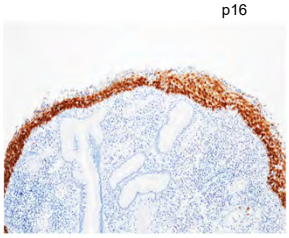




Diferencialna diagnoza PIL/SIL

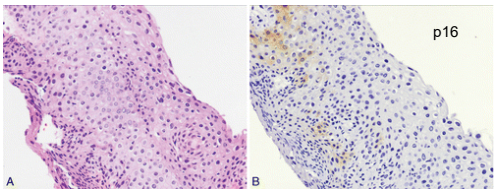
PIL VS + vnetje



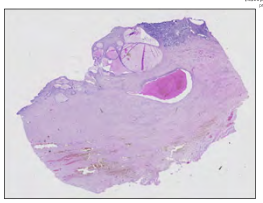


Diferencialna diagnoza PIL/SIL

Tangencialno rezanje



Primer 2



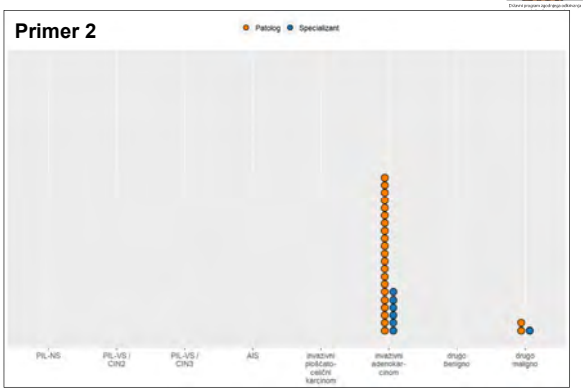
- 45 let stara ženska
- izvid BMV: normalen (eno leto pred histerektomijo)
- desnostranska adneksektomija zaradi atipičnega proliferativnega mucinoznega tumorja jajčnika (januar 2011)
- abrazija maternične votline zaradi metroragije – diagnoza adenokarcinom, endometrioidnega tipa (marec 2011)
- histerektomija z levostransko adneksektomijo, pelvično disekcijo bezgavk in omentektomijo (april 2011)
- za SZKP preparat vzorca stene cerviksa iz resektata maternice

Primer 2

- največji horizontalni premer tumorja v cerviksu 2,2cm, največja globina invazije v cervikalno stromo 1,1 cm
- pod tumorjem še 2 mm nespremenjene cervikalne strome
- ni vraščanja v parametrije / paracervikalna mehka tkiva
- 6 mm radialni rob, 2,5 cm vaginalni rob
- ni PIL-a, nekaj AIS ?
- tumor se po sluznici in le fokalno miometriju širi v spodnji uterini segment
- jajčnik in jajcevod b.p.
- omentum brez infiltratov
- zasevek v eni pelvični bezgavki levo (1/10), velikosti 2,5 mm, brez vraščanja v perinodalno maščevje

Primer 2

Invazivni endocervikalni adenokarcinom, običajni tip



Zaključna delavnica pilotne shema zagotavljanja kakovosti v patologiji (SZKP)
Ljubljana, 27. januar 2018

Primer 2

- specialisti
  - 21/23 invazivni adenokarcinom
  - 2/23 drugo maligno
- specializanti
  - 6/7 invazivni adenokarcinom
  - 1/7 drugo maligno

Zaključna delavnica pilotne shema zagotavljanja kakovosti v patologiji (SZKP)
Ljubljana, 27. januar 2018

Primer 2

Specializanti

- 6/7 invazivni adenokarcinom
  - 4x primarni endocervikalni
  - 1x serozni karcinom HG
  - 1x invazija karcinoma endometrija
- 1/7 drugo maligno
  - IHK – ?endocervikalni, ?karcinom endometrija, ? serozni karcinom

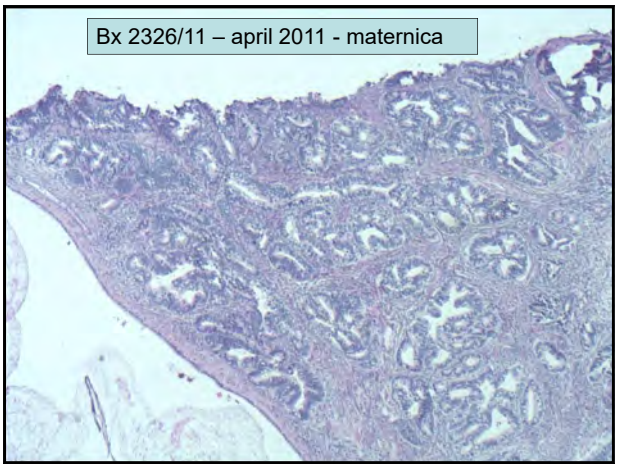
Primer 2 - specialisti

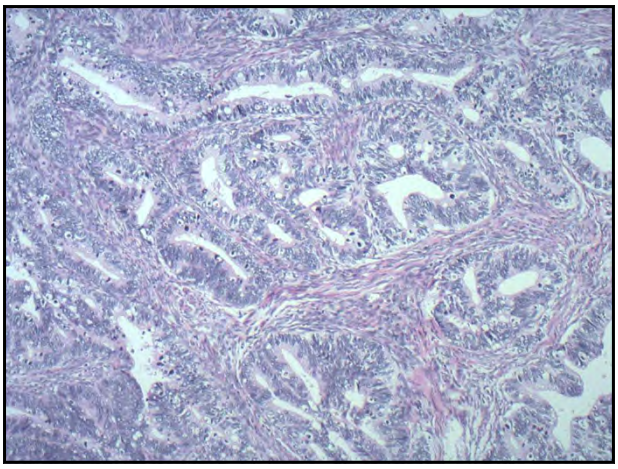
- 21 invazivni adenokarcinom
  - 10x endocervikalni tip 10 x (3 IHK ?) (5 G1, 5x ni G)
  - 3x primarni cerviksa, brez tipa (1 G1, 2 ni G)
  - 8x endometrioidni karcinom (pri 3 verjetno ca. endometrija)
- 2 drugo maligno – oba endometrioidni ca. endometrija

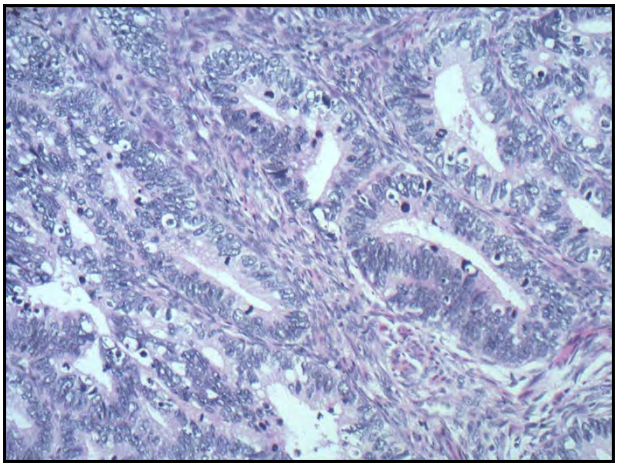
➢ 8 rabi IHK (dif. dg. endometrij /endocerviks)

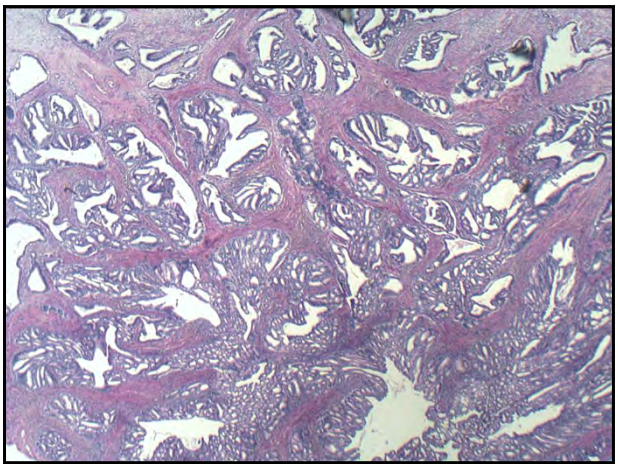
➢ 1 bi primerjal tumor jajčnika

➢ 1 dif.dg. zasevek seroznega karcinoma jajčnika



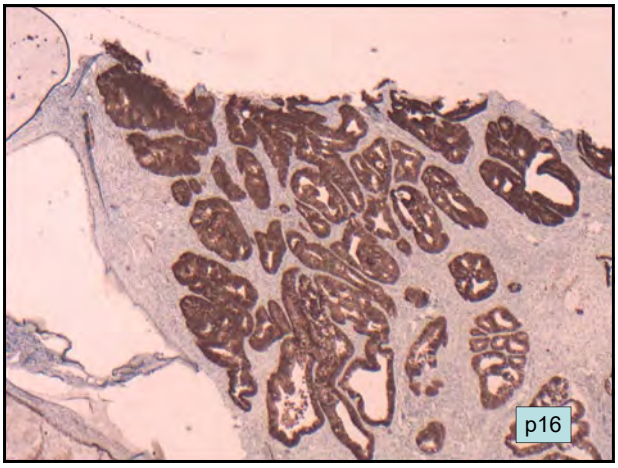


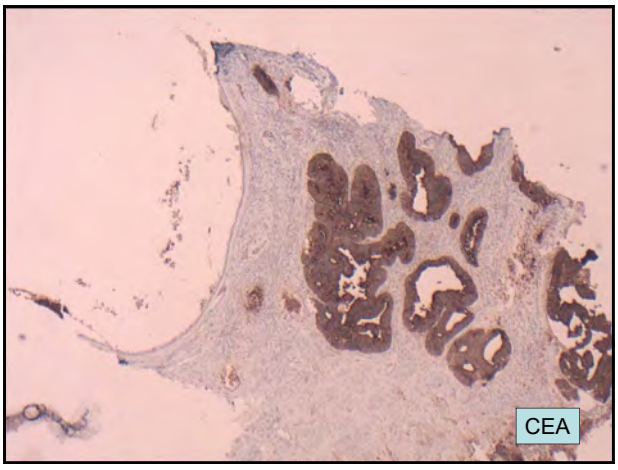


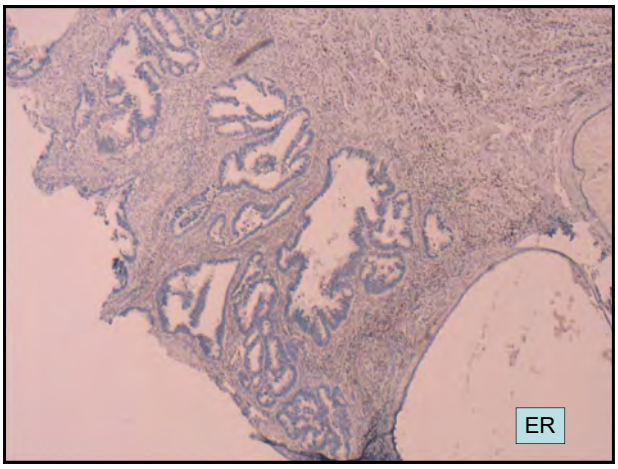


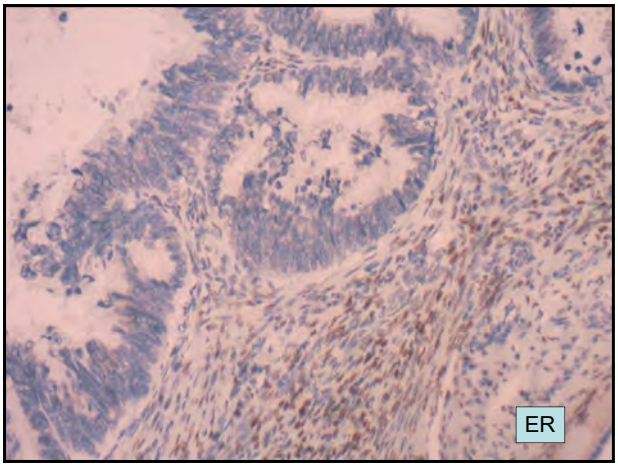
Diferencialna diagnoza

- endometrioidni karcinom – primarni, vraščanje iz korpusa ?






ER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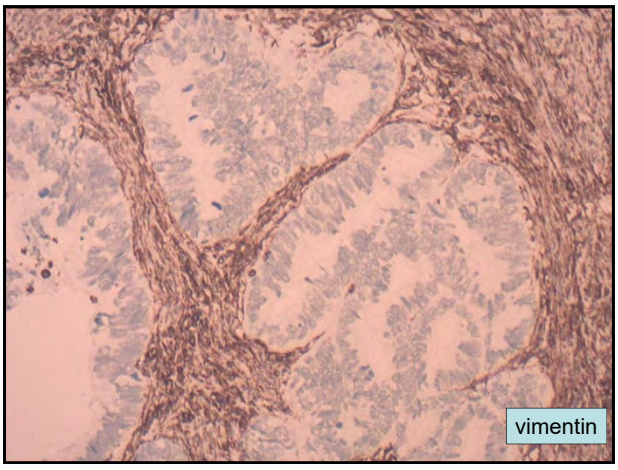
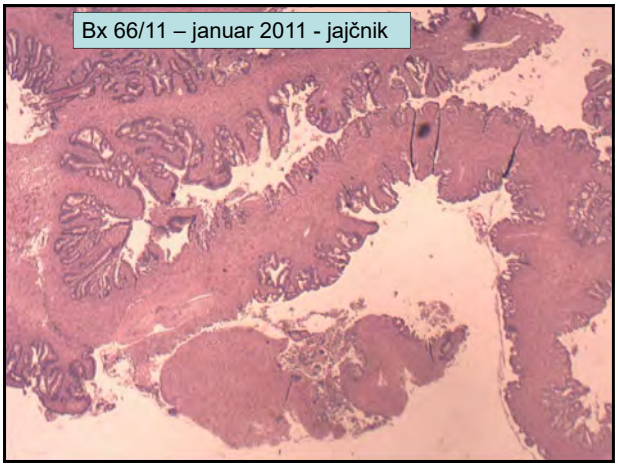
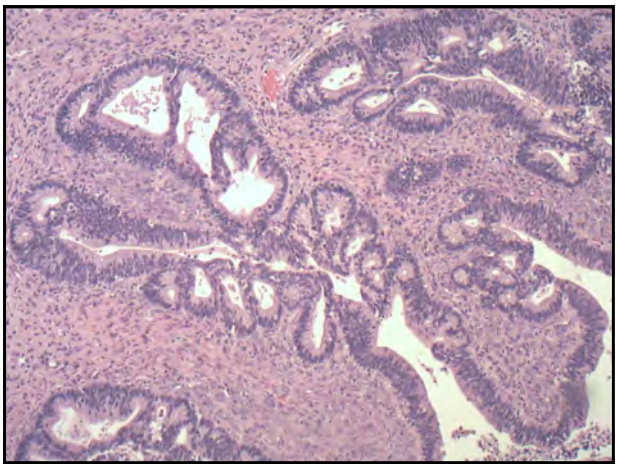
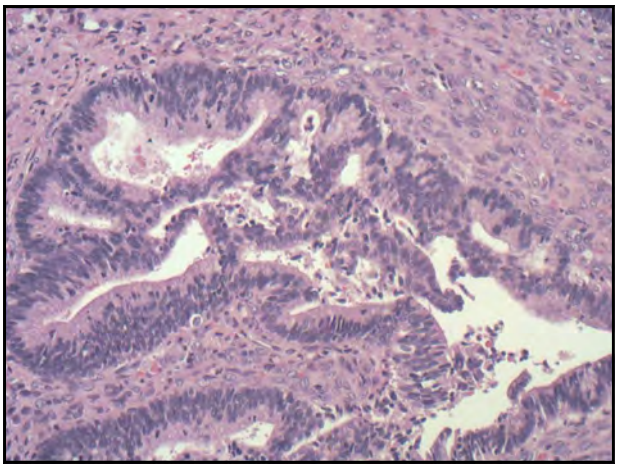

vimentin

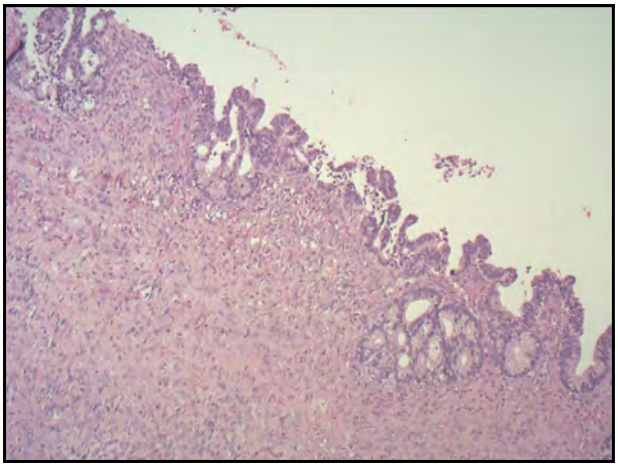
Primer 2

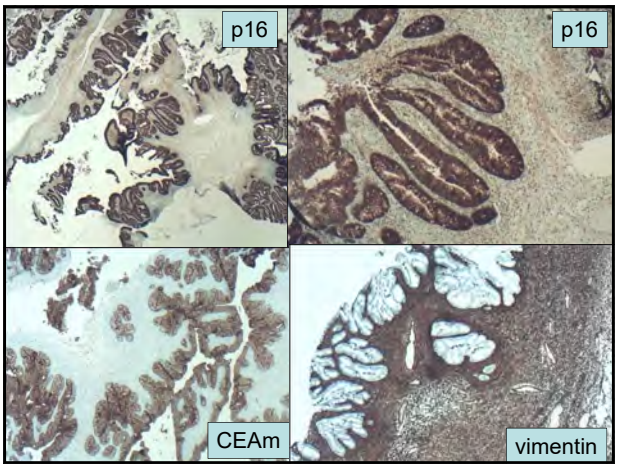
Revizija preparatov tumorja jajčnika (opravljena pred delavnico, decembra 2017)










p16
p16
CEAm
vimentin

Metastatski adenokarcinom cerviksa

follow-up
- april 2012 karcinoza peritoneja
- januarja 2014 je bolnica umrla

Adenokarcinom cerviksa

- večina adenokarcinomov običajnega tipa (>90%) s HPV povezanih (p16 +)
- pri AIS sinhroni PIL v cca 50% primerov
- incidenca narašča
- trenutno 15-25 % vseh rakov materničnega vratu v razvitih državah (v preteklosti le 5-10%)
- povprečna starost ob diagnozi 50 let
- porast incidence pri mlajših ženskah (nerodnice, prvorodnice), sicer zaželjena ohranitev plodnosti

Adenokarcinom cerviksa

- običajno zaseva v pelvične bezgavke in/ali se kontinuirano širi v okolna tkiva v pelvisu
- redko zaseva v jajčnik
- večina primerov sinhronih / metahronih tumorjev v jajčniku in cerviksu je bila do pred kratkim diagnosticiranih kot dva neodvisna tumorja

TNM category	FIGO stage	Definition
T1	I	Cervical carcinoma confined to the uterus (extension to the corpus should be disregarded)
T1a	IA	Invasive carcinoma, diagnosed only by microscopy, with deepest invasion ≤ 5.0 mm and largest extension ≤ 7.0 mm.
T1a1	IA1	Measured stromal invasion ≤ 3.0 mm and ≤ 7.0 mm
T1a2	IA2	Measured stromal invasion of > 3.0 mm and not > 5.0 mm with an extension of not >7.0 mm
T1b	IB	Clinically visible lesion limited to the cervix uteri or pre-clinical cancers greater than stage IA*
T1b1 T1b2	IB1 IB2	Clinically visible lesion ≤ 4.0 cm in greatest dimension Clinically visible lesion > 4.0 cm in greatest dimension
T2	II	Cervical carcinoma invades beyond the uterus but not to the pelvic wall or to lower third of the vagina
T2a	IIA	Without parametrial invasion
T2a1 T2a2	IIA1 IIA2	Clinically visible lesion ≤ 4.0 cm in greatest dimension Clinically visible lesion > 4.0 cm in greatest dimension
T2b	IIB	With obvious parametrial invasion
T3	III	The tumour extends to the pelvic wall and/or involves lower third of the vagina, and/or causes hydronephrosis or non-functioning kidney**
T3a	IIIA	Tumour involves lower third of vagina, with no extension to the pelvic wall
T3b	IIIB	Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney
T4	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 allocated to stage IV.
T4a	IVA	Spread of growth to adjacent organs
M1	IVB	Spread to distant organs

Adenokarcinom cerviksa

- 5-letno preživetje skoraj enako kot pri ploščatoceličnemu karcinomu
- vsi stadiji 77%
  - 100% (IA1), 93% (IA2), 89% (IB1), 83% (IB2)
  - 49% (II),34% (III), 3% (IV)
- pomen histološkega tipa vprašljiv, razen gastričnega tipa mucinoznega karcinoma, ki ima slabšo prognozo (5-letno preživetje 30% za vse stadije), bolj pogosto diagnosticiran v višjem stadiju (ni ga mogoče diagnosticirati v brisu)
- gradus ni napovedni dejavnik

WHO 2014

Glandular tumours and precursors	
Adenocarcinoma in situ	8140/2
Adenocarcinoma	8140/3
Endocervical adenocarcinoma, usual type	8140/3
Mucinous carcinoma, NOS	8480/3
Gastric type	8482/3
Intestinal type	8144/3
Signet-ring cell type	8490/3
Villoglandular carcinoma	8263/3
Endometrioid carcinoma	8380/3
Clear cell carcinoma	8310/3
Serous carcinoma	8441/3
Mesonephric carcinoma	9110/3
Adenocarcinoma admixed with neuroendocrine carcinoma	8574/3

Endometrioid carcinoma of the cervix – WHO 2014

Etiology

When these tumours are morphological variants of usual type adenocarcinomas they are associated with high-risk HPV. Rare tumours thought to arise from cervical endometriosis are not associated with high-risk HPV.

Serous carcinoma of the cervix – WHO 2014

Epidemiology

Serous carcinoma of the cervix is exceedingly rare. Tumours with this morphology that occur in young patients are most often associated with HPV and represent "serous-like" usual type adenocarcinomas {778}, while older patients have tumours with mutant p53 expression akin to their endometrial and adnexal counterparts {1362}.

Viloglandular carcinoma of the cervix – WHO 2014

Prognosis and predictive factors

When superficially invasive, this variant is only rarely associated with lymph node metastasis and has an excellent prognosis. However, some recent reports suggest that these tumours can be aggressive. Therefore, conservative management has been suggested as appropriate only in superficial lesions of pure viloglandular morphology, without high-grade atypia and with no lymphovascular invasion

Histološki gradus EAC ???

Carcinoma of the Cervix
Histopathology Reporting Guide

http://www.iccr-cancer.org/getattachment/Datasets/Published-Datasets/Female-Reproductive-Organs/Cervical-carcinoma/ICCR-cervix-bookmarked-guide-1st-edition-v0-10-with-notes.pdf

Grading of cervical carcinoma

Tumour grade is regularly included in histopathology reports of cervical squamous cell carcinoma (SCC) and adenocarcinoma (ACA). However, at present no particular grading system(s) has achieved universal acceptance and grading of these tumours remains of uncertain clinical value.[40-42] For example, grade is not amongst the factors considered in determining the Gynecology Oncology Group (GOG) score which is used to assess the need for adjuvant therapy following surgery for low-stage cervical carcinomas.[43] Not uncommonly, studies that assess grade as a potential prognostic variable provide no details of the grading system employed, and this is also true of large multicentre investigations such as SEER analyses.[44,45] For these and other reasons (discussed below), tumour grading is not listed as a required but rather a recommended element. Furthermore, no particular grading system for squamous carcinoma or adenocarcinoma is recommended.

Invasive endocervical adenocarcinoma: proposal for a new pattern-based classification system with significant clinical implications: a multi-institutional study, ***Int J Gynecol Pathol 2013; 32 (6):592-601***

"Silva system" (pattern classification)

Pattern A
– Well-demarcated glands with rounded contours, usually forming groups
– No destructive stromal invasion
– No single cells or cell detachment
– No lymphovascular invasion
– Complex intraglandular growth acceptable (cribriform, papillae)
– Lack of solid growth (well-moderately differentiated)
– Irrelevant depth of the tumor or relationship to large cervical vessels

Pattern B
– Localized (limited, early) destructive stromal invasion arising from pattern A glands (well-demarcated glands)
– Individual or small groups of tumor cells, separated from pattern A-type glands, frequently in desmoplastic or inflamed stroma
– Single, multiple, or linear foci at base of tumor
– Lymphovascular invasion (present/absent)
– Lack of solid growth (well-moderately differentiated)

Pattern C
– Diffuse destructive stromal invasion, characterized by: diffusely infiltrative glands, with associated extensive desmoplastic response and glands often angulated or with canalicular pattern, with interspersed open glands
– Confluent growth filling a 4× field (5 mm): glands, papillae (stroma only within papillae), or mucin lakes
– Solid, poorly differentiated component (architecturally high grade); nuclear grade is disregarded
– Lymphovascular invasion (present/absent)

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Ljubljana, 27. januar 2018

TABLE 3. Comparison of Histologic Features Between Patterns A and C

	Pattern A	Pattern C
Diffuse desmoplasia	No	Yes
Gland contours	Round	Angulated
Interspersed open glands*	No	Yes
Cluster or groups of glands	Yes	No
Canalicular pattern†	No	Yes

*Open glands (incomplete glandular structures) describe glands with a discontinuous contour showing a break opening to the stroma, often associated with loosened stroma and/or inflammatory cells.
†Canalicular pattern means labyrinthine, interconnected glands.

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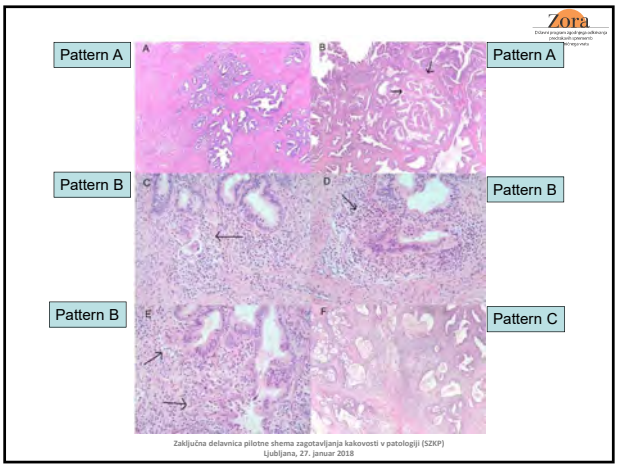
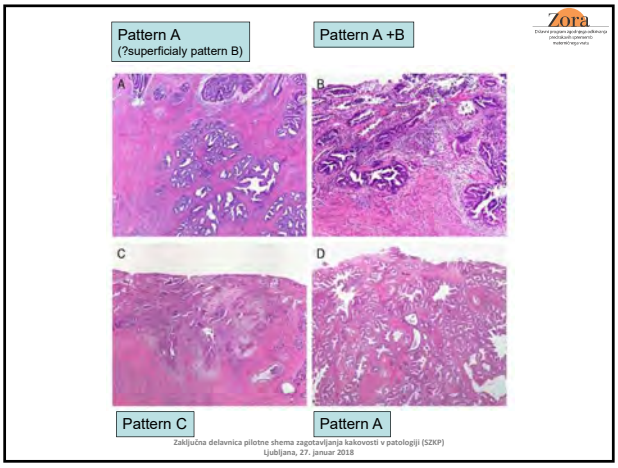
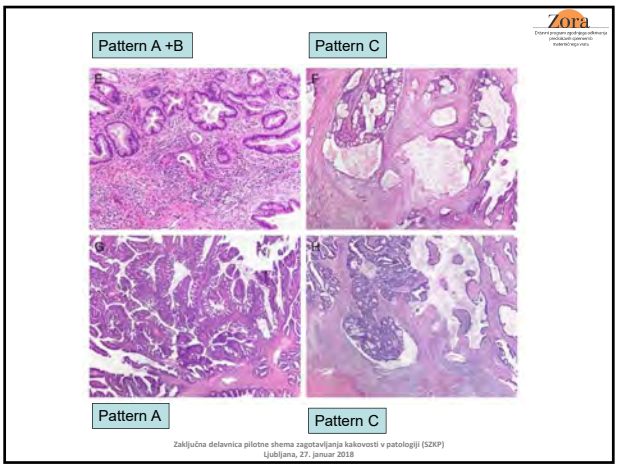

Pattern A
Pattern A
Pattern B
Pattern B
Pattern B
Pattern C
Zaključna delavnica pilotne shema zagotavljanja kakovosti v patologiji (SZKP)
Ljubljana, 27. januar 2018


Pattern A
(?superficialy pattern B)
Pattern A +B
Pattern C
Pattern A
Zaključna delavnica pilotne shema zagotavljanja kakovosti v patologiji (SZKP)
Ljubljana, 27. januar 2018


Pattern A +B
Pattern C
Pattern A
Pattern C
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Invasive Endocervical Adenocarcinoma

A New Pattern-based Classification System With Important Clinical Significance

Andres A. Roma, MD, Andrea Díaz De Vivar, MD,† Kay J. Park, MD,‡ Isabel Alvarado-Cabrero, MD,§ Golnar Rasty, MD,‖ Jose G. Chanona-Vilchis, MD,¶ Yoshiki Mikami, MD,# Sung R. Hong, MD,** Norihiro Teramoto, MD,†† Rouba Ali-Fehmi, MD,‡‡ Joanne K.L. Rutgers, MD,§§ Denise Barbuto, MD,§§ and Elvio G. Silva, MD§§‖‖*

act: A new 3-tier pattern-based system to classify endo- al adenocarcinoma was recently presented. In short, pat- A tumors were characterized by well-demarcated glands ntly forming clusters or groups with relative lobular ar- ture. Pattern B tumors demonstrated localized destructive on defined as desmoplastic stroma surrounding glands irregular and/or ill-defined borders or incomplete glands LNs, and sentinel LN examination could potentially identify these patients. Aggressive treatment is justified in patients with pattern C tumors.

Key Words: invasive endocervical adenocarcinoma, new pattern-based classification system, lymph node metastasis

(*Am J Surg Pathol* 2015;39:667–672)

Gynecol Oncol. 2016 April ; 141(1): 36–42. doi:10.1016/j.ygyno.2016.02.028.

New Pattern-Based Personalized Risk Stratification for Endocervical Adenocarcinoma with Important Clinical Implications and Surgical Outcome

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Outcome data comparing the standard method of tumor evaluation (depth of invasion) versus the newly proposed pattern-based system

	Patients	Patients with metastatic LN	# metastatic LNs	Stage I	Stage II–IV
Standard	352	49 (14%)	83 (1%)	320 (91%)	32 (9%)
Pattern A	73 (20.7%)	0	0	73 (100%)	0
Pattern B	90 (25.6%)	4 (4.4%)	5 (0.2%)	90 (100%)	0
Pattern C	189 (53.7%)	45 (24%)	76 (1.7%)	157 (83%)	32 (17%)

Cherie Paquette, MD, MS, Susanne K. Jeffus, MD,† Charles M. Quick, MD,† Mark R. Conaway, PhD,‡ Mark H. Stoler, MD,* and Kristen A. Atkins, MD**

Abstract: A histologic pattern-based system of risk stratification for endocervical adenocarcinoma has been recently proposed on the basis of tumor-stroma interface and lymph-vascular invasion. The key utility of the system lies in separating cases with very low risk for nodal metastases (pattern A) from those with higher risk (patterns B and C), which may alter the treatment approach. In this study, we determine the reproducibility of applying this system among gynecologic pathologists from 2 institutions using blinded review of 49 adenocarcinomas from 2005 to 2013. κ values and pairwise differences are calculated for the proposed 3-tier system (patterns A, B, and C) as well as a modified version comparing pattern A versus patterns B and C combined (2-tier system). Consensus diagnosis for the 3-tier system is reached in 80% of cases, with majority of κ values indicating fair to almost perfect agreement (range, 0.24 to 0.84). When condensed to 2 tiers, consensus is reached in 81.3% of cases with κ values showing modest improvement (range, 0.33 to 0.92). Pairwise difference analysis reveals diagnosis trends for specific pathologists on the 3-tier system that decrease with 2 tiers. Interpretive variability may be of practical significance in application of the proposed 3-tier pattern–based approach to endocervical adenocarcinoma. Additional studies with larger patient cohorts are needed to confirm the negligible risk for lymph node involvement seen in pattern A patients and to further evaluate the applicability of this new classification system.

Key Words: endocervical adenocarcinoma, observer variation, cervical intraepithelial neoplasia

(*Am J Surg Pathol* 2015;39:93–100)

Endocervical adenocarcinoma represents approximately 10% of cervical carcinomas worldwide, a category dominated by squamous cell carcinoma.[1] In most grading, staging, and treatment guidelines, squamous cell carcinoma and adenocarcinoma are grouped together without strong evidence that they act in a biologically similar manner.[2–6] A key challenge with cervical cancer is determining which patients require lymph node treatment versus those who may be spared the morbidity of these procedures. For most of the world, treatment algorithms are based on the FIGO (International Federation of Gynecology and Obstetrics) staging system based primarily on clinical impression, microscopic size, and disease involvement of other sites.[7] Prognostic factors not included in the FIGO staging include histologic subtype, grade, and presence of lymph-vascular invasion (LVI). Early invasive carcinoma corresponds to FIGO Stage IA1 (< 3 mm in depth) or a combination of FIGO IA1 and IA2 (< 5 mm in depth) and carries a very favorable prognosis (FIGO 1B) also carry a favorable prognosis.[8–11] Baalbergen et al[12] described a 91% 5-year survival in patients without lymph node involvement, compared with 34% for those with lymph node disease (analysis limited to patients with stage I-III disease).

If the risk for nodal disease is low, early invasive cervical carcinoma may be adequately treated by cervical cone, trachelectomy, or simple hysterectomy without lymphadenectomy.[8,7,9,12,14] Separate from evaluation of [illegible] was assessed, as LVI is important as a marker of

Zora

tiers. Interpretive variability may be of practical significance in application of the proposed 3-tier pattern–based approach to endocervical adenocarcinoma. Additional studies with larger patient cohorts are needed to confirm the negligible risk for lymph node involvement seen in pattern A patients and to further evaluate the applicability of this new classification system.

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Pattern Classification of Endocervical Adenocarcinoma: Reproducibility and Review of Criteria

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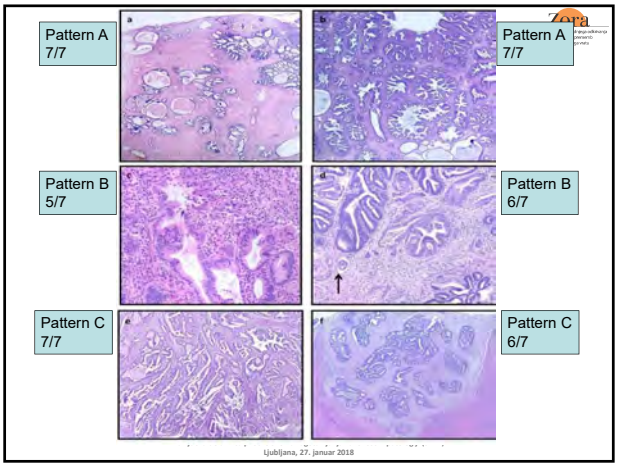
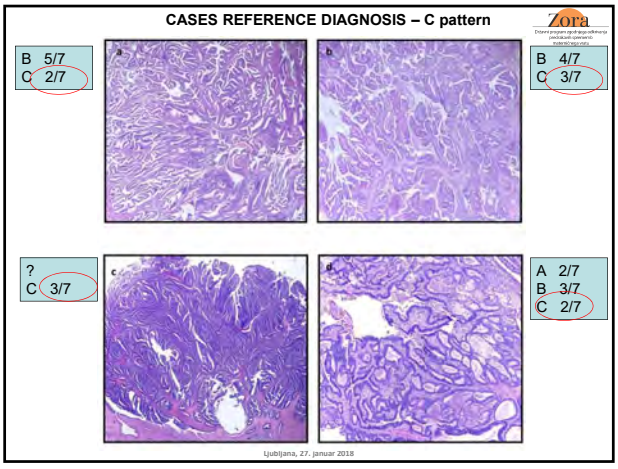
84 cases from the tumor set used in the original study
7 gynecologic pathologist (4 from the original study)

- 24 pattern A , 22 pattern B, 38 pattern C (reference dg)
- complete or near complete agreement in 50%
- overall concordance 74%
- overall kappa 0,49 (moderate agreement)
- further refinement of criteria should allow use of this powerful classification system to delineate which cervical carcinomas can be safely treated consevatively





International Endocervical Adenocarcinoma Criteria and Classification (IECC)

A New Pathogenetic Classification for Invasive Adenocarcinomas of the Endocervix

Simona Stolnicu, MD,* Julia Barsan, MD,* Lien Hoang, MD,† Prabha Patel, MPH,‡ Cristina Terinte, MD,§ Anna Pesci, MD,‖ Sarit Aviel-Ronen, MD,¶ Takako Kiyokawa, MD,# Isabel Alvarado-Cabrero, MD,** Malcolm C. Pike, PhD,‡ Esther Oliva, MD,†† Kay J. Park, MD,‡ and Robert A. Soslow, MD‡

Abstract: We sought to classify endocervical adenocarcinomas (ECAs) based on morphologic features linked to etiology (ie, human papillomavirus [HPV] infection), unlike the World Health Organization 2014 classification. The International Endocervical Adenocarcinoma Criteria and Classification (IECC) criteria), described herein, distinguishes between human papillomavirus–associated adenocarcinoma (HPVA), recognized by the presence of luminal necrosis and apoptosis seen at scanning magnification, and no or limited HPVA features (nonhuman papillomavirus–associated adenocarcinoma (NHPVA)). HPVAs were then subcategorized based on cytoplasmic features (mucin) to provide continuity with preexisting classification schemas), whereas NHPVAs were subclassified based on established criteria (ie, gastric-type, clear cell, etc.). Complete slide sets from 409 cases were collated from 7 institutions worldwide. Tissue microarrays representing 297 cases were constructed; immunohistochemistry (p16, p53, vimentin, progesterone receptor) and chromogenic in situ hybridization using an RNA-based probe set that recognizes 18 varieties of high-risk HPV were performed to validate IECC diagnoses. The 5 most common IECC diagnoses were usual-type (HPVA) (75% of cohort), gastric-type (NHPVA) (10%), mucinous adenocarcinoma of HPV-A type, including intestinal, mucinous not otherwise specified, signet-ring, and invasive stratified mucin-producing carcinoma categories (8%), clear cell carcinoma (NHPVA) (3%) and adenocarcinoma, not otherwise specified (2%). Only 3 endometrioid carcinomas were recognized and all were NHPVA. When excluding cases thought to have suboptimal tissue processing, 90% and 98% of usual-type IECC cases overexpressed p16 and were HPV+, whereas 8% and 3% of NHPVAs were p16+ and HPV+, respectively. The 1 HPV+ gastric-type carcinoma was found to have hybrid HPVA/NHPVA features on secondary review. NHPVA tumors were larger and occurred in significantly older patients compared with HPVA tumors ($P \leq 0.001$). The high-risk HPV chromogenic in situ hybridization probe set had superior sensitivity, specificity, and positive and negative predictive values (0.95, 0.97, 0.99, 0.83, respectively) compared with p16 immunohistochemistry (0.87, 0.63, 0.91, 0.55, respectively) to identify HPV-related uterine carcinoma and mucinous carcinoma. IECC reliably segregates ECAs into HPVA and NHPVA types using morphology alone. This study confirms that usual-type ECAs are the most common type worldwide and that mucinous carcinomas comprise a mixture of HPVA and NHPVA, with gastric-type carcinoma being the major NHPVA type. Endometrioid and serous carcinomas of the endocervix are extraordinarily rare. Should clinical outcomes and genomic studies continue to support these findings, we recommend replacement of the World Health Organization 2014 criteria with the IECC 2017.

Key Words: cervix, endocervical, adenocarcinoma, HPV, classification

Am J Surg Pathol 2018;42:214–226

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Invasive ECAs are classified based on descriptive morphologic characteristics, particularly cytoplasmic features,[4] as assessed on hematoxylin and eosin (H&E)–stained slides. Categorizing ECAs using the WHO 2014 classification has important limitations, as subjective definitions are derived empirically, rather than being linked to clinical or biological features.[4] For example, WHO 2014 defines usual-type ECA as a tumor composed of mucin-poor glands, but criteria to distinguish it from mucinous ECAs with more intracytoplasmic mucin, and the so-called "endometrioid" carcinomas with less intracytoplasmic mucin[4] are obscure. In addition to being mucin-depleted, the so-called "endometrioid" carcinomas are defined as having "endometrioid morphologic features." Similarly vague definitions used in the past led to misclassification of many endometrial and ovarian carcinomas.[14–19] As WHO 2014 maintains heterogenous categories of ECAs that are currently not used in clinical management,[20] we convened an international panel of pathologists to establish a morphologic classification of ECAs, that is linked to etiology, as is commonplace in other organs, including the vulva and oropharynx.

- 409 cases / 7 institutions
- 1st morphological diagnosis (luminal mitosis, apoptosis)
  - HPVA (HPV associated) features
  - NHPVA (no or limited HPV associated features)
- IHC; p16, vimentin, p53, PR
- CISH using an RNA-based probe set that recognizes 18 varieties of high-risk HPV were performed to validate IECC diagnoses
- the high-risk HPV CISH probe set had superior sensitivity, specificity, positive and negative predictive values (0,95, 0,97, 0,99, 0,83) compared to p16 IHC (0,87, 0,63, 0,91, 0,55)
- NHPVA type is significantly more agressive

Human papillomavirus-associated adenocarcinoma (HPVA): apical mitotic figures and apoptotic bodies appreciable at scanning magnification. If those features were not seen at scanning magnification, a cursory examination at ×200 was performed to detect additional cases. Those with easily identified apical mitotic figures and apoptotic bodies were considered HPVA.

Nonhuman papillomavirus-associated adenocarcinoma (NHPVA): No easily identifiable apical mitotic activity and apoptotic bodies at scanning magnification. If focal or equivocal HPVA features were appreciable at ×200, tumors were considered to show "limited HPVA" features and tentatively classified as NHPVA adenocarcinoma.

HPVA ECAs (Fig. 1) were further subcategorized, mostly based on cytoplasmic features, to provide continuity with preexisting classification schemes, as follows:

- Usual-type: 0% to 50% of cells with appreciable intracytoplasmic mucin, with or without benign-appearing squamous differentiation.
- Villoglandular: usual-type cytomorphology with exophytic long slender papillae.
- Mucinous, not otherwise specified (NOS): > 50% of cells with intracytoplasmic mucin in a background of usual-type adenocarcinoma.
- Mucinous, intestinal type: ≥ 50% of cells with goblet morphology in a background of usual-type adenocarcinoma.
- Mucinous, signet ring cell type: ≥ 50% of tumor cells with signet-ring morphology present in a background of usual-type adenocarcinoma.
- Invasive stratified mucin-producing carcinoma (iSMILE): invasive nests of stratified columnar cells with peripheral palisading and variable amounts of intracytoplasmic mucin,[21] resembling its in situ counterpart (stratified mucin-producing intraepithelial lesion [SMILE]).[22]

NHPVA ECAs (Fig. 2) were subclassified based on established published criteria as follows:

- Gastric-type adenocarcinoma: tumor contains cells with abundant clear, foamy or pale eosinophilic cytoplasm, distinct cytoplasmic borders, generally low nuclear-cytoplasmic ratios and irregular basally located nuclei, with no or limited HPVA-like features. Minimal deviation adenocarcinoma of mucinous type was considered part of the spectrum of gastric-type adenocarcinoma.[6,7] Intestinal differentiation in the form of goblet cells and neuroendocrine-like eosinophilic granular cytoplasm was permitted.
- Clear cell adenocarcinoma: solid, papillary, and/or tubulocystic architecture with polygonal cells and highly atypical, but uniform, nuclei.
- Invasive adenocarcinoma NOS: any tumor that could not be classified by WHO or IECC criteria.
- Endometrioid adenocarcinoma: endometrioid morphology with "confirmatory endometrioid features" (at least focally identified low-grade endometrioid glands lined by columnar cells, with pseudostratified nuclei demonstrating no more than moderate atypia, with or without squamous differentiation and/or endometriosis present) and lacking HPVA features.[17]
- Serous carcinoma: papillary and/or micropapillary architecture with cells showing diffusely distributed, highly atypical nuclei in stratified and pseudostratified cells with relative lack of intercellular adhesion. Mimics, such as drop metastases as well as other carcinomas with papillary architecture including usual-type, clear cell, and mesonephric carcinoma were excluded.
- Mesonephric carcinoma: tumors showing an admixture of growth patterns (ductal, tubular, papillary, cord-like, and others), as well as intraluminal eosinophilic colloid-like material resembling mesonephric remnants.

TABLE 4. Endocervical Adenocarcinoma Types: IECC Classification*

IECC (%)† (N = 371)	%
Usual	74
Usual-type	73
Villoglandular	0.8
Gastric (mucinous NHPVA)	10
Mucinous HPVA	8.6
Intestinal	3.0
Mucinous NOS	3.0
iSMILE	2.4
Signet ring	0.3
Clear cell	3.0
Adenocarcinoma, NOS	2.4
Endometrioid	1.1
Serous	0.5
Mesonephric	0.3

*Entities are listed in descending order of prevalence according to the IECC classification scheme.

†Adenosquamous carcinomas are not tabulated, as they are not ECAs, but they represented 9.3% (N = 38) of carcinomas reviewed.

TABLE 3. Clinical and Demographic Information of IECC-classified Cases

IECC Subtypes	Age (N)	Age (Median [IQR]) (y)	Tumor Size (N)	Tumor Size, (Median [IQR]) (mm)	Tumor Stage (N)	Tumor Stage I (%)	Tumor Stage II (%)	Tumor Stage III (%)	Tumor Stage IV (%)
HPVA									
Usual	271	42 (37-53)	201	23 (11-37)	253	92	6.3	1.6	0.4
Mucinous NOS	11	41 (32-50)	8	11 (4-20)	10	80	10	10	—
Mucinous intestinal	11	36 (32-49)	10	5 (2-15)	11	73	27	—	—
Mucinous signet ring	1	50	1	9	1	100	—	—	—
iSMILE	9	45 (35-51)	8	16 (8-27)	9	100	—	—	—
Villoglandular	3	34 (31-39)	1	8	3	100	—	—	—
All HPVA	306	42 (36-52)	229	21 (10-35)	287	91	6.9	1.7	0.4
Adenocarcinoma NOS	9	48 (43-58)	7	33 (15-45)	9	33	44	11	11
NHPVA									
Gastric	37	54 (42-66)	25	38 (21-55)	35	49	43	8.6	—
Clear cell	11	56 (33-75)	9	33 (28-44)	10	60	40	—	—
Endometrioid	4	61 (49-67)	3	40 (30-45)	2	100	—	—	—
Serous	2	64 (59-69)	1	44	2	—	100	—	—
Mesonephric	1	52	1	2	1	100	—	—	—
All NHPVA	55	55 (43-67)	39	38 (21-45)	50	52	42	6	—

NHPVA tumors were larger and occurred in significantly older patients than HPVA tumors ($P < 0.001$ for both measures).
IQR indicates interquartile range (25th to 75th percentile).

- IECC segregates ECAs into HPVA and NHPVA using morphology alone
- the validity of the HPVA and NHPVA categories is supported by p16 IHC and HPV status
- the high-risk HPV probe set is more sensitive and specific than p16 in recognizing usual type ECA
- optimal tissue processing is essential
- HPVA and NHPVA categories differ significantly with respect to age, stage and tumor size

- usual-type HPVA is most common type of ECA
- mucinous carcinomas comprise a mixture of HPVA and NHPVA types
- gastric-type carcinoma is the most common NHPVA type and the second most common type of ECA
- primary endometrioid and serous carcinomas of the cervix are extraordinarily rare, and in the case of serous carcinona, possibly nonexistent

IECC Classification

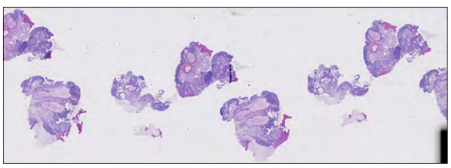
- HPV-associated endocervical adenocarcinoma[1]
- HPV-unassociated endocervical adenocarcinoma
  - Gastric-type[2]
  - Clear cell
  - Endometrioid
  - Mesonephric
  - Miscellaneous and not otherwise specified (NOS)[3]

FIGURE 8. IECC Classification 2017. 1: HPVA encompass those with and without intracytoplasmic or stromal mucin. Examples with mucinous differentiation may contain glands, goblet cells, signet ring cells, or solid nests of tumor cells with intracytoplasmic mucin (ie, iSMILE). Further work is needed to determine whether these histologic variants are biologically and clinically distinctive. The designation "usual-type" HPV-associated ECA can be used for mucin-poor tumors, whereas the designation "mucinous" HPV-associated ECA can be used for cases with obvious intracytoplasmic mucin. 2: Gastric-type adenocarcinoma may contain goblet cells. 3: It is uncertain whether true serous carcinomas arise in the endocervix. Together with the HPV-unassociated NOS category (0.8% to 1.6%), miscellaneous tumors represent at most 2% of all ECAs.

Zaključna delavnica pilotne shema zagotavljanja kakovosti v patologiji (SZKP)
Ljubljana, 27. januar 2018

Primer 3

- 29 let stara ženska v 12. tednu nosečnosti
- HPV +
- Izvid BMV: PIL-VS
- biopsija porcije

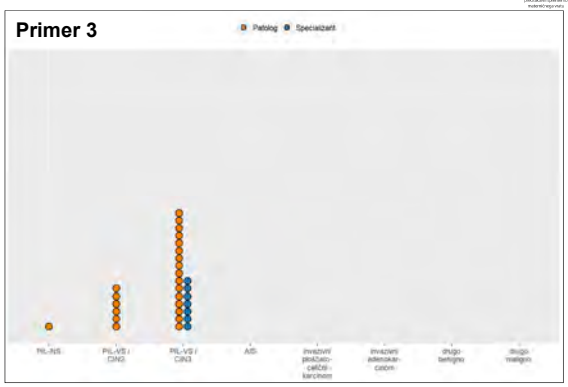


Zaključna delavnica pilotne shema zagotavljanja kakovosti v patologiji (SZKP)
Ljubljana, 27. januar 2018

Primer 3

Ploščatocelična intraepitelijska lezija visoke stopnje (PIL-VS / CIN3) in ektopična decidua

Primer 3



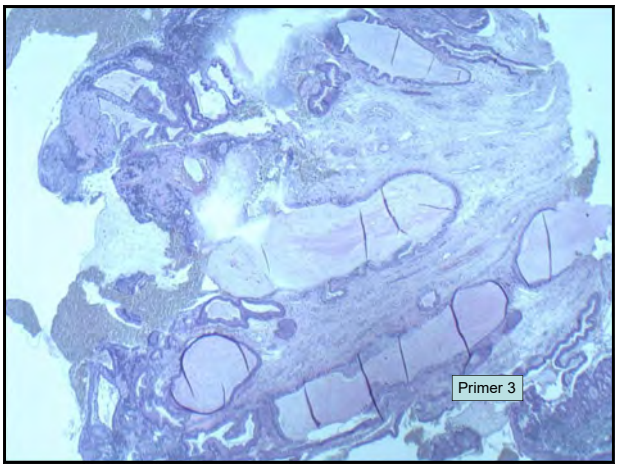
Primer 3

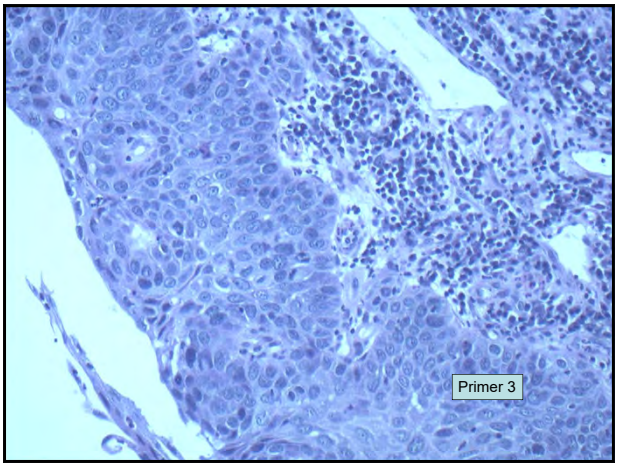
- specialisti
  16/23 PIL-VS / CIN 3
  6/23 PIL-VS / CIN 2

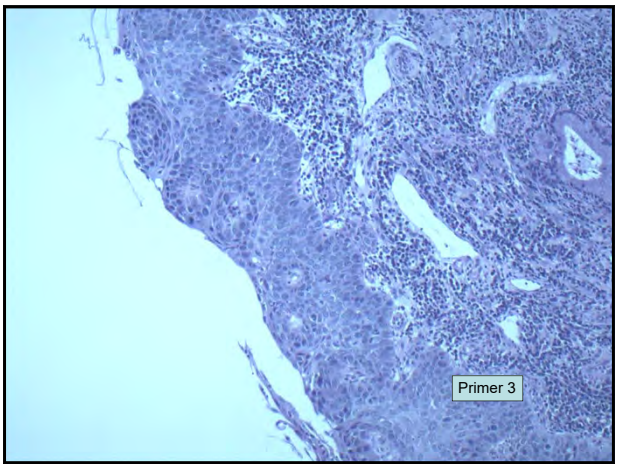
  -13x decidualizacija strome
  - 1x ? mikroinvazivni skvamozni karcinom
  (3x ? IHK – pri vseh treh sicer CIN3)

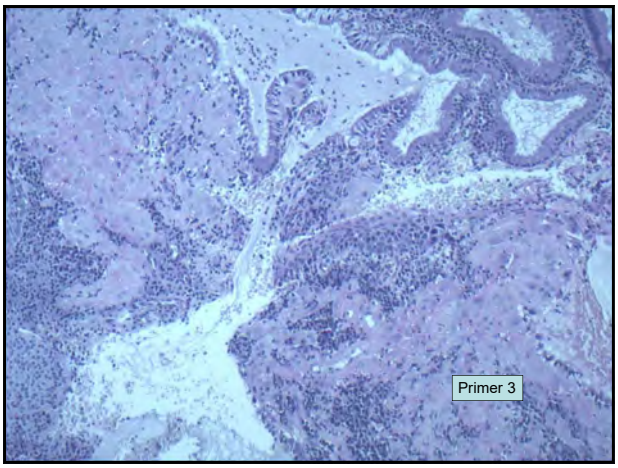
  1/23 PIL-NS (CIN1, koilocitoza)

- specializanti
  7/7 PIL-VS / CIN3 - 2x ? invazija,
  - 1x decidualizacija strome


Primer 3

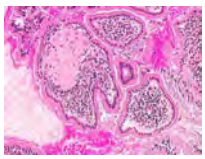

Primer 3


Primer 3



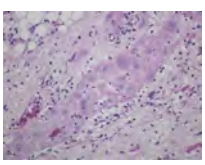
DECIDUALIZACIJA STROME

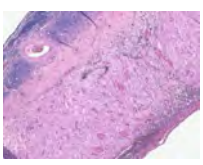
- benigna reakcija strome v nosečnosti:
- v 1/3 biopsij pri nosečnicah;
- v endocervikalni stromi so velike, poligonalne celice z eozinofilno citoplazmo



DECIDUALIZACIJA STROME

- cerviks, jajcevoda, jajčnika, peritonej, slepič;
- + vimentin, dezmin, PR;
- - keratini, kalretinin;





DECIDUALIZACIJA STROME

DIFERNCIALNA DIAGNOZA

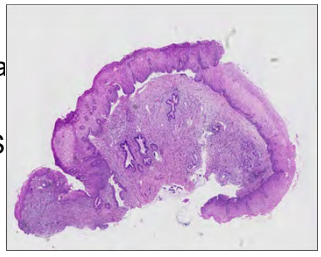
- reaktivne spremembe;
- ploščatocelični karcinom;

CIN V NOSEČNOSTI

- prevalenca CINa med nosečnicami 1%;
- regresija sprememb po porodu je visoka med 37 in 74 %;
- Progresija CIN2 in CIN3 do invazivnega karcinoma med 2 in 28 %;
- TERAPIJA: ko z biopsijo izključimo invazivni karcinom je terapija v nosečnosti spremljanje z BMV in kolposkopija;

Primer 4

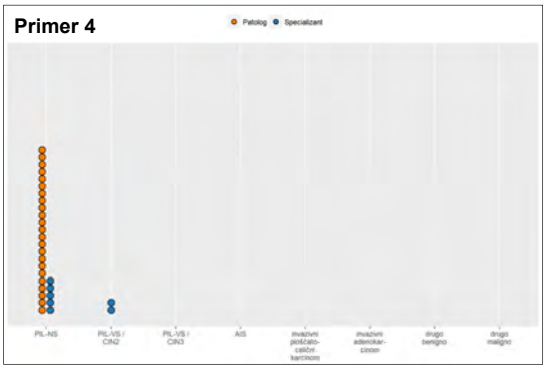
- 34 let stara ženska
- HPV+.
- Izvid BMV: PIL-NS
- biopsije porcije



Primer 4

Ploščatocelična intraepitelijska lezija nizke stopnje (PIL-NS / CIN 1)

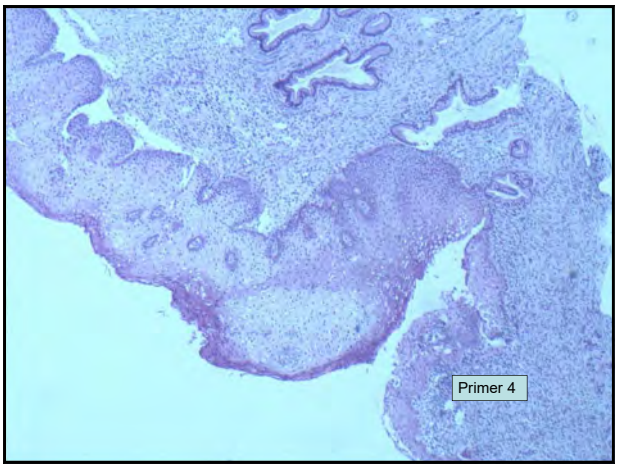
Primer 4

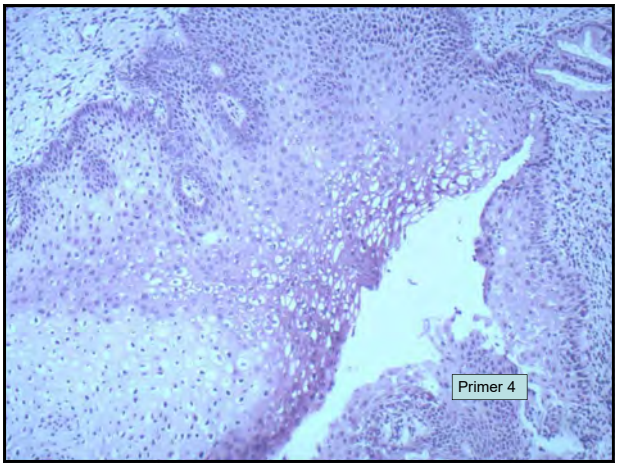


Primer 4

- specialisti
  23/23 PIL-NS
  - 1x koilocitoza
  - 3x CIN 1
  - 19x brez opredelitve
  - 2x dif.dg. PIL-VS / CIN2 (oba p16?)

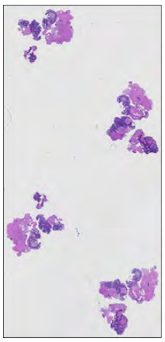
- specializanti
  5/7 PIL-NS (vsi brez opredelitve)
  2/7 PIL-VS / CIN 2 - 1x dif.dg. PIL-NS(p16)
  - 1x dif.dg. PIL-NS, SMILE (p16)





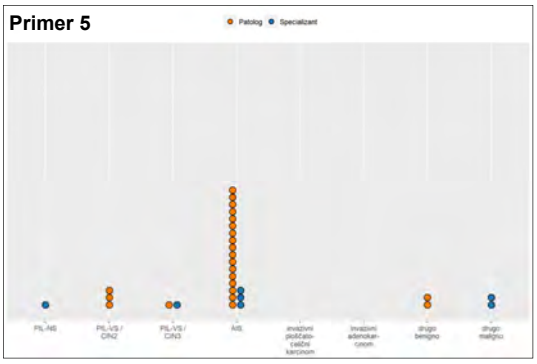
Primer 5

- 33 let stara ženska
- HPV+.
- Izvid BMV: APC-VS
- biopsija porcije



Primer 5

Adenokarcinom in situ (AIS)

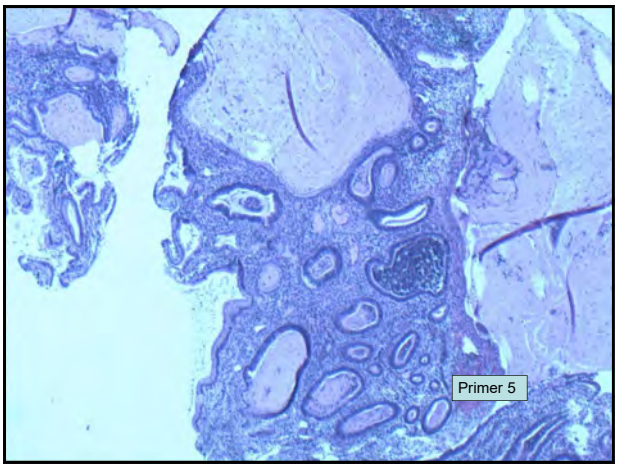


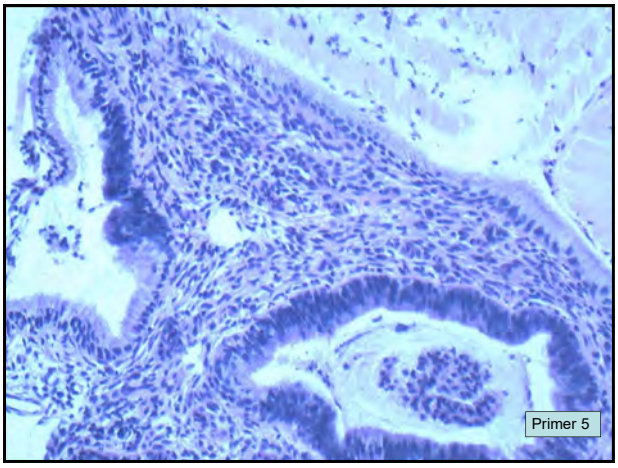
Zaključna delavnica pilotne shema zagotavljanja kakovosti v patologiji (SZKP)
Ljubljana, 27. januar 2018

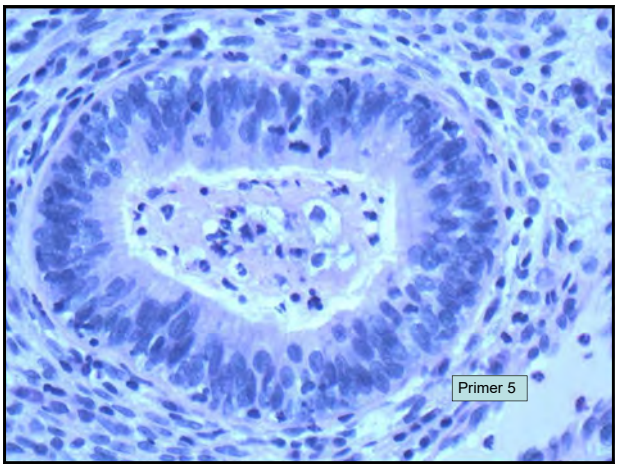
Primer 5

- specialisti
  17/23 AIS 4x tudi CIN 2 (3x tudi PIL-NS), 1x dif.dg. endometrioza
  3/23 PIL-VS / CIN 2 1x tudi AIS, 1x tudi CIN1
  2/23 drugo benigno - oba tubarna metaplazija
  oba dif.dg. AIS (p16, Ki67)
  1/23 PIL-VS / CIN 3 (ni dif.dg.)
- specializanti
  3/7 AIS 1x tudi CIN 3
  1/7 PIL-VS / CIN 3 in tudi AIS (natan.opredelitev)
  2/7 drugo maligno - oba PIL-VS in AIS (1x CIN2, 1x neopredeljeno)
  1/7 PIL-NS

Zaključna delavnica pilotne shema zagotavljanja kakovosti v patologiji (SZKP)
Ljubljana, 27. januar 2018


Primer 5


Primer 5


Primer 5

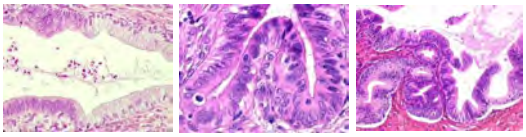
AIS

- in situ adenokarcinom – AIS/ HG CGIN;
- preinvazivna intraepitelna lezija;
- diagnosticirana v populaciji žensk, ki so 10 do 20 let mlajše kot ženske z invazivnim adenokaricnomom;
- večina lezij je povezanih s HPV infekcijo;

AIS

HISTOLOŠKE ZNAČILNOSTI

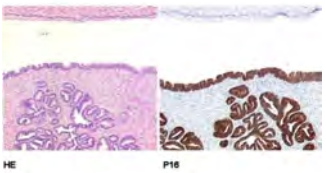
- ostri/nenadni prehodi med regularnim in neopastičnim epitelom
- hiperkromna, psevdostratificirana, povečana in okrogla jedra
- mitoze, v citoplazmi nad jedri
- v zgornjem polu manj mucina



AIS

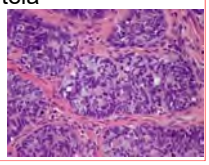
IMUNOHISTOKEMIJA

- p16 – močna jedrna in citoplazemska reakcija;



SMILE

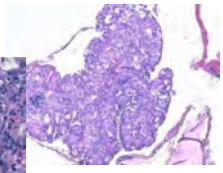
- **S**tratificirana **M**ucin producirajoča **I**ntraepitelna **Le**zija
- v povrhnjem in žleznem epitelu – stratificiran, neoplastični epitel, kjer so v citoplazmi diskretne vakuole, čez celo debelino epitela

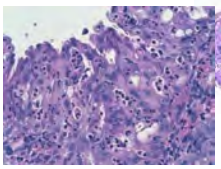


DIFERENCIALNA DIAGNOZA

REAKTIVNA ATIPIJA

- posamezne celice s hiperkromnimi jedri;
- večjedrne velikanke;
- ni mitoz;
- p16 - ;

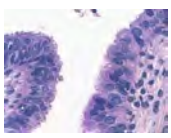




DIFERENCIALNA DIAGNOZA

TUBARNA - TUBOENDOMETRIOIDNA METAPLAZIJA

- blaga do zmerna jedrna atipija;
- mitoze;
- p16 „šekasta“ reakcija;



DIFERENCIALNA DIAGNOZA

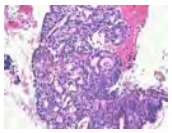
ENDOMETRIOZA

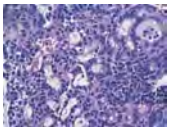
- psevdostratifikacija, ni jedrnih atipij;
- mitoze;
- žleze obdaja endometrijska stroma;
- p16 - ;

DIFERENCIALNA DIAGNOZA

MIKROGLANDULARNA HIPERPLAZIJA

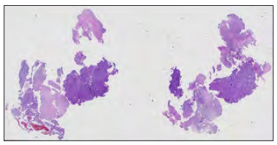
- tesno, druga ob drugi ležeče, drobne žleze, ponekod so svetline;
- epitel izoprizmatski;
- subnuklearne vakuole v citoplazmi;
- vnetni infiltrat;
- redke mitoze;





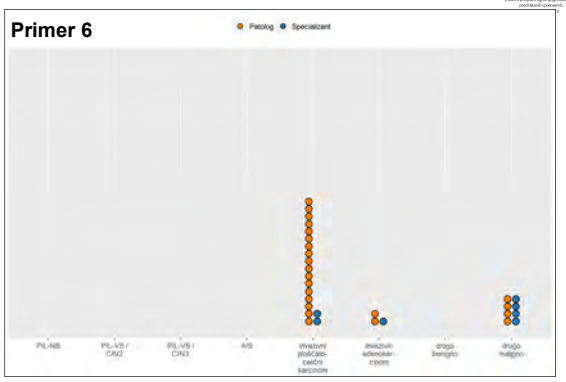
Primer 6

- 69 let stara ženska.
- v registru Zora ni prejšnjih izvidov BMV ali prejšnjih histoloških izvidov
- S/P operaciji karcinoma vratu maternice in radioterapiji
- sepsa zaradi radionekroze tkiva medeničnega dna
- sum na recidiv tumorja v slepem koncu vagine
- biopsija slepega konca vagine



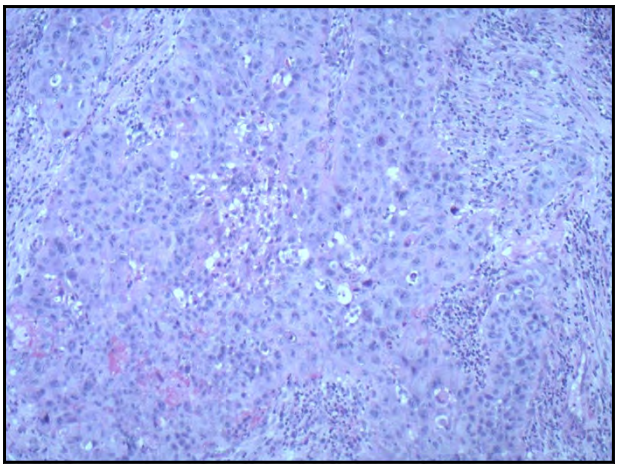
Primer 6

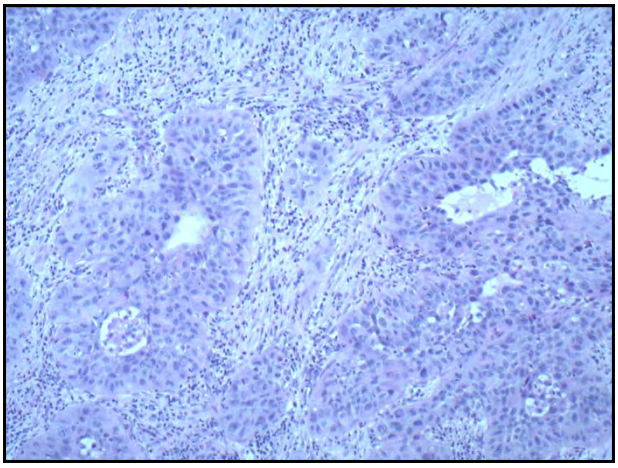
Invazivni ploščatocelični karcinom,
slabo diferenciran (recidivni)

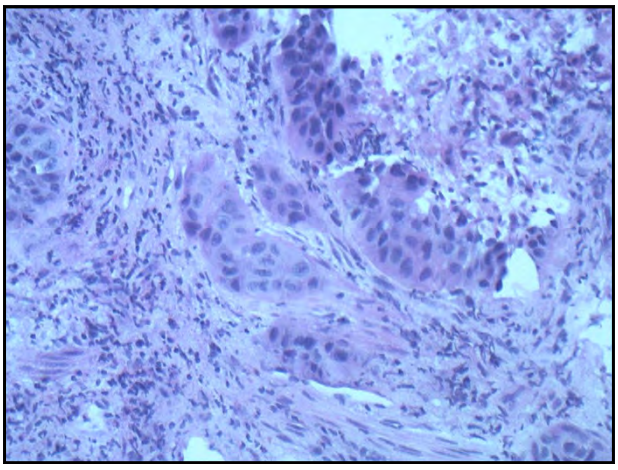


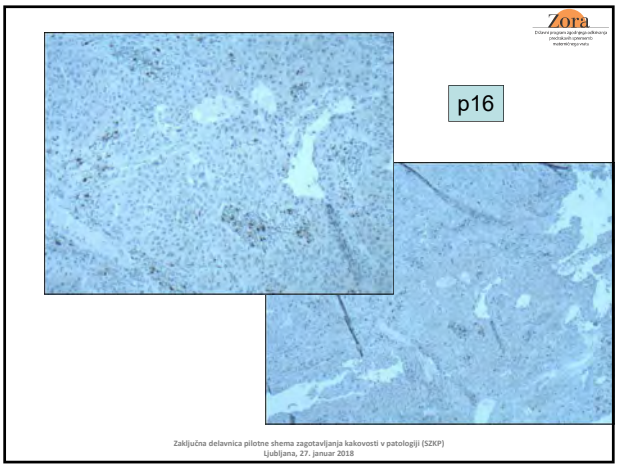
Primer 6

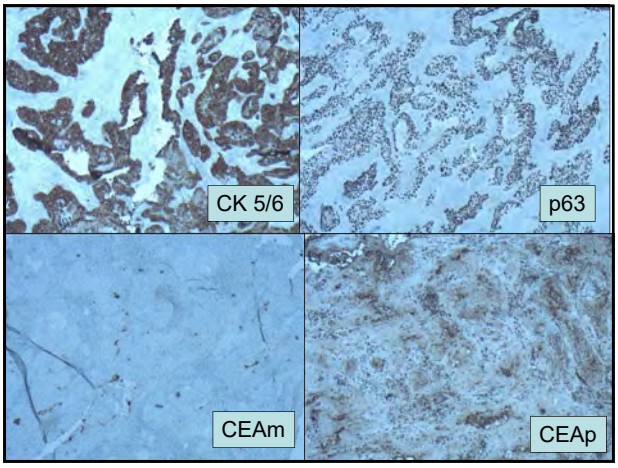
- specialisti
  17/23 invazivni ploščatocelični karcinom
  4/23 drugo maligno 1x adenoskvamozni ?
  1x skvamocelularni infiltrativni karcinom
  1x slabo diferenciran karcinom (? IHK – skvamozni / adeno)
  2/23 invazivni adenokarcinom – oba dif.dg. skvamozni karcinom
  (1x prejšnja biopsija, Kreyberg in CK5/6)
- specializanti
  2/7 invazivni ploščatocelični karcinom
  1/7 invazivni adenokarcinom (IHK - CK7, CK20, CD34, dif.dg angiosarkom, metastaza)
  4/7 drugo maligno
  3x samo invazivni karcinom (1x slabo dif, 1x zmerno dif., 1x nič več)
  1x PIL-VS / CIN 2 in AIS

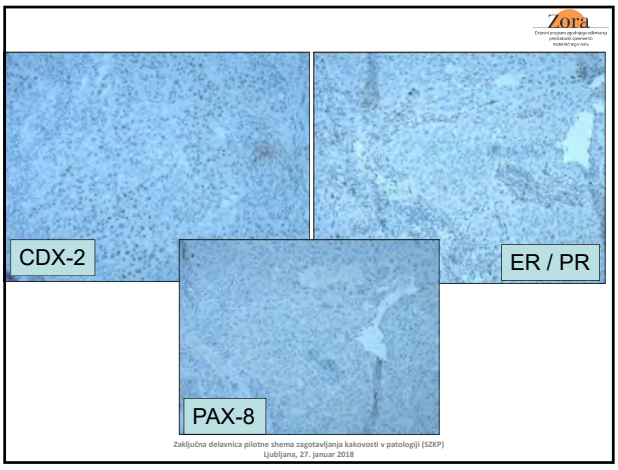







Zora
p16
Zaključna delavnica pilotne shema zagotavljanja kakovosti v patologiji (SZKP)
Ljubljana, 27. januar 2018


CK 5/6
p63
CEAm
CEAp


Zora
CDX-2
ER / PR
PAX-8
Zaključna delavnica pilotne shema zagotavljanja kakovosti v patologiji (SZKP)
Ljubljana, 27. januar 2018

Invazivni ploščatocelični karcinom cerviksa

- 80% vseh invazivnih karcinomov
- povprečna starost 55 let (20 let starejše od PIL-VS)
- 2-10% se jih diagnosticira znotraj 1 leta po negativnem BMV (pogosto lažno negativen)
- asimptomatske ali bolečina, postkoitalna krvavitev
- v 60% primerov zvišan serumski CEA

Invazivni ploščatocelični karcinom cerviksa

- nekeratinizirajoči (bolj pogost) - ni perl, posamezne celice pa pogosto keratinizirajo, nejasne meje med celicami, visoka mitotska aktivnost
- keratinizirajoči – perle (po definiciji), eozinofilna citoplazma, ostre meje med celicami, manj mitoz
- redki; drobnoceličen, “warty”ali kondilomatozni, bazaloiden, papilarni, limfoepiteliomu-podoben, sarkomatoiden, mukoepidermoiden
- “highly differentiated” varianta keratinizirajočega (normalni BMV) – ekstenzivna keratinizacija, invertna oblika rasti, minimalne atipije, ni HPV

Invazivni ploščatocelični karcinom cerviksa

- 20-35% vsebuje intracitoplazemski mucin (d.d. adenoskvamozni karcinom)
- z glikogenom bogata svetla citoplazma (d.d. svetlocelični karcinom)
- “benigni” videz invazije (d.d. vraščanje PIL-VS v kripte)
- sebacealna diferenciacija
- melanocitna diferenciacija (pigmentacija)(d.d.melanom)

Invazivni ploščatocelični karcinom cerviksa

- spremembe strome:
  - masivna inflamatorna komponenta eozinofilcev (v DKS eozinofilija, eozinofilci v bezgavkah)
  - amiloidni depoziti (pozitivni na CK)
  - prominentna hialinizirana in/ali miksoidna stroma

Diferencialna diagnoza

- ne-neoplastične spremembe
  - floridna skvamozna metaplazija
  - post-bioptična psevdoinvazija
  - ektopična decidua
  - nodul placentarnega mesta
- PIL-VS v kriptah
- slabo diferenciran adenokarcinom (morfologija, IHC)
- epiteloidni trofoblastni tumor (v d.d. pomaga serumski hCG, p16-, inhibin fokalno+, CK18+, CD10+, CK5/6 -, prisotnost PIL-VS, ne pomaga p63)
- svetlocelični karcinom
- sekundarna infiltracija cerviksa – kolorektalni karcinom, urotelijski karcinom (IHC)

Prognostični dejavniki

- klinični stadij (5-letno preživetje)
  - 90% stadij I, <20% stadij IV
- velikost in globina invazije
  - velikost ≤1cm 93%, >3cm 60%
  - globina invazije ≤ 5 mm 92%, >10 mm 60%
- vzorec invazije
  - kapljična (“spray”) - višji stadiji, LVI+ in N+
- LVI – napoveduje N+, OS, DFS
- infiltracija parametrijev, status bezgavk
- molekularni markerji:
  - DNA ploidija (aneuploidnost neugoden dejavnik)
  - HPV-DNA (16,18 slabši – v višjem stadju, pogosteje LVI in N+)
  - p16 (negativni slabši)
  - E-cadherin, β katenin, vimentin (več E-cadherina in β katenina ter manj vimentina ugodni dejavniki)

HPV-negative carcinoma of the uterine cervix: a distinct type of cervical cancer with poor prognosis

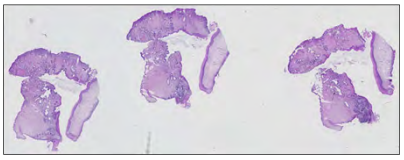
L Rodríguez-Carunchio,[a] I Soveral,[b] RDM Steenbergen,[c] A Torne,[b] S Martinez,[b] P Fusté,[b] J Pahisa,[b] L Marimon,[a] J Ordi,[a] M del Pino[a]

Accepted 3 July 2014. Published Online 17 September 2014.

- 14/136 women (10.2%) were negative for HPV by HC2
- after reanalysis by PCR-based techniques only 8/136 (5.8%) were confirmed as HPV-negative
  - 15.6% (5/32) adenocarcinomas
  - 2.9% (3/104) squamous cell carcinomas
- patients with CCs with confirmed HPV-negativity had significantly worse DFS than women with HPV-positive tumours
- in the multivariate analysis HPV-negativity and FIGO staging were associated with increased risk of progression and mortality

Primer 7

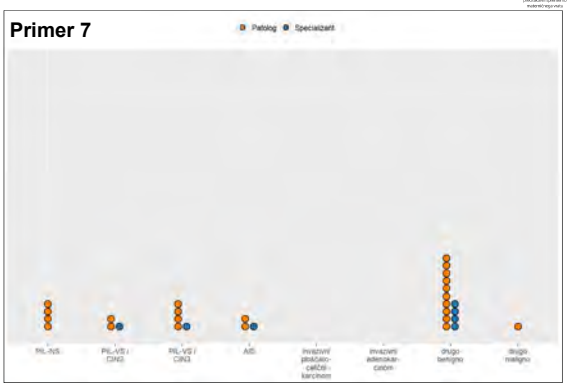
- 33 let stara ženska
- Izvid BMV: AŽC-N
- biopsija ni bila opravljena
- opravljen LLETZ



Primer 7

Endometrioza cerviksa

Primer 7



Primer 7 – specialisti

10/23 drugo benigno
- 8x endometrioza
- 1x vnetje
- 1x nezrela metaplazija in PIL-NS

4/23 PIL-NS
- 1x natančnejša opredelitev endometrioza, dif.dg CIN 2, p16
- 1x komentar endometrioza, za izključitev AIS p16
- 1x natančnejša opredelitev nezrela metaplazija, koilociti
- 1x možnost PIL-VS v nezreli metaplaziji

4/23 PIL-VS / CIN 3
- 1x komentar tudi endometrioza
- 1x dif.dg. fokus AIS, nezrela metaplazija, komentar: tubarna metaplazija in PIL-NS, p16 / Ki67
- 2x prisoten tudi AIS (1x pod natančnejša opredelitev. 1x pod komentar v tem omenjen tudi SMILE)

2/23 PIL-VS / CIN 2
- 1x natančnejša opredelitev – tudi endometrioza, večinoma CIN 1, mestoma CIN 2

2/23 AIS
- 2x in PIL-VS / CIN 3 (1x pod natančnejša opredelitev, 1x pod komentar)

1/23 drugo maligno – SMILE + cervikalna endometrioza

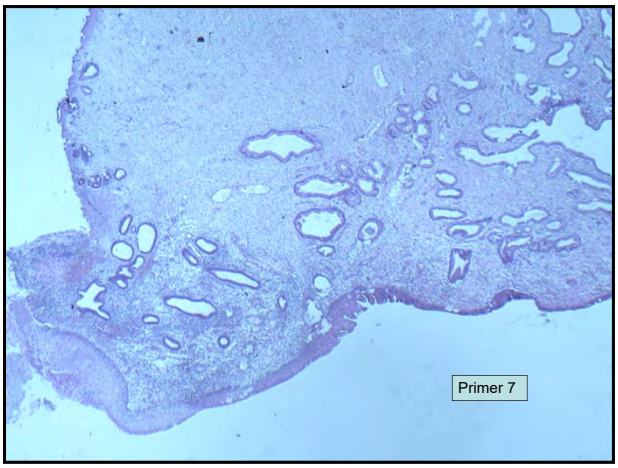
Primer 7 – specializanti

4/7 drugo benigno
- 3x endometrioza
- 1x tubarna metaplazija, mikroglandularna metaplazija (p16, Ki67)

1/7 PIL-VS / CIN 3
- še CIN 2 in AIS – alcian blue, Ki67, p16

1/7 PIL-VS / CIN 2
- p16 (ni razlage)

1/7 AIS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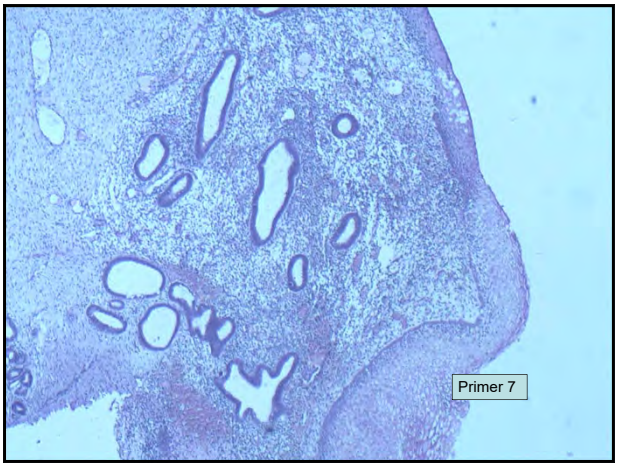
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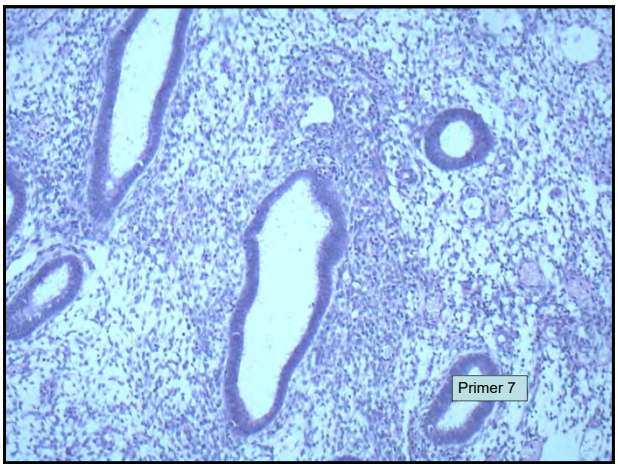
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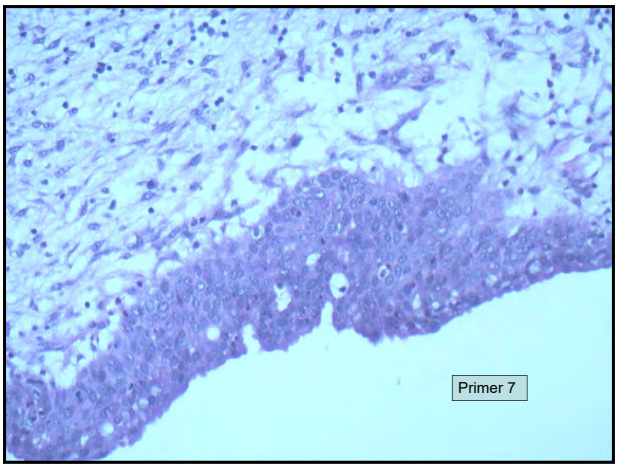


Endometrioza cerviksa

- povrhnja ali globoka
- po prejšnji biopsiji / konizaciji – implantacija endometrija ali s travmo povzročena metaplazija
- globoka je običajno v sklopu peritonealne, globoke endometrioze

Endometrioza cerviksa

- povrhnja običajno asimptomatska, lahko pa:
  - zadebeljena, granulirana, hemoragična sluznica
  - abnormalni BMV
- najbolj pogosto tik pod epitelom

Diferencialna diagnoza

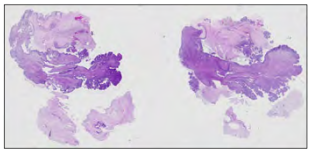
- običajno ni težavna
- stroma: CD10+, WT1+, CD34- (periglandularne stromalne celice so lahko CD10+), spiralne arteriole, hemoragija
- epitel: p16 običajno le fokalno +, bcl-2 +

diferencialno diagnostično

- AIS - ni apoptoze, ni znatnih atipij, stroma, bcl-2 + (p16 lahko +, Ki67 lahko višji)
- stromalni sarkom - pri t.i. stromalni endometriozi (morfologija, način rasti)

Primer 8

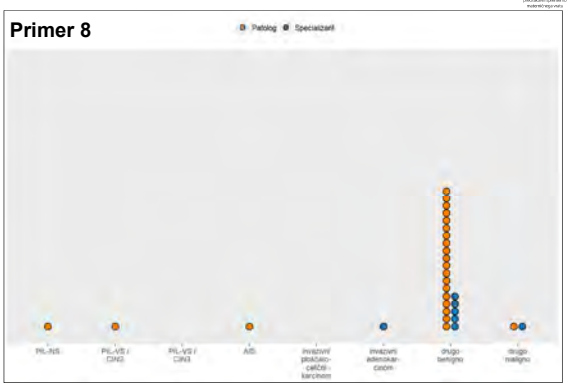
- 50 let stara ženska
- klinično polip materničnega vratu
- izvid BMV: normalen bris
- ekscizija polipa materničnega vratu



Primer 8

Cervikalni polip z mikroglandularno metaplazijo in ploščatocelično metaplazijo

Primer 8



Primer 8 - specialisti

20/23 drugo benigno

- 9x polip z mikroglandularno hiperplazijo (MGH)
- 3 x samo polip brez MGH
- 8x samo MGH

1/23 AIS - nič dodatno

1/23 PIL-NS – natanč. opred. – CIN 1 in MGH v polipu

1/23 PIL-VS / CIN 2 – natanč. opred. – CIN 2 v polipu

Primer 8 - specializanti

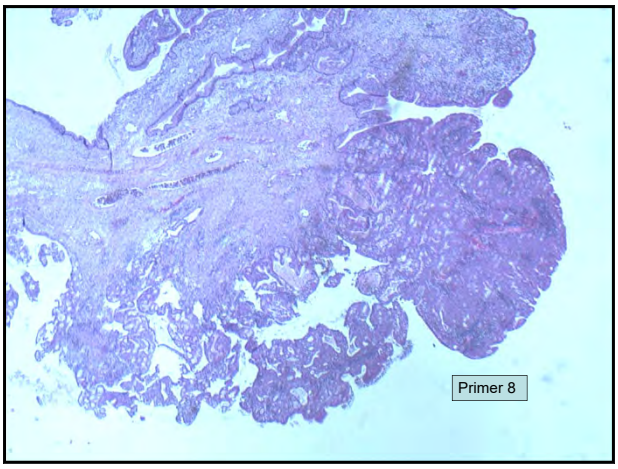
5/7 drugo benigno

- 1x polip z mikroglandularno hiperplazijo (MGH)
- 4 x samo polip brez MGH (3x metaplastične spremembe)

1/7 drugo maligno – endometrioidni ca. v polipu (zasevek)

1/7 invazivni adenokarcinom

- običajni tip, polip z MGH, p16/Ki67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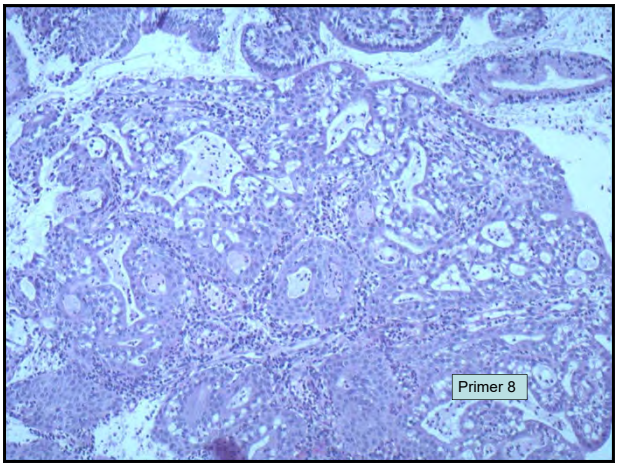
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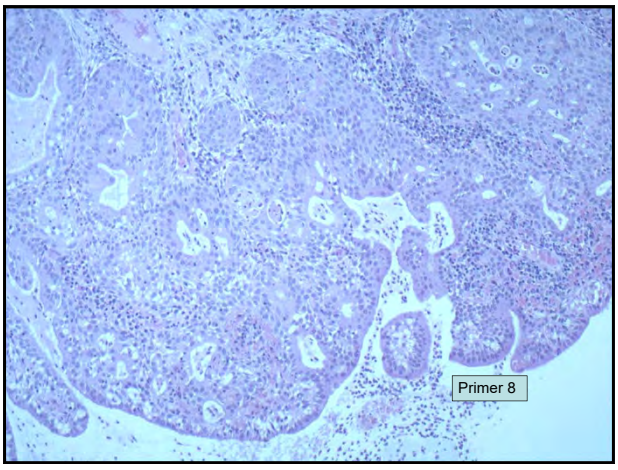

Primer 8

Mikroglandularna hiperplazija

- proliferacija endocervikalnih kript, pogosto povezana z estrogensko i progesteronsko stimulacijo (OKT, nosečnost)
- običajno v reproduktivni dobi (<5% pomenopavzalnih)
- običajno asimptomatske, v časih krvavitev in/ali izcedek
- običajno ni makroskopsko vidne spremembe, lahko pa se vidi kot erozija ali polip ali celo suspektno za karcinom
- pogosta znotraj cervikalnega polipa

MGH – mikroskopski videz

- gosto razporejene žleze, varirajo v videzu od drobnih okroglih do večjih, cističnih, ki varirajo v obliki
- v lumenu mucin in vnetnice
- v stromi vnetje
- epitel kuboidalen, kolumnarni, sploščen, pogosto subnuklearne vakuole
- skvamozna metaplazija, rezervnocelična hiperplazija

MGH – nenavadne slike

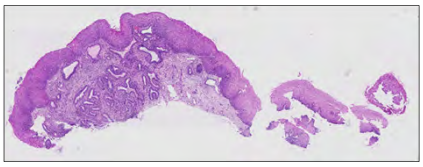
- solidni / retikularni / trabekularni vzorec
- edematozna / hializirana / miksoidna stroma (psevdoinfiltrativni vzorec razporeditve žlez v tej stromi)
- vretenastocelični tip celic / obilna eozinofilna citoplazma / pečatnicam podobne celice
- atipije in/ali mitoze (atipična / mitotsko aktivna MGH)

MGH – diferencialna diagnoza

- endometrioidni karcinom z MGH-podobnim vzorcem rasti
- endocervikalni adenokarcinom

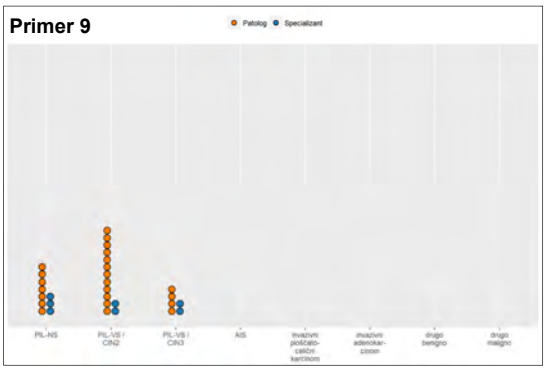
Primer 9

- 25 let stara ženska.
- izvid BMV: PIL-VS.
- biopsija maternične vratu



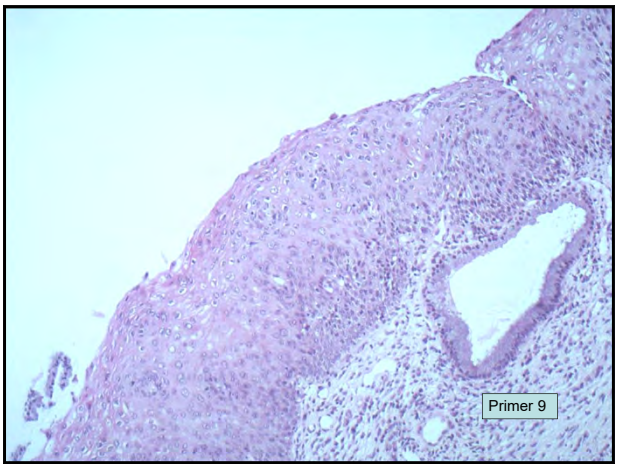
Primer 9

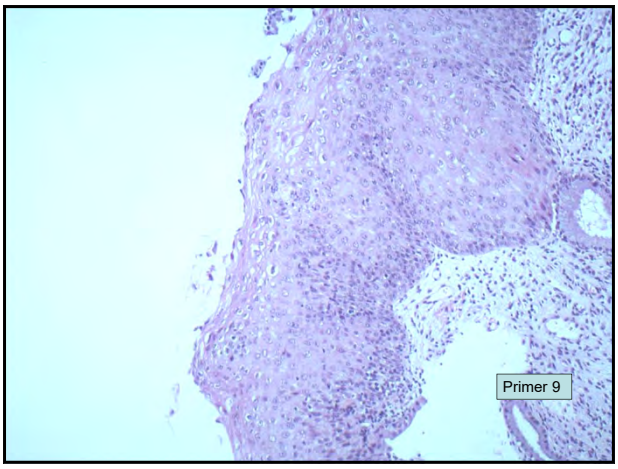
Ploščatocelična intraepitelijska lezija visoke stopnje (PIL-VS / CIN 2)



Primer 9

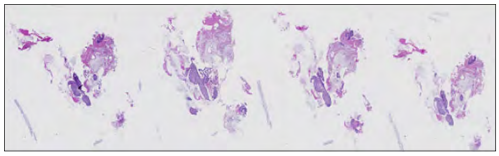
- specialisti
  12/23 PIL-VS / CIN 2 – 2x dif.dg. PIL-NS (1xIHK), 2x IHK
  4/23 PIL-VS / CIN 3 – 1x v globini adenoma malignum
  7/23 PIL-NS – 1x dif.dg. PIL-VS (IHK), 1x globlji (PIL-VS?)
- specializanti
  3/7 PIL-NS – nič več
  2/7 PIL-VS / CIN 2 – nič več
  2/7 PIL-VS / CIN 3 – 1x nič več, 1x dif.dg.PIL-NS (IHK)





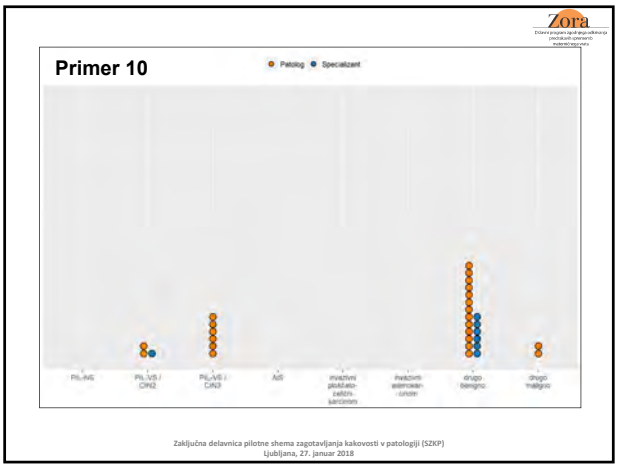
Primer 10

- 72 let stara ženska.
- izvid BMV: normalen bris
- biopsija materničnega vratu



Primer 10

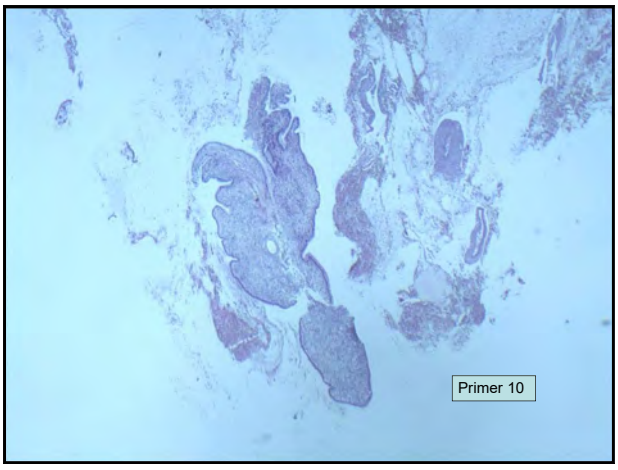
Atrofija ploščatoceličnega epitela

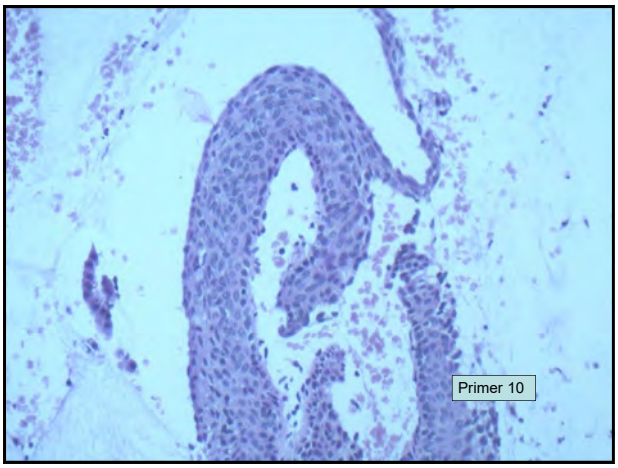


Primer 10

- specialisti
  13/23 drugo benigno
  12x atrofija (3x dif.dg PIL-VS, 4x IHK, 3x polip)
  1x samo polip
  6/23 PIL-VS / CIN 3 – 1x IHK (p16)
  2/23 PIL-VS / CIN 2 – 1x IHK (p16), morda tudi CIN 3
  2/23 drugo maligno
  1x neoplastični ploščatocelični epitel, PIL-VS in polip
  1x urotelni karcinom, papilarni, visoke stopnje malignosti
- specializanti
  6/7 drugo benigno - 6x atrofija – 4x dif.dg. PIL-VS (IHK)
  1/7 PIL-VS / CIN 2 – IHK (p16)

Zaključna delavnica pilotne shema zagotavljanja kakovosti v patologiji (SZKP)
Ljubljana, 27. januar 2018

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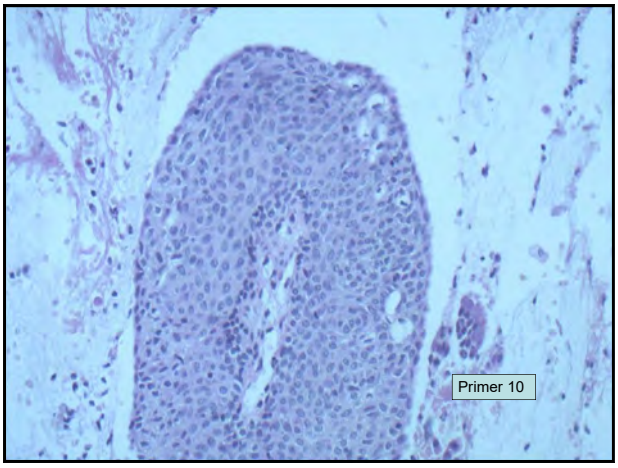
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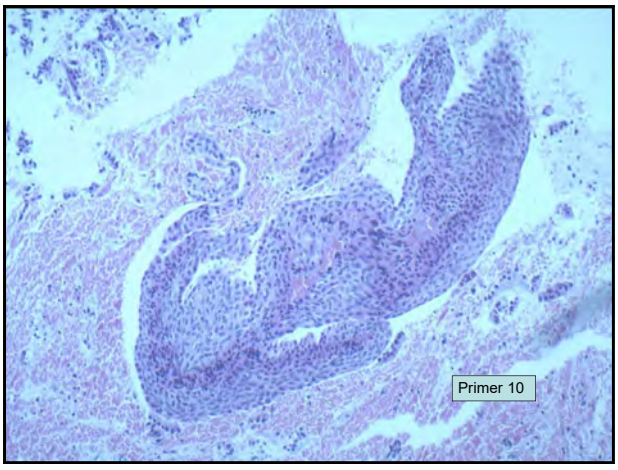
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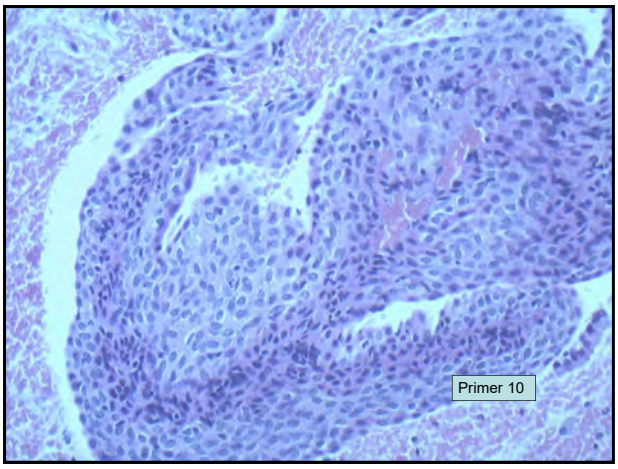
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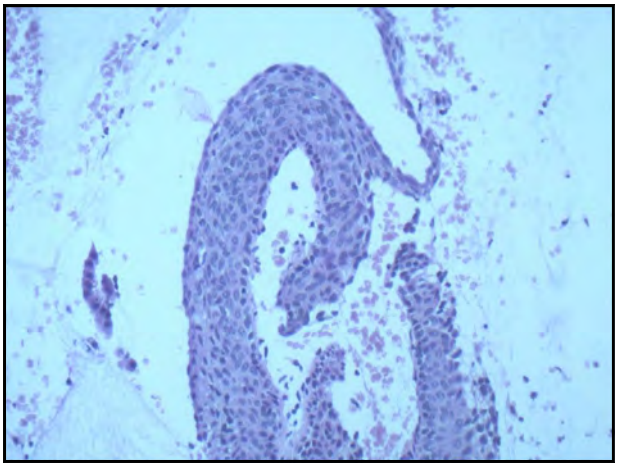
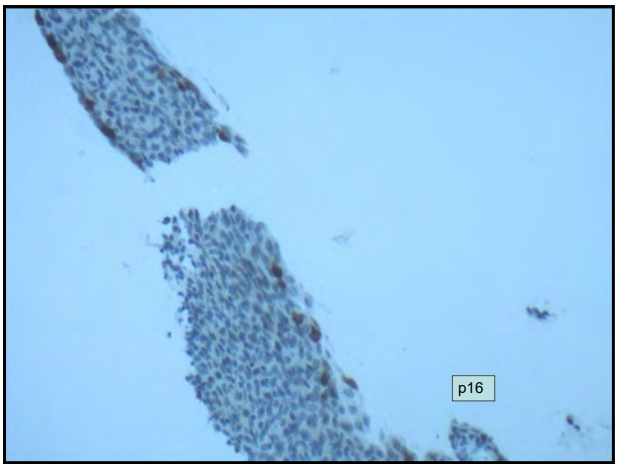
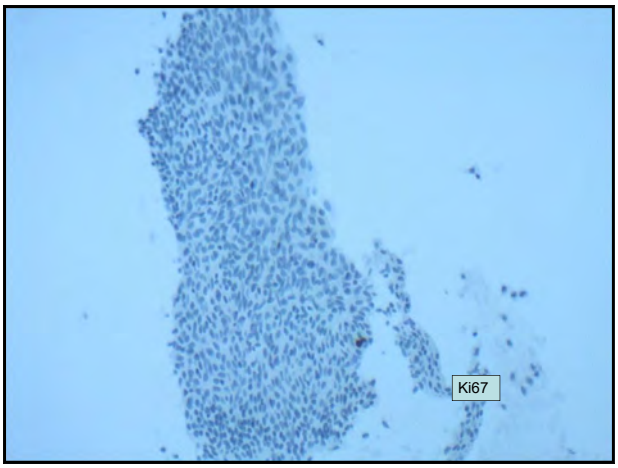
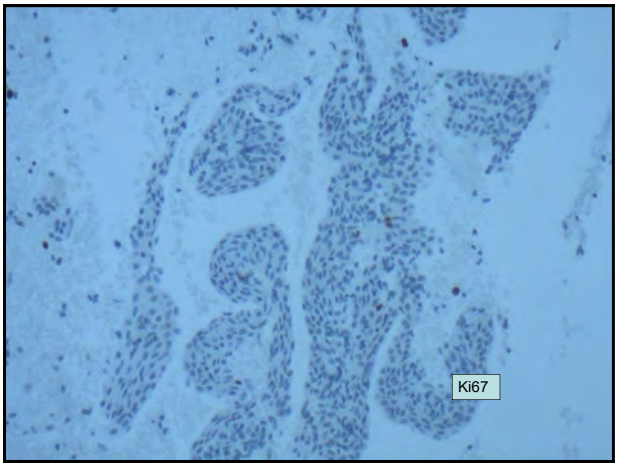



p16





Atrofija

- posledica pomanjkanja estrogenov
- skvamozni epitel grajen in bazalnih in parabazalnih celic – ni maturacije
- ovalna ali podolgovata / vretenasta jedra, horizontalno orientirana – t.i. “picket fence” (lesena ograja)
- ni mitoz, ni proliferacijske aktivnosti v Ki67, ni atipij
- epitel je lahko hipercelularen, hiperkromatski
- p16 negativen

Rezultati po patologih za vse primere

popolno ujemanje z diagnozo strokovne skupine

+/- ena stopnja

+/- dve stopnji

Zaključna delavnica pilotne shema zagotavljanja kakovosti v patologiji (SZKP)
Ljubljana, 27. januar 2018

		1.	2.	3.	4.	5.	6.	7.	8.	9.	10.
	Št. Bx	PIL-VS / CIN3	inv.adenoca	PIL-VS / CIN 3	PIL-NS	AIS	inv.ploščc.ca	endometrioza	polip+MGH	PIL-VS / CIN 2	atrofija
Patolog	0-24	PIL-VS / CIN3	inv.adenoca	PIL-VS / CIN3	PIL-NS	AIS	inv.ploščc.ca	drugo benigno	drugo benigno	PIL-NS	drugo benigno
Patolog	0-24	PIL-VS / CIN3	inv.adenoca	PIL-VS / CIN2	PIL-NS	PIL-VS / CIN3	drugo maligno	PIL-VS / CIN2	AIS	PIL-NS	PIL-VS / CIN3
Patolog	0-24	PIL-VS / CIN3	inv.adenoca	PIL-VS / CIN3	PIL-NS	AIS	drugo maligno	PIL-VS / CIN2	PIL-NS	PIL-VS / CIN2	PIL-VS / CIN2
Patolog	0-24	PIL-VS / CIN3	inv.adenoca	PIL-VS / CIN3	PIL-NS	AIS	inv.ploščc.ca	drugo benigno	drugo benigno	PIL-VS / CIN2	drugo benigno
Patolog	0-24	PIL-VS / CIN3	inv.adenoca	PIL-VS / CIN3	PIL-NS	AIS	inv.ploščc.ca	AIS	drugo benigno	PIL-VS / CIN3	drugo benigno
Patolog	0-24	PIL-VS / CIN3	inv.adenoca	PIL-VS / CIN3	PIL-NS	AIS	inv.ploščc.ca	PIL-VS / CIN3	drugo benigno	PIL-VS / CIN3	drugo benigno
Patolog	0-24	PIL-VS / CIN3	inv.adenoca	PIL-VS / CIN3	PIL-NS	PIL-VS / CIN2	inv.ploščc.ca	PIL-VS / CIN3	drugo benigno	PIL-VS / CIN3	drugo benigno
Patolog	0-24	PIL-VS / CIN3	drugo maligno	PIL-NS	PIL-NS	AIS	drugo maligno	PIL-NS	drugo benigno	PIL-VS / CIN2	drugo maligno
Patolog	25-99	PIL-VS / CIN3	inv.adenoca	PIL-VS / CIN3	PIL-NS	drugo benigno	inv.ploščc.ca	PIL-VS / CIN3	drugo benigno	PIL-NS	drugo benigno
Patolog	25-99	PIL-VS / CIN3	inv.adenoca	PIL-VS / CIN3	PIL-NS	drugo benigno	inv.ploščc.ca	drugo benigno	drugo benigno	PIL-NS	drugo benigno
Patolog	100-299	PIL-VS / CIN3	inv.adenoca	PIL-VS / CIN3	PIL-NS	PIL-VS / CIN2	inv.ploščc.ca	PIL-VS / CIN3	drugo benigno	PIL-VS / CIN2	drugo benigno
Patolog	100-299	PIL-VS / CIN3	inv.adenoca	PIL-VS / CIN2	PIL-NS	AIS	inv.ploščc.ca	drugo benigno	drugo benigno	PIL-VS / CIN2	PIL-VS / CIN3
Patolog	100-299	PIL-VS / CIN3	drugo maligno	PIL-VS / CIN2	PIL-NS	AIS	inv.ploščc.ca	drugo benigno	drugo benigno	PIL-VS / CIN2	drugo maligno
Patolog	100-299	PIL-VS / CIN3	inv.adenoca	PIL-VS / CIN3	PIL-NS	AIS	drugo maligno	PIL-NS	drugo benigno	PIL-VS / CIN2	PIL-VS / CIN3
Patolog	100-299	PIL-VS / CIN3	inv.adenoca	PIL-VS / CIN2	PIL-NS	AIS	inv.adenoca	PIL-NS	PIL-VS / CIN2	PIL-VS / CIN2	PIL-VS / CIN2
Patolog	100-299	PIL-VS / CIN2	inv.adenoca	PIL-VS / CIN3	PIL-NS	AIS	inv.ploščc.ca	drugo benigno	drugo benigno	PIL-VS / CIN2	drugo benigno
Patolog	100-299	PIL-VS / CIN3	inv.adenoca	PIL-VS / CIN3	PIL-NS	AIS	inv.ploščc.ca	drugo benigno	drugo benigno	PIL-NS	drugo benigno
Patolog	100-299	PIL-VS / CIN3	inv.adenoca	PIL-VS / CIN3	PIL-NS	AIS	inv.ploščc.ca	drugo benigno	drugo benigno	PIL-NS	drugo benigno
Patolog	300+	PIL-VS / CIN3	inv.adenoca	PIL-VS / CIN2	PIL-NS	AIS	inv.ploščc.ca	drugo benigno	drugo benigno	PIL-VS / CIN2	drugo benigno
Patolog	300+	PIL-VS / CIN3	inv.adenoca	PIL-VS / CIN2	PIL-NS	AIS	inv.ploščc.ca	drugo maligno	drugo benigno	PIL-NS	PIL-VS / CIN3
Patolog	300+	PIL-VS / CIN3	inv.adenoca	PIL-VS / CIN3	PIL-NS	AIS	inv.adenoca	AIS	drugo benigno	PIL-VS / CIN3	PIL-VS / CIN3
Patolog	300+	PIL-VS / CIN3	inv.adenoca	PIL-VS / CIN3	PIL-NS	PIL-VS / CIN2	inv.ploščc.ca	PIL-NS	drugo benigno	PIL-VS / CIN2	PIL-VS / CIN3
Patolog	300+	PIL-VS / CIN3	inv.adenoca	PIL-VS / CIN3	PIL-NS	AIS	inv.ploščc.ca	drugo benigno	drugo benigno	PIL-VS / CIN2	drugo benigno

če upoštevamo dif.dg. / komentarje / izpustimo primer 10 (atrofijo) in upoštevamo pomen razlike v diagnozi

		1.	2.	3.	4.	5.	6.	7.	8.	9.
	Št. Bx	PIL-VS / CIN3	inv.adenoca	PIL-VS / CIN 3	PIL-NS	AIS	Inv.ploščc.ca	endometrioza	polip+MGH	PIL-VS / CIN 2
Patolog	0-24	PIL-VS / CIN3	inv.adenoca	PIL-VS / CIN3	PIL-NS	AIS	inv.ploščc.ca	drugo benigno	drugo benigno	PIL-NS
Patolog	0-24	PIL-VS / CIN3	inv.adenoca	PIL-VS / CIN2	PIL-NS	PIL-VS / CIN3	drugo maligno	PIL-VS / CIN2	AIS	PIL-NS
Patolog	0-24	PIL-VS / CIN3	inv.adenoca	PIL-VS / CIN3	PIL-NS	AIS	drugo maligno	PIL-VS / CIN2	PIL-NS	PIL-VS / CIN2
Patolog	0-24	PIL-VS / CIN3	inv.adenoca	PIL-VS / CIN3	PIL-NS	AIS	inv.ploščc.ca	drugo benigno	drugo benigno	PIL-VS / CIN2
Patolog	0-24	PIL-VS / CIN3	inv.adenoca	PIL-VS / CIN3	PIL-NS	AIS	inv.ploščc.ca	AIS	drugo benigno	PIL-VS / CIN3
Patolog	0-24	PIL-VS / CIN3	inv.adenoca	PIL-VS / CIN3	PIL-NS	AIS	inv.ploščc.ca	PIL-VS / CIN3	drugo benigno	PIL-VS / CIN3
Patolog	0-24	PIL-VS / CIN3	inv.adenoca	PIL-VS / CIN3	PIL-NS	PIL-VS / CIN2	inv.ploščc.ca	PIL-VS / CIN3	drugo benigno	PIL-VS / CIN3
Patolog	0-24	PIL-VS / CIN3	drugo maligno	PIL-NS	PIL-NS	AIS	drugo maligno	PIL-NS	drugo benigno	PIL-VS / CIN2
Patolog	25-99	PIL-VS / CIN3	inv.adenoca	PIL-VS / CIN3	PIL-NS	drugo benigno	inv.ploščc.ca	PIL-VS / CIN3	drugo benigno	PIL-NS
Patolog	25-99	PIL-VS / CIN3	inv.adenoca	PIL-VS / CIN3	PIL-NS	drugo benigno	inv.ploščc.ca	drugo benigno	drugo benigno	PIL-NS
Patolog	100-299	PIL-VS / CIN3	inv.adenoca	PIL-VS / CIN3	PIL-NS	PIL-VS / CIN2	inv.ploščc.ca	PIL-VS / CIN3	drugo benigno	PIL-VS / CIN2
Patolog	100-299	PIL-VS / CIN3	inv.adenoca	PIL-VS / CIN2	PIL-NS	AIS	inv.ploščc.ca	drugo benigno	drugo benigno	PIL-VS / CIN2
Patolog	100-299	PIL-VS / CIN3	drugo maligno	PIL-VS / CIN2	PIL-NS	AIS	inv.ploščc.ca	drugo benigno	drugo benigno	PIL-VS / CIN2
Patolog	100-299	PIL-VS / CIN3	inv.adenoca	PIL-VS / CIN3	PIL-NS	AIS	drugo maligno	PIL-NS	drugo benigno	PIL-VS / CIN2
Patolog	100-299	PIL-VS / CIN3	inv.adenoca	PIL-VS / CIN2	PIL-NS	AIS	inv.adenoca	PIL-NS	PIL-VS / CIN2	PIL-VS / CIN2
Patolog	100-299	PIL-VS / CIN2	inv.adenoca	PIL-VS / CIN3	PIL-NS	AIS	inv.ploščc.ca	drugo benigno	drugo maligno	PIL-VS / CIN2
Patolog	100-299	PIL-VS / CIN3	inv.adenoca	PIL-VS / CIN3	PIL-NS	AIS	inv.ploščc.ca	drugo benigno	drugo benigno	PIL-NS
Patolog	100-299	PIL-VS / CIN3	inv.adenoca	PIL-VS / CIN3	PIL-NS	AIS	inv.ploščc.ca	drugo benigno	drugo benigno	PIL-NS
Patolog	300+	PIL-VS / CIN3	inv.adenoca	PIL-VS / CIN2	PIL-NS	AIS	inv.ploščc.ca	drugo benigno	drugo benigno	PIL-VS / CIN2
Patolog	300+	PIL-VS / CIN3	inv.adenoca	PIL-VS / CIN2	PIL-NS	AIS	inv.ploščc.ca	drugo maligno	drugo benigno	PIL-NS
Patolog	300+	PIL-VS / CIN3	inv.adenoca	PIL-VS / CIN3	PIL-NS	AIS	inv.adenoca	AIS	drugo benigno	PIL-VS / CIN3
Patolog	300+	PIL-VS / CIN3	inv.adenoca	PIL-VS / CIN3	PIL-NS	PIL-VS / CIN2	inv.ploščc.ca	PIL-NS	drugo benigno	PIL-VS / CIN2
Patolog	300+	PIL-VS / CIN3	inv.adenoca	PIL-VS / CIN3	PIL-NS	AIS	inv.ploščc.ca	drugo benigno	drugo benigno	PIL-VS / CIN2

Združenje za patologijo in sodno medicino SZD

SMERNICE ZA STANDARDIZACIJO POSTOPKOV IN HISTOPATOLOŠKIH IZVIDOV NA PODROČJU GINEKOLOŠKE PATOLOGIJE - CERVIKALNA NEOPLAZIJA

Priporočila 2015

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Komentar	Priporočila so pripravili člani delovne skupine: Margareta Strojan Fležar, Snježana Frković Grazio, Helena Gutnik Sprejeta priporočila so bila predstavljena na srečanju Združenja za patologijo in sodno medicino 24.10.2015.

SMERNICE ZA STANDARDIZACIJO POSTOPKOV IN HISTOPATOLOŠKIH IZVIDOV NA PODROČJU GINEKOLOŠKE PATOLOGIJE

CERVIKALNA NEOPLAZIJA

UVOD

S histopatološko preiskavo biopsijskih vzorcev materničnega vratu podamo diagnozo bolezenskih sprememb, ki je osnova za odločitev o zdravljenju. Histopatološka diagnoza ostaja tudi zlati standard za kontrolo kakovosti citopatološkega izvida brisa materničnega vratu (BMV) in kolposkopskega izvida (1-4). Histopatološke izvide tkivnih vzorcev materničnega vratu so vsi laboratoriji za patologijo v Sloveniji od l. 2005 po Zakonu o zbirkah podatkov s področja zdravstvenega varstva (UL RS št. 65, 2000) dolžni pošiljati v Register ZORA, histopatološke izvide z diagnozo CIN 3 in karcinom materničnega vratu pa zbirajo tudi v Registru raka Republike Slovenije (5).

POŠILJANJE VZORCEV

Manjše vzorce pošiljajo v 10 % pufranem formalinu v ustreznih zaprtih posodah, ki so označene z identifikacijskimi podatki bolnice in oznako mesta odvzema, če je odvzetih več vzorcev iz različnih mest. Priporočljivo je, da bi večje vzorce pošiljali sveže v ustrezni zaprti posodi čimprej do laboratorija.

Za pravilno vrednotenje histopatoloških sprememb potrebujemo popolne podatke o bolnici in vzorcu, kar mora biti označeno na napotnici in/ali samem vzorcu.

1. Podatki o bolnici
   - osebni podatki (ime in priimek, vsaj datum rojstva, naslov)
   - podatki o naročniku preiskave (ustanova, oddelek, napotni zdravnik, kontaktna telefonska številka)
   - indikacije za poseg (citološki izvid BMV, pozitiven triažni test na humane papiloma viruse (TT HPV), patološki kolposkopski izvid, drugo)
   - podatki o drugih, predvsem predrakavih in malignih boleznih in načinu zdravljenja le teh
   - podatki o prejšnjih citoloških in/ali histopatološki izvidih (ustanova/oddelek za patologijo, po možnosti številka izvida in/ali kopija izvida)
   - podatki o drugih vrstah zdravljenja (npr. hormonsko zdravljenje)
   - podatki o menstrualnem ciklusu, nosečnosti
2. Podatki o vzorcu
   - mesto odvzema vzorca (lokalizacija)
   - tip biopsije (način odvzema vzorca)
   - datum/ura odvzema vzorca

Opomba: Za potrebe Registra ZORA mora histološki izvid oz. izvid biopsije vsebovati naslednje podatke: osebno identifikacijo ženske in vzorca, vrsto vzorca, datum odvzema, identifikacijo ginekologa in patologa, histološki izvid (5).

ODŠČIP/ MANJŠA EKSCIZIJA/ ABRAZIJA CERVIKSA

*Odščip/manjša ekscizija***:** je običajno majhen košček tkiva, dolžine nekaj milimetrov (običajno 4 do 7 mm), debeline od 2 do 4 mm, ki ga iz sluznice materničnega vratu odščipnejo z biopsijskimi kleščami (forceps) ali odvzamejo s skalpelom ali električno zanko.
Abrazija cervikalnega kanala: s kireto postrgajo tkivo s sten cervikalnega kanala.

Makroskopski opis

Vzorce je potrebno makroskopsko opisati in/ali vzorce fotografirati (z vsebnikom, na katerem je vidna oznaka in označene kasete z vzorci).

Makroskopski opis naj vsebuje:

Za odščip / manjšo ekscizijo:
- število koščkov
- lastnosti tkiva (barvo in konzistenco)
- za vsak vzorec velikost (vsaj največji premer vzorca, prekritega s sluznico)

Za *abrazijo cervikalnega kanala:*
- lastnosti tkiva (barvo in konzistenco),
- ocenimo približno skupno velikost tkiva v treh premerih

Postopek vzorčenja:

Poslano tkivo v celoti vložimo v kasete.

Priporočljivo je, da vsak košček porcije materničnega vratu vložimo v svojo kaseto. V nasprotnem primeru lahko v eno kaseto vložimo največ 2 do 3 koščke (odvisno od velikosti – po presoji patologa). Večje vzorce (običajno večje od pribl. 6-7mm) po presoji patologa vzdolžno prerežemo pravokotno na površino sluznice.

Če so v vzorcu abradata drobci tkiva različnih lastnosti in velikosti, jih je priporočljivo vložiti v ločene kasete.

Nadaljnja obdelava vzorcev:

Iz standardno pripravljenih tkivnih blokov režemo tkivne rezine debeline 3-5 µm, v večih nivojih (najmanj 5 nivojev), pri tem razmik med rezinami (globino rezanja) prilagodimo debelini koščka - z narezovanjem naj bi zajeli vsaj polovico debeline vzorca (zato razmak med rezinami lahko variira od 50 µm do 150 µm, iz istega razloga lahko varira tudi število rezin).

Globlji rezi so potrebni v primerih, če stopnja bolezenskih sprememb v bioptičnem vzorcu ni skladna s napotno diagnozo.
Standardna metoda barvanja tkivnih rezin je hematokslin in eozin (HE).
Po presoji uporabljamo dodatna specialna ali imunohistokemična barvanja.

EKSCIZIJSKE BIOPSIJE: KONIZACIJA IN LLETZ

Namen ekscizijske biopsije materničega vratu je odstraniti celotno trasformacijsko cono. Vključuje vzorce konizacije s skalpelom (klasična konizacija), laserske konizacije in ekscizije transformacijske cone z električno zanko (angl. Large Loop Excision of Transformation Zone – LLETZ). V idealnih primerih dobijo s konizacijo s skalpelom ali laserjem stožčasto oblikovan del porcije materničnega vratu z bazo na sluznici, z metodo LLETZ pa diskoidno obliko dela porcije. Predvsem vzorci LLETZ so lahko poslani odprti na enem koncu (oblika črke U), ali poslani v več koščkih.

Makroskopski opis:

Izmerimo velikost konusa v 3 dimenzijah; dva največja premera na bazi konusa in višino. Opišemo lego cervikalnega kanala v ekscizatu (centralno, paracentralno, marginalno, v robu), opišemo vidne lezije in zabeležimo morebitne oznake orientacije vzorca.

Če dobimo v pregled več koščkov (pogosteje pri metodi LLETZ), zabeležimo, ali je sluznica vidna, in v vsakem koščku izmerimo dve največji dimenziji površine prekrite s sluznico ter debelino vzorca.

Kirurške robove vzorcev klasičnega konusa obarvamo s tušem. Vzorcev LLETZ običajno ne barvamo. Če je ekscizat orientiran (npr. šiv na 12. uri) rob vsake ustne označimo z drugo barvo tuša (zabeležimo).

Postopek vzorčenja:

Poslano tkivo vzorčimo v celoti.

Opisane so različne tehnike rezanja konusov. Najpogosteje uporabljamo dve tehniki:

- radialno rezanje: sveže tkivo konusa odpremo s škarjami skozi cervikalni kanal, pripnemo na ustrezno podlago s sluznično stranjo navzgor, fiksiramo (čez noč), nato serijsko zaporedno režemo na 2-3 mm.
- serijsko zaporedno rezanje celega fiksiranega konusa od leve proti desni (ali obratno) na 2-3 mm. Če je vzorec orientiran, zabeležimo smer rezanja.

Ekscizat, ki je povsem razprt ali posamezne vzorce pri eksciziji v večih delih režemo na zaporedne serijske rezine prečno na daljšo os površine ekscizata, ki je prekrita s sluznico.

Posamezne rezne ploskve ekcizata polagamo zaporedno v kasete, število in oznako kaset zabeležimo v makroskopskem opisu.

Nadaljnja obdelava:

Iz standardno pripravljenih tkivnih blokov režemo 3-5 µm tkivne rezine. Tkivna rezina ustrezna za oceno sprememb je rezina, na kateri je zajeta celotna povšina sluznice in vsi ekscizijski robovi - večinoma to dosežemo z rezanjem stopničaste serije rezin (običajno vsaj 5 rezin v razmaku pribl. 200 µm).
Globlji rezi so potrebni v primerih, če stopnja bolezenskih sprememb v bioptičnem vzorcu ni skladna s napotno diagnozo.
Standardna metoda barvanja tkivnih rezin je hematokslin in eozin (HE).
Po presoji uporabljamo dodatna specialna ali imunohistokemična barvanja.

HISTEREKTOMIJA / TRAHELEKTOMIJA Z ALI BREZ PELVIČNE LIMFADENEKTOMIJE

Radikalno histerektomijo naredijo zaradi histološko potrjenega karcinoma materničnega vratu. Vzorec zajema maternico s parametriji, nožnično manšeto ter pelvične in paraaortne bezgavke, običajno tudi adnekse. Izjemoma naredijo enostavno histerektomijo (vzorec zajema samo maternico) zaradi predrakavih sprememb ali ponavljajočih se patoloških izvidov v brisih materničnega vratu. Trahelektomijo običajno naredijo pri zgodnjih stadijih raka materničnega vratu, ko želijo ohraniti plodnost. Vzorec zajema maternični vrat, parametrije, nožnično manšeto in pelvične bezgavke.

Makroskopski opis

Orientiramo resektat glede na peritonej na zadnji steni maternice, glede na adnekse (jajčniki ležijo za jajcevodi) ali ligamentum rotundum. Navedemo vse anatomske dele, zajete v resektatu (nožnična manšeta, maternica, parametriji, jajcevodi, jajčniki). Izmerimo jih in opišemo. Kirurške robove obarvamo s tušem pred odpiranjem organov.

Način fiksacije in narezovanja vzorca prilagodimo legi in velikosti tumorja / spremembe. Svežo maternico odpremo v celoti ali delno in fiksiramo, maternični vrat lahko ločimo od telesa maternice (po presoji patologa).

Opišemo položaj (natančna anatomska lega spremembe in vsa tkiva, ki so zajeta s spremembo) in velikost makroskopsko vidnih sprememb / tumorja (v treh dimenzijah), oddaljenost od resekcijskih robov (globokega in nožničnega), opišemo natančno tudi vsa ostala tkiva/organe v resektatu in odnos tumorja do ostalih struktur.

Za vsako lokacijo navedemo število izoliranih bezgavk, velikost bezgavk in makroskopski videz (morebitne makroskopsko vidne tumorske infiltrate in preraščanje kapsule bezgavke).

Postopek vzorčenja:

Pri majhnih tumorjih in v primerih, ko ni makroskopko vidnega tumorja, vzorčimo maternični vrat v celoti (glej napotke za konizacijo).

Vzorce iz tumorja materničnega vratu jemljemo tako, da prikažemo največjo globino invazije in resekcijske robove (proti nožnici, sprednji del proti mehurju, zadnji del proti rektovaginalnemu septumu, in parametrijem/paracervikalnemu tkivu).

Velike tumorje vzorčimo po principu: 1 tkivni blok na 1 cm največjega premera tumorja.

Vzorčimo tako, da iz odvzetih vzorcev lahko ocenimo globino invazije, oddaljenost tumorja do globokega in distalnega roba ter debelino nespremenjene cervikalne stene pod tumorjem.

Dodatne bloke jemljemo iz okolice tumorja, da bi dokazali morebitne preostanke ploščatocelične intraepitelijske lezije (PIL) ali endocervikalnega adenokarcinoma *in situ* (AIS).

Odvzamemo vzorce celotne debeline spodnjega uterinega segmenta za oceno morebitnega vraščanja proti telesu maternice.

Maternico in adnekse vzorčimo glede na standardne protokole (reference smernic za druge organe), če ni makroskopko vidnega tumorja. Dodatno vzorčimo makroskopsko vidne tumorske infiltrate.

Bezgavke, v katerih makroskopsko ni povsem jasnih zasevkov vzorčimo v celoti. Iz metastatskih bezgavk izjemoma (npr. večjih od 2cm) lahko vzamemo le reprezentativen vzorec s perinodalnimn maščevjem. Če makroskopsko v poslanem tkivu ni jasnih bezgavk, vzorčimo celotno tkivo.

Kasete ustrezno označimo glede na izvor tkiva. Število in oznako kaset zabeležimo v makroskopskem opisu.

Nadaljnja obdelava:

Iz standardno pripravljenih tkivnih blokov režemo 3-5 µm tkivne rezine. Tkivna rezina ustrezna za oceno sprememb je rezina, na kateri je zajeta celotna površina sluznice in vsi ekcizijski robovi, ki so zajeti v vzorcu. Globlji rezi so potrebni v primerih, če stopnja bolezenskih sprememb v bioptičnem vzorcu ni skladna s napotno diagnozo.
Standardna metoda barvanja tkivnih rezin je hematokslin in eozin (HE).
Po presoji uporabljamo dodatna specialna ali imunohistokemična barvanja.

HISTOPATOLOŠKI IZVID

Histopatološki izvid vsebuje makroskopski opis in izvid svetlobnomikroskopske preiskave (tudi specialna barvanja, imunohistokemična barvanja).
V diagnozi navedemo:

- anatomsko lokalizacijo odvzema vzorca / vrsto tkiva in način odvzema,
- histopatološko diagnozo.

Predrakave spremembe
V histopatološkem izvidu uporabljamo za diagnozo predrakavih sprememb na ploščatem epiteliju klasifikacijo po WHO, objavljeno leta 2014: ploščatocelična intraepitelijska lezija nizke stopnje (PIL-NS) in ploščatocelična intraepitelijska lezija visoke stopnje (PIL-VS) (6). Do nadaljnega za PIL-VS obvezno navedemo tudi prejšnjo klasifikacijo po WHO, ki je opredelila predrakave spremembe na ploščatem epiteliju kot cervikalno intraepitelijsko neoplazijo stopnje 2 ali 3 (CIN2, CIN3) (7, 8). Razlog za dodatno navajanje CIN2 je, da se ginekolog pri mlajših bolnicah s to diagnozo lahko odloči za spremljanje in odloži kirurško zdravljenje. CIN3 pa zaenkrat še vedno posebej beležijo tudi v Registru raka RS in ne samo v Registru ZORA, zato potrebujejo v izvidu več kot samo diagnozo PIL-VS.
PIL-NS je širša kategorija kot CIN1 in vključuje tudi condyloma accuminatum, koilocitozo in koilocitno atipijo; te specifične diagnoze lahko navedemo ob PIL-NS v oklepaju.
Predrakava sprememba na žleznem epiteliju je po WHO klasifikaciji iz 2014 samo endocervikalni adenokarcinom in situ (AIS) (9, 10). V nekaterih državah (npr. v Veliki Britaniji) uporabljajo za predrakave spremembe na žleznem epiteliju terminologijo cervikalna glandularna (žlezna) intraepitelijska neoplazija (CGIN). V tej terminologiji CGIN visoke stopnje (VS) ustreza AIS (4, 9, 10). Glede kategorije CGIN nizke stopnje navajajo, da kriteriji niso ponovljivi in dorečeni, zato ni navedena kot posebna entiteta.
V novi WHO uvrščajo stratificirano mucin-producirajočo intraepitelijsko lezijo (SMILE) v endocervikalni AIS (9).
V histopatološki izvid predrakavih sprememb moramo pri konizaciji obvezno vključiti izvid za resekcijske robove (glejte prilogo: Protokol za histopatološki izvid za biopsije/konizacije). Lahko navedemo tudi diagnoze za neneoplastične spremembe epitelija.

Biološki označevalci za ploščatocelične intraepitelijske lezije povezane z okužbo s HPV
Biološki označevalec p16, ki je povezan s transformirajočo okužbo s HPV in odraža aktivacijo celične proliferacije po aktivaciji onkogena E6/7, je uporaben v diagnostiki ploščatoceličnih lezij materničnega vratu (11). Imunohistokemično barvanje na p16 ocenimo kot pozitivno, kadar je barvanje močno in difuzno pozitivno v bloku (v jedrih ali v jedrih in citoplazmi) v 2/3 ali celotni debelini epitelija, ki morfološko lahko ustreza PIL-VS. Neenakomerna (heterogena) in šibka obarvanost jeder je nespecifična in jo lahko najdemo v reaktivni ploščatocelični metaplaziji ali spremembah nizke stopnje (PIL-NS).
Imunohistokemično barvanje na p16 je priporočeno:

- za razlikovanje PIL-VS (CIN2 ali CIN3) od morfološko podobnih sprememb ploščatega epitelija (spremembe, za katere vemo, da nimajo neoplastičnega potenciala: npr. nezrela ploščatocelična metaplazija, atrofija, reparativne spremembe epitelija, tangencialno rezan epitelij);
- za oceno diagnostično težavnega CIN2: močna difuzna pozitivna reakcija v bloku je značilna za predrakave spremembe visoke stopnje, negativna ali fokalno neenakomerno pozitivna reakcija pa za spremembe nizke stopnje ali spremembe, ki niso povezane s HPV;
- kot dodatna metoda, kadar se ocene diagnostično težavnih ploščatoceličnih sprememb med različnimi patologi ne ujemajo in je v diferencialni diagnozi PIL-VS (CIN2 ali CIN3).

- izjemoma v vzorcih, ki jih morfološko ocenimo manj kot ali enako CIN1, vendar obstaja tveganje, da bomo spregledali morebitne spremembe visoke stopnje; tvegani primeri so tisti, ki imajo predhodno citološko oceno PIL-VS, APC-VS, APC-N/ HPV16+, AŽC-N.

Imunohistokemično barvanje na p16 ni potrebno za histopatološko diagnozo ploščatoceličnih lezij, ki morfološko ustrezajo CIN1 ali CIN3, ali pa ne ustrezajo kriterijem za PIL (negativne).

Invazivni karcinom

Histološki tip in diferenciacijo navedemo po klasifikaciji po WHO (6, 9).
Navedemo globino in širino invazije (glejte opombe spodaj) ter morebitno limfovaskularno invazijo, izvid resekcijskih robov, bezgavk in drugih organov (glejte prilogo: Protokol za histopatološki izvid za biopsije/konizacije ter Protokol za histopatološki izvid za histerektomije).
KOMENTAR: Ker je pri najzgodnejši obliki ploščatoceličnega karcinoma materničnega vratu mogoče konzervativno zdravljenje, lahko podatek o »povrhnje invazivnem ploščatoceličnem karcinomu« dodamo v histopatološki izvid. V zadnji WHO klasifikaciji najzgodnješa oblika ploščatoceličnega karcinoma ni več navedena kot ločena kategorija (9). Nasprotno pa projekt LAST (The lower anogenital squamous terminology standardization project for HPV-associated lesions) za najzgodnejšo obliko ploščatoceličnega karcinoma materničnega vratu predlaga termin povrhnje invazivni ploščatocelični karcinom (*angl.* superficially invasive squamous cell carcinoma), ki ga privzemamo. Povrhnje invazivni ploščatocelični karcinom je opredeljen kot invazivni karcinom, ki ni makroskopsko viden, z globino invazije do 3 mm in širino horizontalne rasti do 7 mm (kar ustreza stadiju pT1a1 oz. FIGO IA1) (11).

Merjenje globine invazije (ref. 2, str. 10, primer na skici št.4):

a) Če karcinom neposredno izrašča iz displastičnega epitelija, izmerimo globino invazije od baze epitelija iz katerega izrašča karcinom (površinski epitelij ali žlezna kripta) do najglobljega mesta invazije
b) Če invazivni fokus ni v stiku z displastičnim epitelijem, izmerimo globino invazije od baze najbližje displastične kripte ali povrhnjega displastičnega epitelija do najglobljega mesta invazije
c) Če ni jasnega epitelijskega izvora (displazije), izmerimo globino invazije od baze najbližjega neneoplastičnega povrhnjega epitelija do najglobljega mesta invazije (slika)

Merjenje širine invazije - horizontalna rast (ref. 2, str. 10, primer na skici št.4):
FIGO predvideva 2 dimenziji meritev tumorja (globina in širina).

d) V primeru enega fokusa invazije, ki izvira iz displastičnega epitelija, izmerimo njegovo širino.
e) Za primere <u>multifokalne tumorske rasti</u> obstajajo različna strokovna mnenja glede načina merjenja horizontalne rasti. V histopatološkem izvidu mora biti jasno navedeno, da je tumor multifokalen, navedene morajo biti dimenzije ločenih fokusov invazije in opredeljeno, kako je bil določen FIGO stadij. Take primere naj bi obravnavali na multidisciplinarnih konzilijih za ponoven pregled, oceno in mnenje.

Merjenje tretje dimenzije (ref. 2, str. 10, primer na skici št.6):
Če zajema invazivni karcinom več kot 2 - 3 tkivne bloke, je njegova širina lahko več kot 7 mm, kar pomeni, da je FIGO stadij višji od IA2. V tem primeru določimo tretjo dimenzijo glede na seštevek debeline posameznih tkivnih blokov*.

Navedemo oceno FIGO stadija, TNM stadija – končni stadij določijo na multidisciplinarnem konziliju.
Navedemo šifro histopatološke diagnoze po ICD/SNOMED.

*Podrobna navodila za merjenje invazije in skice so dostopna na spletni strani presejalnega programa za maternični vrat v Veliki Britaniji (2):
http://www.cancerscreening.nhs.uk/cervical/publications/nhscsp10.pdf

Komentar k histopatološki diagnozi
Če s histopatološko preiskavo ne najdemo pričakovanih sprememb, mora biti to jasno navedeno v histopatološkem izvidu. V teh primerih patolog oceni, ali je vzorec reprezentativen (ocenimo npr., ali je zajeta transformacijska cona).
Priporočljiva je primerjava histopatološke diagnoze z napotno histopatološko diagnozo prejšnje biopsije materničnega vratu (odščip, abrazija, prejšnja konizacija). Pri neujemanju moramo narediti dodatne globlje tkivne rezine, še posebej če je prejšnja histopatološka diagnoza potrdila neoplazijo (12).
Globlje rezine režemo tudi pri histoloških znakih sumljivih za invazijo (12).
Navedemo tudi, če biopsija ni tehnično ustrezna (termične poškodbe, itd).

ZAGOTAVLJANJE KAKOVOSTI DELA

1. LABORATORIJ

Laboratoriji oziroma oddelki za patologijo morajo imeti dovoljenje za delo Ministrstva za zdravje RS.
Laboratorij mora imeti standardizirane postopke, ki upoštevajo pričujoče »Smernice za standardizacijo postopkov in histopatoloških izvidov na področju ginekološke patologije« in morajo biti dostopni v pisni obliki (navodila, standardni operativni postopki (SOP).
Priporočljivo je sodelovanje v shemah zunanje kontrole kakovosti dela (npr. UK NEQAS za imunohistokemična barvanja).

2. PATOLOG

Patolog mora imeti veljavno licenco ZZS in sodelovati v predvidenem strokovnem nadzoru ZZS in državnega programa za presejanje raka materničnega vratu ZORA.
Skrbeti mora za ustrezno kontinuirano strokovno izobraževanje na področju ginekološke patologije.
Sodelovati mora v posvetih pri težavnih primerih RMV v svojem laboratoriju, regionalno in na nivoju države.
Sodelovati mora v nadzoru (auditu) pri ponovnih histo/citopatoloških pregledih novo diagnosticiranih primerov RMV.

3. HISTO/CITOPATOLOŠKO UJEMANJE

Histopatološki izvid mora biti zapisan v takšni obliki, da lahko preverimo ujemanje s citološkim izvidom BMV in kolposkopskim izvidom. Ustrezati (slediti) mora standardiziranemu izvidu (protokolu za histopatološki izvid), ki je priloga teh smernic.
Priporočljivo je dodati opombo na koncu izvida, ali se histopatološki izvid ujema s citološkim izvidom BMV.
V primeru, da je stopnja sprememb po histopatološkem pregledu nižja od citoloških sprememb v BMV, je potrebna ponovna biopsija, če je prva neustrezna (ni povrhnjega epitelija, mehanske, termične poškodbe), nereprezentativna, oziroma ponoven pregled BMV za pojasnitev neujemanja.
Navedene primere je priporočljivo obravnavati na multidisciplinarenem konziliju, ki opredeli ustrezno nadaljnjo obravnavo bolnice.

4. DODATNA MERILA ZA ZAGOTAVLJANJE KAKOVOSTI

- Laboratoriji morajo upoštevati priporočila RSK za patologijo in sodno medicino o željenih časih za zaključevanje biopsij (13).
- Kontrola kakovosti histopatoloških izvidov v laboratoriju: ponovno pregledovanje naključno izbranih biopsij materničnega vratu in ugotavljanje ujemanja diagnoz med patologi (realizacija odvisna od delovnih obremenitev).

5. KONZILIJI ZA PREDRAKAVE SPREMEMBE IN RAK MATERNIČNEGA VRATU

Zaželjeni so multidisciplinarni sestanki med patologi, citopatologi, ginekologi - kolposkopisti, ki predstavijo in uskladijo izvide vseh preiskav in načrtujejo nadaljnje postopke pri bolnicah s predrakavimi spremembami na maternicnem vratu.
Multidisciplinarna obravnava bolnic z rakom materničnega vratu je opredeljena v Smernicah za zdravljenje bolnic z rakom materničnega vratu (14).

VIRI

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PROTOKOL ZA HISTOPATOLOŠKI IZVID NEOPLASTIČNIH SPREMEMB MATERNIČNEGA VRATU - BIOPSIJE/KONUSI

Priimek in ime bolnice **Številka biopsije / Naziv laboratorija**

_____ _____ / _____

Datum rojstva: _____ Datum sprejema: _____
Št. ZZS: _____ Datum izvida: _____
Napotni zdravnik: _____ Patolog: _____
Napotna ustanova: _____
Napotni oddelek: _____
Št. popisa: _____

Diagnoza (vodilna): _____ **Šifra (ICD/SNOMED): _____**

Opis vzorca:

☐ **Odščip/i**
Število vzorcev: _____
Mere (vsaj dva premera v mm):_____
☐ **Abrazija**
Ocena količine (trije premeri v mm)):_____
☐ **Izrez (ekscizija)**
Število vzorcev:_____
Mere (trije premeri v mm) :_____
☐ **LLETZ**
Število vzorcev:_____
Mere (trije premeri v mm) :_____
☐ **Konus**
Število vzorcev:_____
Mere (trije premeri v mm) :_____

Predrakave spremembe: ☐ **da** ☐ **ne**

PIL ☐ da ☐ ne
Stopnja: ☐ PIL-NS ☐ PIL-VS/CIN2 ☐ PIL-VS/CIN3
AIS (adenokarcinom in situ): ☐ da ☐ ne

Invazivni tumor: ☐ **da** ☐ **ne**

Histološki tip (WHO):
☐ Ploščatocelični karcinom
☐ Adenokarcinom
☐ Drugo _____(napiši)

Diferenciacija
☐ dobro/gradus 1 ☐ zmerno/gradus 2 ☐ slabo/gradus 3 ☐ SNO ☐ ND

Način rasti invazivnega tumorja:

☐ en fokus ☐ multifokalno ☐ ND ☐ *invazivni tumor prisoten v ≥3 zaporednih tkivnih blokih

**v teh primerih je lahko največja dimenzija lezije (ki je sicer ne moremo izmeriti v enem histološkem preparatu) >7mm, kar ustreza stadiju pT1b / FIGO IB in ne pT1a / FIGO IA, kot bi bilo ocenjeno iz enega histološkega preparata*

Mere tumorja:

- največji horizontalni premer _____mm
- največja globina invazije_____ mm

☐ ND

Ektocervikalni rob:	☐ v zdravo	☐ PIL	☐ AIS	☐ Ca	☐ ND
Endocervikalni rob:	☐ v zdravo	☐ PIL	☐ AIS	☐ Ca	☐ ND
Globoki lateralni / radialni rob:	☐ v zdravo	☐ PIL	☐ AIS	☐ Ca	☐ ND

Odaljenost invazivnega tumorja od najbližjega roba: lokacija: _____

Limfovaskularna invazija: ☐ ne ☐ da ☐suspektna

Skupno število blokov/ število stekelc (globine): _____/_____

Dodatne metode: ☐ da ☐ ne _____(naštej)

Komentar:

Podpis patologa: _____ Datum:_____

PIL = *ploščatocelična intraepitelijska lezija*
CIN = *cervikalna intraepitelisjka neoplazija*
Ca *= invazivni karcinom*
ND = *nedoločljivo oz. ne določamo (npr. velikosti tumorja v odščipu)*
SNO *= se ne ocenjuje (npr. histološki gradus pri seroznem karcinomu)*

PROTOKOL ZA HISTOPATOLOŠKI IZVID ZA RAKA MATERNIČNEGA VRATU – HISTEREKTOMIJA

Priimek in ime bolnice **Številka biopsije / Naziv laboratorija**

_____ _____/_____

Datum rojstva:_____ Datum sprejema:_____

Št. ZZS: _____ Datum izvida: _____

Napotni zdravnik: _____ Patolog: _____

Napotna ustanova:_____

Napotni oddelek: _____

Št. popisa: _____

Diagnoza (vodilna): _____ Šifra (ICD/ SNOMED):_____

Opis vzorca:

Organi (označi)	Mere	b.p.	Spremembe (opiši)
☐ Maternica	_____	☐	☐ _____
☐ Parametriji	_____	☐	☐ _____
☐ Desni jajčnik	_____	☐	☐ _____
☐ Levi jajčnik	_____	☐	☐ _____
☐ Desni jajcevod	_____	☐	☐ _____
☐ Levi jajcevod	_____	☐	☐ _____
☐ Nožnica	_____	☐	☐ _____
☐ Sečni mehur	_____	☐	☐ _____
☐ Rektum	_____	☐	☐ _____
☐ Drugo:_____(napiši)	_____	☐	☐ _____

Makroskopsko viden tumor ☐ ne ☐ da

Maksimalna makroskopska dimenzija tumorja _____mm x_____mm

Lokacija tumorja v cerviksu ☐ spredaj ☐ zadaj ☐ desno ☐ levo ☐ cirkumferentno ☐ ektocerviks ☐ endocerviks

Makroskopsko tumor zajema ☐ korpus maternice ☐ vagino ☐ parametrije ☐ paracervikalna tkiva

Diagnoza:

Invazivni tumor ☐ da ☐ ne

Histološki tip (WHO)

☐ Ploščatocelični karcinom ☐ Adenokarcinom ☐ Drugo_____(napiši)

Diferenciacija

☐ dobro/gradus 1 ☐ zmerno/gradus 2 ☐ slabo/gradus 3 ☐ SNO ☐ ND

Način rasti invazivnega tumorja

☐ en tumor/fokus ☐ multifokalno ☐ mikroskopsko invazivni tumor v ≥3 zaporednih tkivnih blokih*

**v teh primerih je lahko največja dimenzija lezije (ki je sicer ne moremo izmeriti v enem histološkem preparatu) >7mm, kar ustreza stadiju pT1b / FIGO IB in ne pT1a / FIGO IA, kot bi bilo ocenjeno iz enega histološkega preparata*

Mere invazivnega tumorja (upoštevajoč makroskopski in/ali mikroskopski izvid)

- maksimalni horizontalni premer tumorja _____mm
- debelina /globina invazije _____mm

Resekcijski robovi (distalni, radialni)

☐ v zdravem ☐ inv. tumor v _____robu ☐ PIL cerviks/AIS/PIL vagina v distalnem robu (označi /obkroži)

Minimalna debelina cervikalne strome brez tumorske infiltracije_____ mm, _____ (lokacija)

Najbližji radialni resekcijski rob (vključuje paracervikalna tkiva) **_____** mm, _____ (lokacija)

Tumorska infiltracija vagine ☐ ne ☐ da

- lokacija _____- odaljenost od distalnega vaginalnega roba _____mm

Tumorska infiltracija paracervikalnih mehkih tkiv ☐ ne ☐ da _____ (lokacija)

Tumorska infiltracija parametrijev ☐ ne ☐ da _____(levo in/ali desno)

Limfovaskularna invazija ☐ ne ☐ da ☐suspektna

Perinevralna invazija ☐ ne ☐ da

Pelvične bezgavke

Desne št.pozitivnih/skupno št.	**Mesto**	**Leve** št.pozitivnih/skupno št.
vzorčene ☐ ne ☐ da ____/____	obturatorne	vzorčene ☐ ne ☐ da ____/____
vzorčene ☐ ne ☐ da ____/____	zunanje iliakalne	vzorčene ☐ ne ☐ da ____/____
vzorčene ☐ ne ☐ da ____/____	notranje iliakalne	vzorčene ☐ ne ☐ da ____/____
vzorčene ☐ ne ☐ da ____/____	skupne iliakalne	vzorčene ☐ ne ☐ da ____/____

Para-aortne bezgavke

vzorčene ☐ ne ☐ da ____/____ (št.pozitivnih / skupno št.)

Širjenje tumorja v ekstranodalno maščevje

☐ ne ☐ da _____(lokacija)

Prisotnost predrakavih sprememb

PIL: ☐ ne ☐ PIL-NS ☐ PIL-VS/CIN2 ☐ PIL-VS/CIN3

AIS: ☐ ne ☐ da

Mikroskopske spremembe drugih tkiv in organov

Tkivo / organ	b.p.	Spremembe (opiši)
☐ Endometrij	☐	☐ _____
☐ Miometrij	☐	☐ _____
☐ Desni jajčnik	☐	☐ _____
☐ Levi jajčnik	☐	☐ _____
☐ Desni jajcevod	☐	☐ _____
☐ Levi jajcevod	☐	☐ _____
☐ Nožnica	☐	☐ _____
☐ Drugo:_____(napiši)	☐	☐ _____

FIGO stadij* _____
TNM stadij* _____
**upoštevati/primerjati izvid konusa/LLETZa – končni stadij sledi oceni ginekološko-onkološkega konzilija)*

Skupno število blokov/ število stekelc: _____/_____

Dodatne metode: ☐ ne ☐ da
_____(naštej)

Komentar:

Podpis patologa:_____ Datum:_____

***b.p.**= brez posebnosti*
PIL = ploščatocelična intraepitelijska lezija
***CIN =** cervikalna intraepitelijska neoplazija*
***AIS** = adenokarcinom in situ*
VAIN = vaginalna intraepitelijska neoplazija
***SNO** = se ne ocenjuje (npr. histološki gradus pri seroznem karcinomu)*
***ND=** nedoločljivo (npr. zaradi avtolitičnih sprememb tumorja ni mogoče določiti gradusa)*

Revizijsko stanje:

Revizija	Datum revizije	Izdaja	Opis sprememb
1	24.10.2015	2	Uskladitev klasifikacije z WHO iz 2014 - uvedba PIL, navodila za uporabo p16 (LAST), komentar za povrhnje invazivni ploščatocelični karcinom (LAST).

Carcinoma of the Cervix
Histopathology Reporting Guide

Family/Last name

Given name(s)

Date of birth DD – MM – YYYY

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
  - ○ Type not specified
  - ○ Radical
- ☐ Hysterectomy
  - ○ Simple
  - ○ Part of exenteration
  - ○ Radical
  - ○ Type not specified
- ○ 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
- ☐ 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

Scope

This dataset has been developed for the pathology reporting of primary cervical carcinomas. Specimens include loop/cone excisions, trachelectomies, simple and radical hysterectomies and exenterations. The dataset applies to epithelial neoplasms only and does not apply to small biopsy specimens.

Note 1 - Prior treatment (Recommended)

Reason/Evidentiary Support

Prior chemotherapy, chemoradiation and radiation therapy may significantly alter the original tumour size. Patients with clinical stage IB2 to IIB cervical cancer usually receive chemotherapy, radiation or chemoradiation and this is followed by hysterectomy in some institutions.[1-6] Studies have shown that the cervical tumour totally disappears in the majority of the cases with only a third of hysterectomy specimens containing residual tumour after neoadjuvant chemoradiation. Chemotherapy, chemoradiation or radiation may also introduce histological changes that were not present in the untreated tumour, such as multinucleate tumour giant cells and degenerate nuclei. Metastatic carcinomas may mimic primary cervical malignancies and knowledge of the patient's cancer history is important for the diagnostic workup (immunohistochemistry or molecular studies) of a newly discovered cervical malignancy. Finally, histological findings (tumour size, histological type and grade and sometimes other parameters) in a prior cervical loop or cone excision may be important for the ultimate tumour staging and grading in a hysterectomy specimen. In patients with a prior loop excision, the size of the tumour in the original loop has to be taken into consideration in determining the overall tumour size (see section on **TUMOUR DIMENSIONS**).[1-6]

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Note 2 - Specimen/s submitted (Required)

Reason/Evidentiary Support

The type of operative procedure undertaken, such as a simple or radical hysterectomy, is defined by the surgeon. A radical trachelectomy or hysterectomy includes parametrectomy with resection of the para-uterine node-bearing tissue. While the nature of the specimen(s) submitted for pathological assessment can usually be deduced from the procedure, in some cases the tissue submitted may be incomplete or include more components than expected and therefore specifying the anatomical structures included in the specimen(s) provides complementary information and confirmation that entire organ(s) have been resected and submitted.

Gynaecological oncologists typically divide lymph nodes into anatomical sub-groups and this should be documented in the report.

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Note 3 - Specimen dimensions (Required and Recommended)

Reason/Evidentiary Support

Cervical specimens include loop/cone excisions, simple and radical hysterectomies, simple and radical trachelectomies, and pelvic exenterations. The cervix is a cylindrical structure and taking into account the various surgical procedures that are carried out to remove it, this means that a conventional approach to measuring the size of the cervix in 3 dimensions is difficult to apply. Measurement is further complicated by differences between laboratories in how they fix and grossly examine the specimens. In loop/cone excisions and trachelectomies, the diameter of the ectocervix (two dimensions) and the depth (thickness) of the specimen should be recorded in millimetres (mm). The metric should be accurate and reproducible since it may be important for documentation, diagnostic and prognostic purposes and therapeutic decision-making.

The minimum and maximum cranio-caudal lengths of the vaginal cuff, when present, should be measured in mm. If a parametrectomy has been performed, a measurement from the side of the uterus to the lateral edge of each unstretched parametrium (lateral extent) should be recorded in mm. Surgically dissected parametrium (formal parametrectomy) is not part of a simple hysterectomy specimen. Fragments of paracervical/parametrial soft tissue may be included in the sections of cervix from a simple hysterectomy. Some pathologists may submit this tissue as a paracervical/parametrial shave. Although paracervical/parametrial tissue is present, this does not represent a formal parametrectomy.

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Note 4 - Macroscopic appearance of tumour(s) (Recommended)

Reason/Evidentiary Support

Documentation of the macroscopic appearance of cervical tumours allows correlation with the clinical and radiological assessment of the tumour. Clinically visible cervical cancers are, by definition, FIGO stage IB1 at least.[7]

Exophytic/polypoid carcinomas may have a growth pattern that results in very little or even no invasion of the underlying stroma and ulcerated tumours may entirely or predominantly supplant the surface epithelium. In both these circumstances, it may be necessary to measure tumour "Thickness" rather than "Depth of Invasion" and it is helpful to document the macroscopic appearance to provide context and explanation for the use of the alternative measurements. In large circumferential tumours, there is a risk of overestimating the maximum horizontal extent of the tumour (see section on **TUMOUR DIMENSIONS**). Bulky ($\geq$ 4 cm) barrel-shaped cervical tumours had a significantly worse overall and disease-free survival in one study, but bulky exophytic cervical tumours had the same surgical morbidity, overall and disease-free survival as non-bulky cervical tumours.[8]

The macroscopic appearance of the tumour influences tumour sampling. For cases where there is no macroscopically visible tumour either because there has been a prior surgical procedure or prior therapy the entire cervix should be blocked. For cases with a large visible tumour, it is not necessary to block the whole tumour, but instead careful block selection ensuring representative sampling of the tumour, accurate assessment of margins and tumour extent is required. The blocks should be taken to include the nearest margin(s) and show the maximum depth of stromal invasion. In departments where the facility for processing oversize blocks is available, a good overview of the tumour and resection margins can be obtained. In departments where this facility is not available, large blocks may need to be subdivided; in such cases, the relationship of the blocks to one another should be clearly documented.

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Note 5 – Macroscopic tumour site (Required)

Reason/Evidentiary Support

The gross location of cervical tumours in all resection specimens, including hysterectomy specimens and trachelectomies, must be documented. In addition to providing the tumour dimensions (see section on **TUMOUR DIMENSIONS** below) and the proximity of the tumour to surgical resection margins, the relationship to local anatomical structures such as the vaginal cuff, the resected parametrial tissue (if present) as well as involvement of the lower uterine segment and uterine corpus should be documented. Because there may be an increased risk of para-aortic lymph node spread[9] and a higher rate of ovarian metastases[10] in cases with invasion of the uterine corpus, the presence of macroscopic involvement of the uterine corpus should be recorded.

The exact anatomical location of the cervical tumour should be stated (e.g. anterior or posterior cervical lip, right or left lateral, ectocervix or endocervix) and it may be helpful to provide a precise location according to the position on a clock face for localised tumours, or to specify circumferential cervical involvement when appropriate. Specifying the exact site of the tumour allows detailed comparison with radiological findings and also facilitates careful block selection and embedding of tissue slices with respect to the resection margins. Sometimes in cases where a previous loop excision has been undertaken or prior chemotherapy, chemoradiation or radiation therapy has been administered, no grossly visible tumour is identified in the hysterectomy or trachelectomy specimen. In the event that sub-categorisation of the tumour site with respect to laterality or anterior/ posterior location is not possible (for example, in an unorientated trachelectomy specimen), then only the main/primary site, (ectocervix, endocervix etc) should be recorded.

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Note 6 - Block identification key (Recommended)

Reason/Evidentiary Support

The origin/designation of all tissue blocks should be recorded. This information should ideally be documented in the final pathology report and is particularly important should the need for internal or external review arise. The reviewer needs to be clear about the origin of each block in order to provide an informed specialist opinion. If this information is not included in the final pathology report, it should be available on the laboratory computer system and relayed to the reviewing pathologist. It may be useful to have a digital image of the specimen and record of the origin of the tumour blocks in some cases.

Recording the origin/designation of tissue blocks also facilitates retrieval of blocks for further immunohistochemical or molecular analysis, research studies or clinical trials.

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Note 7 – Tumour dimensions (Required)

Reason/Evidentiary Support

Reasons for accurate tumour measurement

Measurement of tumour dimensions in cervical carcinomas is important for accurate FIGO staging of early cervical cancers, patient management and patient prognostication. Tumours should be measured in mm in three dimensions, namely two measurements of horizontal extent and the depth of invasion (Figure 1). There are multiple problems with regard to measuring cervical tumours and these are discussed in detail in this section. In addition, it may not be possible to provide accurate tumour dimensions in fragmented or thermally damaged specimens. In situations where the tumour extends to resection margins, the tumour dimensions should be qualified by use of the term 'at least' to indicate that the measurements may not indicate the true/final tumour size.

In most datasets, separate gross and microscopic measurements are mandated but this may result in confusion if different measurements are given. Some tumours (especially larger ones) are more accurately measured grossly while others (especially smaller tumours and some larger tumours with a diffusely infiltrative pattern or with marked tumour associated fibrosis) are best measured (or can only be measured) microscopically. In this dataset, separate gross and microscopic measurements are not included but rather one set of measurements is required which is based on a correlation of the gross and microscopic features with gross examination being more important in some cases and microscopic examination in others. A few other points are emphasised:-

1. In providing the final tumour dimensions, the measurements in any prior specimens, for example loop/cone excisions, will need to be taken into account. Although it may overestimate the maximum horizontal extent, it is recommended to add together the maximum horizontal measurement in different specimens when calculating the final horizontal extent. The depth of invasion can be taken as the maximum depth of invasion in the two different specimens. Similar comments pertain if loop/cone excisions are received in more than one piece and where multifocal tumour can be excluded.
2. Many cervical carcinomas of large size or advanced stage are treated by chemoradiation, without surgical resection, once the diagnosis has been confirmed on a small biopsy specimen. In such cases, the tumour dimensions will be derived from clinical examination and the radiological appearances. As indicated previously, this dataset applies only to excision/resection specimens and not to small biopsy specimens.
3. Occasionally resections are undertaken following chemoradiation for cervical carcinoma. In such cases, there may be no residual tumour or only small microscopic foci making it impossible to assess the tumour dimensions. In such cases, the pre-treatment clinical or radiological tumour dimensions should be used for staging.

Specific situations where tumour measurements are important

These include:-

1. Small carcinomas where accurate measurement is paramount in distinguishing between FIGO stage IA1, IA2 and IB1 neoplasms.[7] As well as providing an accurate stage, this may also be critical in dictating patient management. For example, FIGO IA1 neoplasms are often treated by local excision ensuring that the margins are clear of pre-invasive and invasive disease while IA2 and IB1 neoplasms are usually treated by radical surgery (radical hysterectomy or trachelectomy).
2. In patients with FIGO stage IB tumours treated by radical hysterectomy, the tumour size is often one of the parameters used (in conjunction with tumour differentiation, presence or absence of lymphovascular invasion and distance to margins) in assessing the need for adjuvant therapy.

3. The tumour measurements may be important in helping to determine whether radical hysterectomy or trachelectomy is performed; sometimes a cut-off size of 2 cm is used for performing a radical trachelectomy, although some surgeons would still perform this procedure for larger size lesions. Following radical trachelectomy, the recurrence rate is statistically higher with tumour size greater than 2 cm and rates of adjuvant treatment are higher.[11,12] There is also a trend towards more conservative surgery (simple as opposed to radical hysterectomy) in patients with tumours less than 2 cm as the probability of parametrial infiltration is very low.
4. Several studies have shown that in FIGO stage IB1 cervical carcinomas, a cut-off size of 2 cm may be of prognostic value.[13,14]
5. A cut-off of 4 cm is similarly of prognostic significance in distinguishing between FIGO IB1 and IB2 neoplasms and between IIA1 and IIA2 neoplasms.[7,15]

Measurement of horizontal extent of tumour (Figures 1 and 2)

The horizontal extent (two dimensions, i.e. both tumour length and width, measurements 'b' and 'c' in Figure 1) must be measured in all cases. As discussed earlier, in large tumours, this may best be done grossly if large block processing is not available, because in many cases these neoplasms will need to be submitted in multiple cassettes and the maximum tumour dimension may not be represented on a single slide. If a gross measurement is not performed in large circumferential tumours, there is a risk of overestimating the maximum horizontal extent of the tumour. This can occur when a circumferential tumour is "opened-up" and submitted in several sequential cassettes. When the other horizontal dimension (the third dimension) is calculated by adding up sequential slices in this situation (see below), this may result in an artificially greater measurement than is accurate.

In smaller neoplasms, the horizontal extent is best determined histologically (Figure 2). One dimension is the measurement in a single slide in which the extent of invasion is the greatest (measurement 'e', Figure 2). If the invasive focus is only represented in 1 block, then the other horizontal dimension is taken to be the thickness of the block (usually 2.5-3 mm, or estimated as indicated below). In some cases, the maximum horizontal extent may need to be calculated in the manner below if this is not represented in one section but is spread over several adjacent sections (measurement 'c', Figure 1). If invasive carcinoma is present in several adjacent sections of tissue and the invasive foci co-localise in the sections, the horizontal extent of the carcinoma should be calculated by an estimate of the thickness of the blocks, which is determined from the macroscopic dimensions of the specimen and the number of blocks taken. However, pathologists should be mindful that thickness of large or outsize blocks can vary from block to block, as compared with standard-sized blocks. Whilst it is acknowledged that measurements from calculating block thickness may be somewhat inaccurate, it will in some cases be the only way to determine the maximum horizontal extent and this may affect staging, especially in small tumours. A few points regarding measurement of the horizontal extent of tumours are listed below:-

1. in a case where a single tongue of stromal invasion is seen in continuity with the epithelium of origin (surface or glandular), the width of the single focus of invasion is measured across the invasive tongue.
2. where clustered foci of stromal invasion arise close together from a single crypt or from dysplastic surface epithelium as detached cell groups, the maximum horizontal extent must encompass all the foci of invasion in the immediate area and the horizontal extent should be measured from the edge at which invasion is first seen to the most distant edge at which invasion is detected.
3. where several foci of invasion arise in one single piece of cervical tissue as separate foci of invasion, but in close proximity (see section below on **MEASUREMENT OF MULTIFOCAL CARCINOMAS**), either as contiguous tongues of invasion or detached epithelial groups, the maximum horizontal extent is taken from the edge at which invasion is first seen to the most distant edge at which invasion is detected. The small amount of intervening tissue with no invasion (usually with in situ neoplasia) is included in the measurement.

Measurement of depth of invasion (Figure 2)

The maximum depth of invasion must be measured in all cases. This measurement is taken from the base of the epithelium (surface or crypt) from which the carcinoma arises to the deepest point of invasion, as specified in the FIGO classification.[7] If the deepest point of invasion involves the deep margin of the specimen, comment should be made regarding the possibility of underestimation of the depth of invasion; this is particularly applicable to loop/cone specimens. When the invasive focus is in continuity with the dysplastic epithelium from which it originates, this measurement is straightforward. If the invasive focus or foci are not in continuity with the dysplastic epithelium, the depth of invasion should be measured from the tumour base (deepest focus of tumour invasion) to the base of the nearest dysplastic crypt or surface epithelium (Figure 2, measurements 'a' and 'c'). If there is no obvious epithelial origin despite multiple levels of the tissue block, the depth is measured from the tumour base (deepest focus of tumour invasion) to the base of the nearest surface epithelium, regardless of whether it is dysplastic or not (Figure 2, measurement 'd').

There are some situations where it is impossible to measure the depth of invasion. In such cases, the tumour thickness may be measured and this should be clearly stated on the pathology report along with the reasons for providing the thickness rather than the depth of invasion. In such cases, the pathologist and clinician should equate the tumour thickness with depth of invasion for staging and management purposes.

Situations where it may be necessary to measure the tumour thickness rather than the depth of invasion include:-

1. in some glandular lesions, it may be impossible to accurately assess where adenocarcinoma in situ (AIS) ends and where invasive adenocarcinoma begins. This is because, in general, identification of invasion in a glandular lesion is more difficult than in a squamous lesion and this is an area where a specialist opinion may be of value. In some cases where the thickness is measured (from the epithelial surface to the deepest point of the tumour) because the point of origin is impossible to establish, this may result in overestimation of the depth of invasion.
2. in ulcerated tumours with no obvious origin from overlying epithelium, the thickness may need to be measured. In this situation, measurement of tumour thickness may result in an underestimate of the depth of invasion.
3. uncommonly, squamous carcinomas, adenocarcinomas and other morphological subtypes are polypoid with an exclusive or predominant exophytic growth pattern. In such cases, the carcinoma may project above the surface with little or even no invasion of the underlying stroma. These should not be regarded as in-situ lesions and the tumour thickness will need to be measured in such cases (from the surface of the tumour to the deepest point of invasion). Depth of invasion i.e. the extent of infiltration below the level of the epithelial origin, should not be provided in these cases as it may not be a true reflection of the biological potential of such tumours.

Avoid the term microinvasive carcinoma

The term "microinvasive carcinoma" does not appear in the FIGO staging system for cervical cancer.[7] Furthermore, use of the term "microinvasive carcinoma" has different connotations in different geographical areas. For example, in the United Kingdom, microinvasive carcinoma was considered to be synonymous with FIGO stage IA1 and IA2 disease in most, but not all, institutions (some used the term "microinvasive carcinoma" to denote only FIGO stage IA1 tumours). In the United States and Canada where the Lower Anogenital Squamous Terminology (LAST)[16] recommendations have been adopted, the term superficially invasive squamous cell carcinoma (SISCCA) is used to describe FIGO stage 1A1 tumours with negative margins, and the term "microinvasive squamous cell carcinoma" is no longer in routine use. Confusingly, however, the American Society of Gynecologic Oncology (SGO) has its own definition of stage IA tumours, which is limited not only by the depth of tumour invasion, but, in contrast to FIGO and TNM, also by the absence of lymphovascular invasion.[17] According to the SGO, cancers invading less than 3 mm but with lymphovascular involvement are classified as FIGO stage IB1. Thus, in order to avoid confusion, it is

recommended to avoid using the term “microinvasive carcinoma” for all morphological subtypes and to use the specific FIGO stage.

Measurement of multifocal carcinomas

Early invasive carcinomas of the cervix, especially squamous, are sometimes multifocal comprising tumours that show multiple foci of invasion arising from separate sites in the cervix and separated by uninvolved cervical tissue. Specifically, multifocal tumours should be diagnosed if foci of invasion are:

- separated by blocks of uninvolved cervical tissue (levels must be cut to confirm this)
- located on separate cervical lips with discontinuous tumour, not involving the curvature of the canal
- situated far apart from each other in the same section (see below).

The individual foci of stromal invasion may be attached to, or discontinuous from, the epithelium from which they arise. Multifocal carcinomas should not be confused with the scenario in which tongues or buds of invasion originate from more than one place in a single zone of transformed epithelium and will, over time, coalesce to form a single invasive tumour which represents unifocal disease (and should be measured as indicated above, in three dimensions).

The frequency of multifocality in FIGO stage IA1 cervical squamous carcinomas has been reported to be between 12 and 25%[18-20] although multifocality in larger, advanced tumours is uncommon. There are few (and some rather dated) guidelines regarding measurement of multifocal carcinomas. Although pre-invasive disease may be present, when foci of stromal invasion arise from separate sites or are separated by cervical tissue without invasion (after levels/deeper sections have been cut to confirm this), the foci of invasion should be measured separately, in 3 dimensions, as described above, and staged according to the dimensions of the larger/largest tumour with a clear statement that the tumour is multifocal. However, in the last of the scenarios mentioned above (foci of stromal invasion situated far apart from each other in the same section) measurement of the multifocal disease is problematical. Options include measuring from the edge of one invasive focus to the edge of the furthest invasive focus according to FIGO guidelines (irrespective of the distance between foci of invasion), adding the maximum horizontal extent of each invasive focus together (which clearly does not reflect the biological potential of the individual invasive foci) or regarding widely separated foci as representing small independent areas of invasion.[18-22] For tumours with a shallow depth of invasion (up to 3mm), the assessment and measurement of multifocal disease have implications for staging. It is in the context of these early, shallow tumours in loop/cone excisions that management may be significantly affected if the maximum horizontal extent is taken from the edge of one invasive focus to the edge of the furthest invasive focus, when the invasive foci are separate from each other. This may upstage a small superficially invasive carcinoma to FIGO stage IB1, leading to radical surgery (radical hysterectomy or trachelectomy) in patients who are often young and wish to retain their fertility. An alternative view is that when widely separated, these foci of invasion could be regarded as separate foci of IA1 disease, which can be treated by local excision or simple hysterectomy.

The SHAPE trial[23] sets out to address this problematic issue. However, two recent studies have regarded such lesions as representing multiple foci of invasion (multifocal FIGO IA1 carcinomas) if the foci of invasion are clearly separated. However, the distance of separation is not defined and FIGO provides no guidance on this matter. An arbitrary minimum distance of 2 mm between each separate focus of invasion has been applied in the 2 studies.[18,19] Follow-up of patients in these two studies, which include a combined total of 46 cases of ‘‘multifocal IA1 cervical squamous carcinomas’’ treated by local excisional methods (loop/cone excision) with margins clear of premalignant and malignant disease, has shown no evidence of recurrent premalignant or malignant disease with median follow-up periods of 45 months and 7 years respectively.[18,19] Moreover, one of the studies also showed that the prevalence of residual pre-invasive (20%) and invasive disease (5%) on repeat excision were comparable to data available for unifocal FIGO stage IA1 cases.[19] These studies included cases which would have been regarded as FIGO stage IB1 had the horizontal extent been measured from the edge of one invasive focus to the edge of the furthest invasive focus, as per FIGO guidelines. Although limited by a relatively small number of cases and the selection of an arbitrary distance of separation of 2 mm, the findings support the hypothesis that with regard to tumour staging and management, it may be appropriate

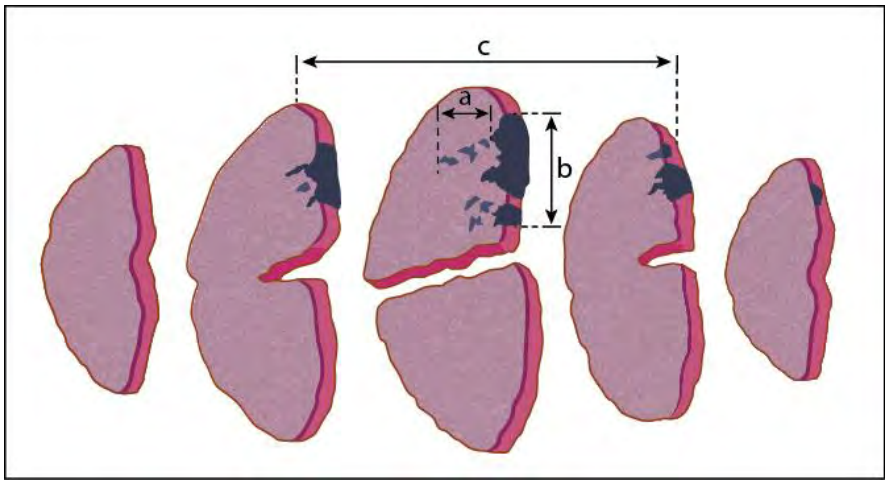
to consider superficial, widely separated foci of invasion as representing multifocal lesions, to measure each focus separately, and to determine the FIGO stage on the basis of the invasive focus with the higher/highest FIGO stage. Of course, the possibility that such lesions behave as FIGO stage IA1 tumours may reflect the shallow depth of invasion, which clinicians do not seem to take account of when faced with a tumour whose maximum horizontal width is 7 mm or more, and the spectre of a FIGO IB1 tumour is raised.

Although the ICCR does not have a mandate to implement an approach based only on 2 studies involving 46 patients in total, the ICCR recommends that this approach be considered and discussed at the Tumour Board/multidisciplinary team (MDT) meetings to avoid unnecessary surgery in young patients who wish to preserve their fertility in this specific clinical situation. This approach needs to be verified by additional larger collaborative studies and trials. It is also stressed that in such cases, the tissue blocks containing the invasive foci and those in between should be levelled to confirm that the invasive foci are truly separate and ensure that there is no occult stromal invasion in the intervening areas. If this approach is adopted, the pathology report should clearly indicate how the measurements have been obtained to arrive at a diagnosis of multifocal invasion, provide the dimensions of the separate foci of invasion and indicate how the FIGO stage has been ascertained. Such cases may need to be referred to Cancer Centres for review and, as indicated above, should be discussed individually at the tumour board/MDT meeting. There have been no similar studies for multifocal adenocarcinomas but anecdotally these are less common than multifocal squamous carcinomas and until further evidence becomes available, a similar approach is recommended.

Measurement of tumour volume

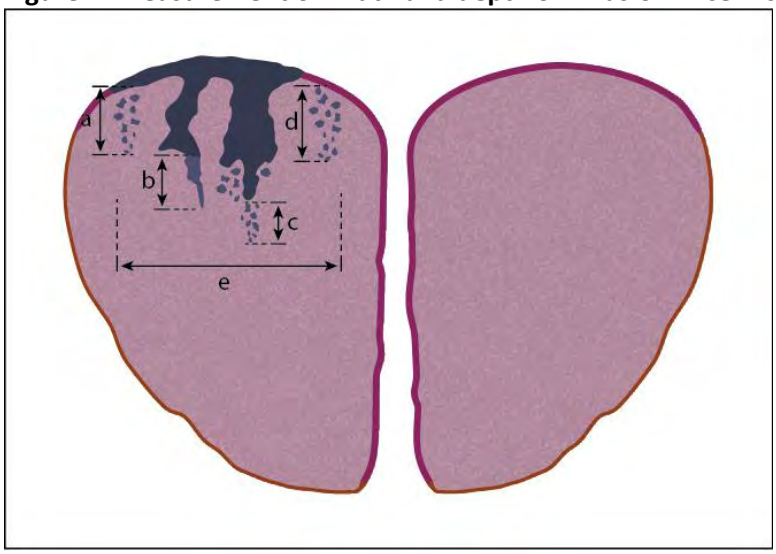
In most studies, tumour size is based on measurement of two dimensions but in a few studies, tumour volume (based on the three measured tumour dimensions) has been shown to predict prognosis more reliably than measurements in only one or two dimensions. Some older studies have suggested tumour volume as a reliable prognostic factor for early stage tumours: a volume of less than 420 mm^3 has been suggested to be associated with no lymph node metastasis.[24-26] This is one of the main reasons for recommending that three tumour dimensions (two of horizontal extent and one of depth of invasion or tumour thickness) are provided. However, only a few centres continue to routinely factor tumour volume into patient management.

Figure 1: Measurement of cervical tumours in three dimensions



CIN3 with involvement of endocervical gland crypts is represented by the dark blue-coloured areas, non-dysplastic squamous epithelium is pink, and grey areas indicate foci of stromal invasion. The depth of invasion, (a), and horizontal tumour dimension/width, (b) are measured in unifocal disease.
Third dimension: when stromal invasion is present in three or more consecutive blocks of a loop or cone biopsy the third tumour dimension, (c), may exceed 7 mm, i.e. the carcinoma may be more than FIGO stage IA2. This dimension is determined by calculating the block thickness (usually 2.5 - 3.0 mm) from the macroscopic specimen dimensions and multiplying this by the number of sequential blocks through which the invasion extends.

Figure 2: Measurement of width and depth of invasion in cervical tumours



The dark blue-coloured areas represent CIN3 with involvement of endocervical gland crypts, non-dysplastic squamous epithelium is pink, and grey areas indicate foci of stromal invasion.
Depth of invasion: when invasion originates from the surface epithelium, (a), or gland crypts (b and c), the depth of invasion is taken from the base of the epithelium from which the invasive carcinoma arises, to the deepest focus of invasion, as specified in the FIGO classification. Measurements are taken in the same way, regardless of whether the invasive foci remain attached to the gland crypt (b) or not (c). Where invasion occurs and no obvious surface (or crypt) epithelial origin is seen, the depth of invasion is measured from the deepest focus of tumour invasion, to the base of the nearest non-neoplastic surface epithelium, (d).
Horizontal dimension/width in unifocal tumours, (e): this is measured in the slice of tissue in which the width is greatest (from the edge at which invasion is first seen, to the most distant edge at which invasion is identified), in sections where the foci of invasion arise in close proximity to each other, even if those foci are separated by short stretches of normal epithelium.

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Note 8 – Histological tumour type (Required)

Reason/Evidentiary Support

All cervical carcinomas should be typed according to the 2014 WHO classification.[27] Carcinosarcoma is also included since, although it is included in the category of mixed epithelial and mesenchymal tumours, it is essentially a carcinoma which has undergone sarcomatous differentiation/metaplasia. The major subtypes of cervical carcinoma are squamous cell carcinoma (SCC), adenocarcinoma (with various subtypes), adenosquamous carcinoma and neuroendocrine tumours. While it is beyond the remit of this document to detail the morphological appearances of the different tumour types in detail, a few points should be noted.

SCCs are nearly all caused by high-risk human papillomavirus (HPV) with rare exception[28,29] and are subclassified by the WHO based on their histological growth pattern and the presence of keratinization. However, the subclassification of SCC seems to have little or no bearing on clinical behaviour and so it is not considered necessary to specify the subtype (keratinizing, papillary, basaloid, warty, verrucous etc). However, it may be useful to record unusual subtypes, for example lymphoepithelioma-like, since the behaviour of these is not well established.

There are several subtypes of cervical adenocarcinoma, the most common being the usual type which, in the majority of cases, is associated with high-risk HPV. The other, less common subtypes (gastric type, mesonephric, clear cell and others) are generally unassociated with HPV infection and have different and distinct histologic appearances. While there is limited information regarding the clinical behaviour of the adenocarcinoma subtypes, it is now well established that gastric type adenocarcinomas of the cervix

(adenoma malignum or mucinous variant of minimal deviation adenocarcinoma is the morphologically well differentiated end of the spectrum of gastric type adenocarcinoma) have a particularly aggressive behaviour with poor prognosis, even in early stage disease.[30-32] Therefore, it is extremely important from both a prognostic stance as well as an aetiologic and epidemiologic perspective (in light of widespread HPV vaccination programs) to correctly identify these tumour subtypes. The ubiquitous use of and reliance on p16 immunohistochemistry to diagnose cervical adenocarcinoma may cause diagnostic problems for HPV negative tumours, since these do not exhibit the diffuse block-type immunoreactivity characteristic of HPV-related tumours (see section on **ANCILLARY STUDIES**).[33,34] In addition, in the era of molecular characterization and targeted therapy, correct identification of the tumour subtypes will be even more crucial for understanding tumour biology and discovery of potential therapeutic targets.

Adenosquamous carcinomas (defined in WHO 2014 blue book as a malignant epithelial tumour comprising both adenocarcinoma and squamous carcinoma[27]) are usually related to high-risk HPV. To make a diagnosis of adenosquamous carcinoma, malignant squamous and glandular components should be identifiable on routine haematoxylin and eosin stained sections. The demonstration of foci of intracytoplasmic mucin by mucin stains in an otherwise typical squamous carcinoma should not result in diagnosis of an adenosquamous carcinoma. Carcinomas which lack evidence of squamous differentiation (intercellular bridges, keratinisation) but have abundant mucin-producing cells should be diagnosed as poorly-differentiated adenocarcinomas. Adenosquamous carcinoma should also be distinguished from a spatially separate squamous carcinoma and adenocarcinoma, which occasionally occurs. While some studies have indicated a worse outcome than pure squamous or adenocarcinomas, there is not robust evidence to confirm these findings.[35,36]

Primary serous carcinoma of the cervix is exceedingly rare and some doubt its existence, although it is included in the 2014 WHO Classification. Most cases reported as primary cervical serous carcinoma are likely to represent a metastasis from the corpus or extrauterine sites or a usual HPV-related adenocarcinoma with marked nuclear atypia. Metastasis should be excluded before diagnosing a primary cervical serous carcinoma. Usual type cervical adenocarcinomas can have a papillary growth pattern and may show high-grade nuclear atypia, which can mimic serous carcinoma. Whether true p53 mutation-associated serous carcinoma of the cervix exists is unresolved at this time.

While endometrioid type adenocarcinoma of the cervix is a subtype listed in the 2014 WHO classification, in the past this has been an over-used diagnostic category and some even doubt its existence as a primary cervical neoplasm. Most adenocarcinomas classified as primary cervical endometrioid adenocarcinomas in the literature represent usual type cervical adenocarcinomas with mucin depletion. These are different from true endometrioid type adenocarcinomas of the uterine corpus or adnexa which are driven by hormones and not HPV-associated. If endometrioid adenocarcinoma occurs as a primary neoplasm in the cervix, it is most likely in the setting of endometriosis and has the same histologic and immunohistochemical profiles as endometrioid adenocarcinomas of the uterine corpus or ovary. As with serous carcinoma, extreme caution should be exercised before diagnosing a primary cervical endometrioid adenocarcinoma.

Neuroendocrine carcinomas (NECs) (small cell and large cell neuroendocrine carcinoma) are uncommon but well described in the cervix and can occur in pure form or associated with another tumour type, typically adenocarcinoma, squamous carcinoma or adenosquamous carcinoma. These are referred to in the WHO 2014 blue book as high-grade neuroendocrine carcinomas. The term 'small cell neuroendocrine carcinoma' is preferred to 'small cell carcinoma' since a small cell variant of squamous carcinoma occurs and if the term "neuroendocrine" is not applied, this may result in confusion. When mixed with another tumour type, the percentage of the neuroendocrine component should be given. Regardless of the percentage of NEC, it is recommended that the tumour be reported as mixed since all tumours containing a component of NEC have a very poor prognosis and the NEC component may be underestimated in a limited sample.[37] Several studies of small cell neuroendocrine carcinomas of the cervix have shown that adjuvant chemotherapy after surgery for early stage disease provides significant clinical benefit compared to surgery alone and therefore, it is extremely important to correctly diagnose any component of NEC. Additionally, in many institutions surgical resection is not undertaken for a NEC even if early stage but instead chemotherapy treatment is given. Diagnosing NEC or a component of NEC can be difficult, especially in small samples, but a combination of

synaptophysin, chromogranin, CD56, TTF1 and p63 has been shown to be helpful in making the distinction between NEC and poorly-differentiated non-NEC (see section on **ANCILLARY STUDIES**).[38,39]

WHO classification of tumours of the uterine cervix

Epithelial tumours	
Squamous tumours and precursors	
Squamous intraepithelial lesions	
High-grade squamous intraepithelial lesion	8077/2
Squamous cell carcinoma, not otherwise specified	8070/3
Keratinizing	8071/3
Non-keratinizing	8072/3
Papillary	8052/3
Basaloid	8083/3
Warty	8051/3
Verrucous	8051/3
Squamotransitional	8120/3
Lymphoepithelioma-like	8082/3
Glandular tumours and precursors	
Adenocarcinoma in situ	8140/2
Adenocarcinoma	8140/3
Endocervical adenocarcinoma, usual type	8140/3
Mucinous carcinoma, NOS	8480/3
Gastric type	8482/3
Intestinal type	8144/3
Signet-ring cell type	8490/3
Villoglandular carcinoma	8263/3
Endometrioid carcinoma	8380/3
Clear cell carcinoma	8310/3
Serous carcinoma	8441/3
Mesonephric carcinoma	9110/3
Adenocarcinoma admixed with neuroendocrine carcinoma	8574/3
Other epithelial tumours	
Adenosquamous carcinoma	8560/3
Glassy cell carcinoma	8015/3
Adenoid basal carcinoma	8098/3
Adenoid cystic carcinoma	8200/3
Undifferentiated carcinoma	8020/3
Neuroendocrine tumours	
Low-grade neuroendocrine tumour	
Carcinoid tumour	8240/3
Atypical carcinoid tumour	8249/3
High-grade neuroendocrine carcinoma	
Small cell neuroendocrine carcinoma	8041/3
Large cell neuroendocrine carcinoma	8013/3
Mixed epithelial and mesenchymal tumours	
Carcinosarcoma	8980/3

The morphology codes are from the International Classification of Diseases for Oncology (ICD-O). Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; and /3 for malignant tumours.

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Note 9 – Histological tumour grade (Recommended)

Reason/Evidentiary Support

Grading of cervical carcinoma

Tumour grade is regularly included in histopathology reports of cervical squamous cell carcinoma (SCC) and adenocarcinoma (ACA). However, at present no particular grading system(s) has achieved universal acceptance and grading of these tumours remains of uncertain clinical value.[40-42] For example, grade is not amongst the factors considered in determining the Gynecology Oncology Group (GOG) score which is used to assess the need for adjuvant therapy following surgery for low-stage cervical carcinomas.[43] Not uncommonly, studies that assess grade as a potential prognostic variable provide no details of the grading system employed, and this is also true of large multicentre investigations such as SEER analyses.[44,45] For these and other reasons (discussed below), tumour grading is not listed as a required but rather a recommended element. Furthermore, no particular grading system for squamous carcinoma or adenocarcinoma is recommended.

General considerations

1. As with tumours arising in other anatomical sites, grading of cervical carcinomas has a considerable subjective component and this probably explains, at least in part, the variable proportion of well, moderately, and poorly-differentiated tumours reported in different studies. However, some investigators have demonstrated reasonable intra- and inter-observer agreement using more complex multifactor grading schemes in SCC (discussed below).

2. Almost all cervical SCCs are HPV-associated and given that HPV-associated SCCs very commonly have a "basaloid" morphology with minimal keratinisation, they are very commonly poorly-differentiated.

3. Most clinically advanced cervical carcinomas are treated with primary chemoradiation rather than surgery and histological sampling may be limited to a small diagnostic biopsy. This may not be fully representative due to tumour heterogeneity and could be potentially misleading as regards tumour differentiation or grade.[40] This may be particularly relevant since less differentiated appearing tumour elements may be located more deeply towards the invasive margin.[41]

4. There is an implicit correlation between tumour subtype and grade in certain cervical carcinomas and therefore a separate grade may not be applicable. For example, pure villoglandular ACA of the cervix is by definition a low-grade neoplasm while serous and clear cell carcinoma, as in the endometrium, are considered high-grade by default. Similarly, 'gastric-type' cervical ACAs and NECs are clinically aggressive regardless of their histological pattern and therefore are best considered high-grade automatically.[30,31] There is no published grading system for cervical mesonephric ACAs. Several variants of cervical SCC are also recognised, although most do not differ from conventional SCC in terms of prognosis or therapy.[46]

5. It is uncertain whether a truly 'undifferentiated' cervical carcinoma should be regarded as a separate tumour subtype analogous, for example, to similar tumours arising in the endometrium.

6. Grading of very small superficially ('early') invasive carcinomas of either squamous or glandular type is probably not possible or relevant.

Grading of Cervical SCC

Historically, cervical SCCs were graded using Broder's system or modifications thereof based upon the degree of keratinisation, cytological atypia and mitotic activity. In some schemes, the pattern of invasion (pushing versus infiltrating) has also been taken into account. Traditionally, SCCs have also been subclassified into large cell keratinising, large cell non-keratinising and small cell non-keratinising categories, with these sometimes being regarded as approximately equivalent to well, moderately and poorly-differentiated,

respectively. As noted above, this raises the issue whether such categorisation represents a tumour subtype (arguably not further graded), or a grade within a spectrum of a single type of tumour. It should be noted that some studies have found that the keratinising variant of large cell SCC actually has a poorer prognosis than the non-keratinising variant, an apparently paradoxical finding if keratinisation is deemed to be evidence of better differentiation. It is also uncertain what proportion of "small cell SCCs" reported in the older literature would now be classified as high-grade NECs (small cell NEC), and this could potentially bias the supposedly poor outcome of this tumour category.

More complex multifactor grading systems (MGS) that include both tumour and host/stromal parameters have been assessed in cervical carcinomas, mainly SCC.[47-51] For example, the system employed by Stendahl et al,[47] based upon that used in head and neck SCC, comprised eight features, 4 of which were tumour-related (growth pattern, differentiation, pleomorphism and mitoses) and four of which were stromal-related (pattern of invasion, stage/depth of invasion, vascular invasion and inflammatory reaction). Each factor was scored from 1 to 3 and thus the potential total MGS score ranged from 8-24 points. Simplified modifications to the MGS have also been described including systems that selectively focus upon the invasive tumour border or the patterns of tumour invasion.[52-55] However, the "cut-off value" for tumour grade has varied in different studies and not all have demonstrated a correlation with prognosis.[41,56,57] At present, none of these grading systems has been widely adopted in routine diagnostic practice.

Grading of Cervical ACA

As with SCC, it is controversial whether grading has independent prognostic value in cervical ACA. Whilst a correlation between higher grade and adverse outcomes has been reported,[58-62] at least for poorly differentiated tumours, this has not been a universal finding.[63,64] It should also be noted that some studies have included a variable proportion of less common histological subtypes such as adenosquamous carcinoma, mesonephric, gastric-type and clear cell carcinoma[58,61,62] and often tumour details are not provided. Therefore, it is not clear whether the reported grading data are applicable to usual-type cervical ACA or have been biased by the inclusion of other more aggressive tumour subtypes (for example, gastric-type ACA).

Most grading systems for cervical ACA have been based upon the relative proportion of glandular differentiation, typically following the FIGO system for endometrial endometrioid adenocarcinoma (EEC). However, the maximum permitted extent of solid growth for a grade 1 cervical ACA has been variably specified to be 5%[65,66] or 10%.[62,67] As with EEC, an upward grade adjustment has been suggested for those tumours exhibiting more marked cytological atypia. However, it is pertinent that usual-type cervical ACAs typically demonstrate more marked nuclear atypia, mitotic and apoptotic activity than architecturally similar EECs. [68] There are no separate grading systems for the various non-HPV related cervical ACAs.

Recently, a system of assessing cervical ACAs based upon their invasive growth pattern has been developed, and this has been shown to be reproducible amongst pathologists and to correlate with the risk of lymph node metastasis and patient outcomes.[69-72] If these findings are confirmed by additional studies it may be argued whether this system could be considered a complement to, or even an alternative to, conventional grading. The latter has traditionally been based upon the cytoarchitectural pattern of the neoplasm itself but as noted above, tumour-stromal relationships including the pattern of stromal invasion have been included in earlier grading schemes of cervical SCC.

Grading of Cervical Adenosquamous Carcinoma

Although it has been suggested that adenosquamous carcinomas are graded on the basis of the degree of differentiation of both the glandular and squamous components, there is no well-established grading system for these neoplasms which has been shown to be of prognostic significance.

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Note 10 – Lymphovascular invasion (Required)

Reason/Evidentiary Support

Lymphovascular invasion (LVI) does not affect FIGO or TNM staging (for example if there is LVI in tissues outside the cervix but the tumour itself is confined to the cervix, this is still FIGO stage I) but should be clearly documented in the pathology report. The significance of LVI in cervical carcinoma has been debated for predicting overall survival (OS), disease free interval (DFI), recurrence free survival (RFS) and regional lymph node metastasis for decades. Although studies conflict, there is general agreement that LVI is an independent predictor of adverse outcome.[41,73-82] Early studies indicated that LVI was an independent predictor of DFI with one study reporting a 1.7 times higher rate of recurrence in patients with LVI compared to those without LVI in low-stage cervical carcinoma.[75] This has been confirmed in later studies, particularly in low-stage (FIGO stage IB) cervical carcinoma.[41] The significance of LVI in superficially invasive squamous cell carcinoma (SISCCA) is unclear, likely due to the rarity of adverse outcomes including lymph node metastasis in SISCCA. Studies have shown that LVI does not predict lymph node metastasis in cases of SISCCA with a depth of invasion of $\leq$3 mm.[83-86,]

Lack of standardised criteria and marked variability in recognition of LVI have undoubtedly lead to conflicting outcomes in previous studies. Fixation retraction around tumour cell groups is a well-recognized artifact which mimics LVI. Features that may help in the recognition of LVI include a tumour nest within a space associated with other vascular structures, the presence of an endothelial lining, adherence of the tumour cell group to the side of the space, the contour of the intravascular component matching the contour of the vessel and the presence of adherent fibrin. Immunohistochemical demonstration of an endothelial cell lining may assist but is not performed routinely. D2-40 (recognizing lymphatic endothelium) and CD31 and CD34 (recognizing both lymphatic and blood vascular endothelium) may be useful in confirming the presence of LVI.[87-90]

In rare situations when specimens are severely traumatised or diathermied, LVI may be suspected but it may not be possible to reliably determine whether or not LVI is present. In these circumstances 'indeterminate' should be recorded in the reporting guide, although it is expected this will be a rare response.

Most studies which have examined the significance of LVI in cervical carcinoma have not distinguished between lymphatic and blood vessel invasion and there is little evidence to support separating out the type of invasion, especially since this is not reliable in haematoxylin and eosin stained sections. Occasional studies have found blood vessel invasion to have a worse prognosis than lymphatic invasion and to be a predictor of ovarian involvement.[91] However, there is insufficient evidence to warrant inclusion of blood vessel and lymphatic invasion as separate data items.

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Note 11 – Coexistent pathology (Required and Recommended)

Reason/Evidentiary Support

Carcinomas of the cervix are often associated with premalignant precursor lesions, which are mostly squamous or glandular in type. Their pathology is well described and illustrated in the WHO 2014 Classification of Tumours of Female Reproductive Organs and a number of published reviews.[27,92,93] There are also numerous benign squamous or glandular lesions which can be broadly classified as inflammatory, metaplastic and neoplastic. Their importance is in recognizing the lesions as benign as they can morphologically mimic premalignant or malignant glandular or squamous lesions, and result in a false positive diagnosis.

It is important to report co-existing premalignant lesions and document whether they involve resections margins since this may influence patient management and follow up. All clearly defined premalignant lesions are caused by HPV. The terminology of HPV-associated premalignant squamous lesions was revised in WHO

2014 to Squamous Intraepithelial Lesion (SIL).[94] The change also harmonizes with The Bethesda System for the reporting of cytological abnormalities in cervical smears. Squamous intraepithelial lesions are divided into low-grade SIL (LSIL) which is a viral infection with a high spontaneous resolution rate, and high-grade SIL (HSIL) which is a true premalignant lesion that can progress to SCC. The corresponding cervical intraepithelial neoplasia (CIN) terms can be included in parentheses.

Adenocarcinoma in situ (AIS) is the HPV-associated precursor lesion of usual HPV-related cervical adenocarcinoma. High-grade cervical glandular intraepithelial neoplasia (HG CGIN) is an alternative terminology used in some jurisdictions.[95] Stratified mucin producing intraepithelial lesion (SMILE) is a premalignant lesion with morphological overlap between SIL and AIS. In WHO 2014, it is regarded as a variant of AIS (and should be coded as such) but others consider it a form of high-grade reserve cell dysplasia and report it separately.[96,97]

The precursor lesions of non-HPV-related cervical adenocarcinomas are not well defined but lobular endocervical glandular hyperplasia (LEGH), atypical lobular endocervical glandular hyperplasia (ALEGH) and adenocarcinoma in situ of gastric type have been proposed as likely precursor lesions of gastric type adenocarcinoma of the cervix.[98]

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Note 12 – Extent of invasion (Required)

Reason/Evidentiary Support

The involvement of any extracervical structures by invasive tumour should be documented. Documentation of the involvement of various extracervical tissues is prognostically significant and is important for tumour staging. Involvement of the pelvic side-wall, vagina, ovary, fallopian tube, parametria, rectum and bladder upstage the tumour. Involvement of the uterine body, whilst not formally part of FIGO or TNM staging, has also been shown to be of prognostic significance.[99] Documentation of the extent of invasion is also important for correlation with clinical and radiological findings.

The **parametria** are composed of fibrous tissue, which surrounds the supravaginal part of the cervix and separates this part of the cervix anteriorly from the bladder and posteriorly from the rectum. The fibrous parametrial tissue extends onto the sides of the supravaginal cervix and between the layers of the broad ligaments. The fibrous connective tissue around the isthmus at the cervix/lower uterine segment junction should be regarded as part of the parametria and included in the sampling of parametrial tissue. Lymph nodes and the uterine blood vessels and lymphatics that supply and drain the cervix are contained within the fibrous parametrial tissue.

The **uterine body** includes both endometrial (glandular/stromal) and myometrial structures.

If the **bladder or rectum** is involved, the pathologist should state which compartments are infiltrated; in particular, if the bladder or rectal mucosa is involved, this implies that the tumour is stage IVA at least.

Lymphovascular invasion (LVI) should be documented wherever it is identified, but anatomical structures where there is *only* LVI and no direct stromal infiltration, should not be recorded as being involved by tumour and the presence of LVI should not alter the FIGO stage.

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Note 13 – Margin status (Required and Recommended)

Reason/Evidentiary Support

The status of all surgical resection margins should be recorded (ectocervical, endocervical, radial/deep stromal and vaginal cuff). At the time of specimen grossing, it may be useful to ink the various resection margins with different colours to assist precise margin recognition.

The recording of margin involvement by tumour is a REQUIRED data element. When invasive carcinoma is close to a surgical margin, documentation of the distance to the margin is RECOMMENDED. No data are available to indicate the optimal margin of clearance of carcinoma in simple hysterectomy, trachelectomy, cone or loop biopsy specimens. Consistent recording of the distance to the margins will enable data to be collected prospectively and provide evidence for future practice. A small number of retrospective studies has assessed the impact of close margins on local and overall recurrence in patients undergoing radical hysterectomy for cervical cancer.[100] The crude local recurrence rate was 20% in 284 patients with FIGO stage IB carcinomas with 'close' margins (close was defined as <1 cm) in one study.[101] In the same study, patients with negative margins, defined as a clearance of ≥1 cm, had a crude recurrence rate of 11%. Another study of close surgical margins after radical hysterectomy in early-stage cervical cancer[102] found that close surgical margins, defined as ≤5 mm, were associated with recurrence rates of 24% as compared with recurrence rates of only 9% in patients with negative margins. In the same study, close surgical margins were significantly associated with positive lymph nodes, parametrial involvement, larger tumour size, deeper stromal invasion and lymphovascular invasion.

In occasional cases where tumour involvement of the margin cannot be determined for various reasons (processing artifact, multiple pieces or poor tissue orientation), the margin status should be specified as "cannot be assessed" and the reason explained. In hysterectomy or trachelectomy specimens, the lateral radial margin may consist of parametrial soft tissue, which should be measured (see section on **SPECIMEN DIMENSIONS**), based on gross examination, and calculated into the margin evaluation. In contrast, anterior and posterior radial/deep stromal margins in a hysterectomy specimen will consist of cervical stromal tissue.

The presence of margin involvement by HSIL, AIS or SMILE should be documented (REQUIRED element); if not involved, the distance to the resection margin is a RECOMMENDED element, although, as with invasive tumour, there are no data available to indicate the optimal margin of clearance. In hysterectomy specimens with stage IA or small IB carcinomas, the entire cervix should be assessed histologically to ensure an accurate measurement of the extent of the disease and surgical margins.[103-106]

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Note 14 - Pathologically confirmed distant metastases (Required)

Reason/Evidentiary Support

Documentation of known metastatic disease is an important part of the pathology report and is important for tumour staging, patient management and prognostication. Such information, if available, should be recorded in as much detail as is possible including the site of involvement and reference to any relevant prior surgical pathology or cytopathology specimens.

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Note 15 - Ancillary studies (Recommended)

Reason/Evidentiary Support:

HPV testing

Human papillomavirus (HPV) is universally accepted to play an aetiological role in cervical carcinogenesis and HPVs are detectable in over 95% of pre-invasive and invasive cervical carcinomas, with HPV 16 and 18 being the most frequent types.[107] Molecular testing for HPV may occasionally be useful in a diagnostic scenario. For example, this may be useful in primary diagnosis when the differential includes an HPV-related cervical cancer and a non HPV-related neoplasm or in confirmation of a metastatic HPV-related cervical neoplasm.

Immunohistochemistry

It is beyond the scope of this document to provide a detailed review of the immunophenotype of cervical neoplasms but some relevant issues should be noted.

p16 Immunohistochemistry

Diffuse immunoreactivity (nuclear and cytoplasmic) for p16 is a surrogate marker for malignant or high-grade, premalignant epithelial lesions associated with high-risk HPV infections.[108] In high-grade premalignant squamous lesions, this is referred to as "block type" immunoreactivity. AIS and high-risk HPV-associated cervical cancers also show strong diffuse p16 nuclear and cytoplasmic staining. However, it should be remembered that other gynaecological malignancies, for example uterine serous carcinoma and high-grade serous carcinoma of the ovary/fallopian tube typically exhibit such strong diffuse immunoreactivity with p16. This should be distinguished from focal/patchy (so-called "mosaic-type") staining, which is not in keeping with a high-risk HPV associated neoplasm.

Immunohistochemistry: Cervical versus Endometrial Adenocarcinoma

Immunohistochemistry can be helpful in the differential diagnosis between a cervical and an endometrial adenocarcinoma.[109] In the distinction between an endometrial and a cervical origin for an adenocarcinoma, the panels of markers which are useful will depend on the morphological subtype and not just the site of origin. In the distinction between a high-risk HPV-related (usual type) cervical adenocarcinoma and a low-grade endometrial endometrioid adenocarcinoma, the most useful immunohistochemical markers are p16 and hormone receptors (oestrogen receptor (ER) and progesterone receptor (PR)) with cervical adenocarcinomas exhibiting diffuse immunoreactivity with p16 and usually being negative or only focally positive with hormone receptors. In contrast, low-grade endometrial endometrioid adenocarcinomas are usually diffusely positive with hormone receptors and exhibit patchy "mosaic-type" staining with p16. Even when low-grade endometrial endometrioid adenocarcinomas exhibit diffuse positivity with p16, this is still usually patchy with alternating positive and negative areas. Vimentin (usually positive in low-grade endometrial endometrioid adenocarcinoma and negative in cervical adenocarcinomas) and CEA (usually positive in cervical adenocarcinomas and negative in low-grade endometrial endometrioid adenocarcinomas) may also be of value. However, it is stressed that there may be unexpected positive and negative staining reactions with any of the markers. HPV studies will be of value in such cases.

In the distinction between a high-risk HPV-related (usual type) cervical adenocarcinoma and a high-grade endometrial adenocarcinoma, p16 and hormone receptors are often of limited value. p53 immunohistochemistry and HPV studies may be of value in this scenario. Most uterine serous carcinomas and many other high-grade endometrial carcinomas exhibit mutation-type p53 staining ("all or nothing" staining) and are HPV negative. High-risk HPV-related cervical adenocarcinomas rarely, if ever, exhibit "mutation-type" p53 expression.

Immunohistochemistry of Non-HPV Related Cervical Adenocarcinomas

Non-HPV related cervical adenocarcinomas have a different immunophenotype than usual HPV related adenocarcinomas. They tend to be negative or only focally positive with p16 and some, such as gastric

type adenocarcinomas, may exhibit mutation-type staining with p53.[110] Gastric type adenocarcinomas are usually positive with gastric markers such as MUC6 and HIK1083 and are flat negative with hormone receptors.[110] There is no specific immunohistochemical marker of mesonephric adenocarcinomas but they tend to be flat negative with hormone receptors and may stain with CD10 and GATA3.[111,112] Clear cell carcinomas are usually hormone receptor negative, exhibit wild-type staining with p53 and may be positive with Napsin A and hepatocyte nuclear factor 1-beta.

Immunohistochemistry of Cervical Neuroendocrine Carcinomas

Cervical neuroendocrine carcinomas are variably positive with the neuroendocrine markers chromogranin, CD56, synaptophysin and PGP9.5. Of these, CD56 and synaptophysin are the most sensitive but CD56 lacks specificity. Chromogranin is the most specific neuroendocrine marker but lacks sensitivity with only about 50% of these neoplasms being positive.[39] Chromogranin positivity is often very focal in small cell neuroendocrine carcinomas with punctate cytoplasmic immunoreactivity which is only visible on high-power magnification. A diagnosis of small cell neuroendocrine carcinoma can be made in the absence of neuroendocrine marker positivity if the morphological appearances are typical. Small cell neuroendocrine carcinoma may be only focally positive (often punctate cytoplasmic staining) or even negative with broad-spectrum cytokeratins. A diagnosis of large cell neuroendocrine carcinoma requires neuroendocrine marker positivity and most of these neoplasms are diffusely positive with broad-spectrum cytokeratins.

A high percentage of primary cervical neuroendocrine carcinomas are TTF1 positive, including some with diffuse immunoreactivity, and this marker is of no value in distinction from a pulmonary metastasis.[39] Most cervical neuroendocrine carcinomas are diffusely positive with p16 secondary to the presence of high-risk HPV.[39] Diffuse p63 nuclear positivity is useful in confirming a small cell variant of squamous carcinoma rather than small cell neuroendocrine carcinoma. However, occasional cervical neuroendocrine carcinomas exhibit p63 nuclear immunoreactivity.[39]

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Note 16 – Lymph node status (Required)

Reason/Evidentiary Support

Lymph node status is one of the most important prognostic factors for survival in patients with cervical cancer.[113] The 5-year survival rate decreases from 85 to 50% when lymph node metastases are identified.[114]

Radical hysterectomy or trachelectomy and pelvic lymphadenectomy are the standard of treatment in most centres for FIGO stage IB1 and IIA1 cervical carcinomas and, in some centres, for stage IA2 carcinomas. There is an increasing trend for a more conservative approach, such as loop/cone excision, in the treatment of FIGO stage IA2 and small stage IB1 carcinomas, particularly if additional risk factors such as lymphovascular invasion are absent. In such cases, lymphadenectomy is often performed. Lymphadenectomy may also occasionally be performed for bulky nodal metastases (>2 cm) which are resistant to radiotherapy and/or chemotherapy; debulking of enlarged pelvic nodes has been shown to reduce the risk of pelvic recurrence but does not benefit survival.[115,116]

Required data items regarding lymph node status are restricted to the number of lymph nodes identified from the various sites and the number involved by tumour. However, some of the other parameters included below may be recorded if locally agreed and recording these parameters (size of lymph node metastasis, extracapsular spread, lymph node ratio) may be useful for future research.

Resected lymph nodes are categorised as regional (paracervical, parametrial and various pelvic lymph node groups, including obturator, internal, common or external iliac, presacral and lateral sacral) or non-regional nodes (para-aortic and inguinal and other nodes)[117] The FIGO staging system does not include lymph node status (see section on **PATHOLOGICAL STAGING**). However, lymph node status is part of TNM staging. In

applying a TNM stage, regional lymph node metastases contribute to the N category, but non-regional node involvement is regarded as distant metastasis. According to the Union for International Cancer Control (UICC), a pelvic lymphadenectomy specimen will ordinarily include 6 or more lymph nodes, but if this node count is not met and the resected lymph nodes are negative, the carcinoma should still be classified as pN0. The mean or median number of lymph nodes removed during pelvic lymphadenectomy varies widely in different studies and ranges from 13 to 56 nodes. Apart from the arbitrary minimum number of nodes proposed by the UICC, there is no internationally accepted minimum for the number of resected lymph nodes required as part of a lymphadenectomy for cervical cancer. A study by Inoue et al reported that the number of positive nodes was of greater prognostic significance than the presence of nodal metastasis per se[118] and a more recent study showed that the number of lymph nodes with metastases is an independent risk factor for reduced survival in patients with cervical cancer.[119]

In many centres, sentinel lymph node biopsy is now being undertaken in patients with presumed low-stage cervical carcinoma.[104,120,121] Overall, in stage I cervical cancer the incidence of pelvic lymph node metastasis is approximately 10%[122] and if the sentinel lymph node is negative, this avoids the morbidity associated with full pelvic lymphadenectomy in the remaining 90% of patients, i.e. sentinel lymph node biopsy is of value in reducing the requirement for a complete lymphadenectomy with its attendant morbidity in a patient population at low risk for lymph node metastases. With regard to the issue of "micrometastases" (which should be staged as pN1) and the use of immunohistochemistry (usually cytokeratin AE1/AE3), a study by Juretzka et al found immunohistochemically-detected micrometastases in 8.1% of patients with initially reported "negative" nodes (comprising 4 of 976 or 0.41% of pelvic lymph nodes examined).[123] The immunohistochemically-detected micrometastases were more frequent in tumours with lymphovascular invasion; another study showed that immunohistochemically-detected micrometastases were a risk factor for tumour recurrence.[124] Other studies have shown higher rates of lymph node micrometastases in early stage cervical carcinomas for example, 10.1% of cases in a study by Cibula et al[125] and 15% in a study by Lentz and co-workers.[126] The latter study also showed that micrometastases were more likely in patients in whom larger numbers of lymph nodes were removed. A study by Horn et al revealed that lymph node micrometastases were prognostically significant; patients with micrometastases had a reduced 5-year survival rate compared with node-negative patients, but fared better than those patients with macrometastases.[127] In the study by Cibula et al[125] isolated tumour cells (ITCs) were detected in 4.5% of cases and were found to be of no prognostic significance. If sentinel lymph node biopsy is carried out, the number of nodes examined and the number of positive nodes should be recorded. It should be noted that in the various studies, the definition of micrometastases and ITCs has generally been the same as that used more commonly in breast cancer. Note that micrometastases are regarded as lymph node involvement and pN1. ITCs, in common with TNM staging practices at other tumour sites, are regarded as node negative (pN0(i+)). It is acknowledged that there are few published data regarding ITCs in cervical cancer and until further data emerge it is recommended that these should be reported in the same way as ITCs at other sites.

The size of lymph nodes with metastatic carcinoma has been reported to be a prognostic factor in one study; patients with lymph nodes >15 mm in short-axis diameter had significantly lower survival rates than nodes of smaller size.[128]

Lymph node ratio (LNR), the ratio of positive to negative lymph nodes, has been assessed in a wide range of different cancers. The significance of LNR in cervical carcinoma has only recently been evaluated and there is insufficient evidence to include this as a data item in the current dataset. However, in early stage cervical cancer, the LNR identifies node-positive patients with a worse prognosis[129] and has been found to be an independent prognostic indicator of overall survival and disease-free survival in patients with SCC.[130]

There are very few studies that assess the significance of extracapsular/extranodal spread of metastatic cervical carcinoma, and the item has not been included in this dataset. One study showed extracapsular spread to correlate with advanced stage disease, the number of involved nodes and the size of metastatic deposits.[131] In another study, patients with extracapsular lymph node spread had a significantly lower 5-year recurrence-free survival rate compared to patients whose nodes showed no extracapsular spread.[132]

The lymph node parameters considered in the last 3 paragraphs have not been included as specific data items due to a lack of supporting evidence. However, as indicated above, individual pathologists or

institutions may choose to include some or all of these items in their own protocols. This may be useful for prospective data collection.

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Note 17 – Provisional Pathological Staging Pre-MDTM (Required and Recommended)

Reason/Evidentiary Support

There are several difficulties inherent in the staging of carcinoma of the uterine cervix: (i) FIGO staging does not include lymph node status, (ii) there are difficulties in obtaining precise tumour measurements in low-stage disease (FIGO IA and IB), (iii) clinical staging, as recommended by FIGO, may under or overestimate true anatomical extent of disease as it does not include information obtained from post-surgical pathology specimens or radiological/surgical techniques which may not be universally available. Reliance on clinical staging tends to occur in underdeveloped or under-resourced countries where surgical facilities and ancillary investigations (such as radiology and pathology) may be limited. In developed countries, patient management tends to be based on the highest recorded anatomical extent of disease, which is based on surgical, pathological and radiological information, and not necessarily the clinical stage. Wherever possible, therefore, pathologists must provide accurate and comprehensive assessment of the pathological extent of disease to optimise patient management. The term "pathological staging" is used in this dataset to indicate that the specific staging data that are provided represent only one component of the composite staging process (which is carried out at the tumour board/multidisciplinary team meeting) and may not represent the final tumour stage, nor indeed, the clinical FIGO stage.

As many cervical carcinomas are not treated surgically, the lymph node status cannot be assessed by routine histologic examination. Rather, imaging techniques (CT scan, PET scan or MRI) are commonly used to detect lymph nodes suspicious or positive for metastatic carcinoma. Since many regions in the world do not have these advanced imaging technologies, lymph node status is not included in the current FIGO staging.[133] Therefore, a patient may be staged as FIGO stage I with or without lymph node metastases. The current FIGO staging does not account for significant differences in prognosis and treatment within the same stage grouping based on the presence or absence of lymph node status. Given this, it is REQUIRED that both FIGO staging and TNM pN category are included on the pathology report when the lymph node status is known. Other TNM parameters are not required elements as is the case for other gynaecological cancers where FIGO staging is a required element and TNM is not.

The difficulties in obtaining precise dimensions for stage I tumours has been discussed in the **TUMOUR DIMENSION** section.

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The Lower Anogenital Squamous Terminology Standardization Project for HPV-Associated Lesions:

Background and Consensus Recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology

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This guideline was developed through a collaboration between the American Society for Colposcopy and Cervical Pathology and the College of American Pathologists, and has been jointly published by invitation and consent in both the *Journal of Lower Genital Tract Disease* and the *Archives of Pathology & Laboratory Medicine*. It has been edited in accordance with the standards established at the *Journal of Lower Genital Tract Disease*.

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• ***Abstract.***—**The terminology for human papillomavirus (HPV)–associated squamous lesions of the lower anogenital tract has a long history marked by disparate diagnostic terms derived from multiple specialties. It often does not reflect current knowledge of HPV biology and pathogenesis. A consensus process was convened to recommend terminology unified across lower anogenital sites. The goal was to create a histopathologic nomenclature system that reflects current knowledge of HPV biology, optimally uses available biomarkers, and facilitates clear communication across different medical specialties. The Lower Anogenital Squamous Terminology (LAST) Project was cosponsored by the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology and included 5 working groups; 3 work groups performed comprehensive literature reviews and developed draft recommendations. Another work group provided the historical background and the fifth will continue to foster implementation of the LAST recommendations. After an open comment period, the draft recommendations were presented at a consensus conference attended by LAST work group members, advisors, and representatives from 35 stakeholder organizations including professional societies and government agencies. Recommendations were finalized and voted on at the consensus meeting. The final, approved recommendations standardize biologically relevant histopathologic terminology for HPV-associated squamous intraepithelial lesions and superficially invasive squamous carcinomas across all lower anogenital tract sites and detail the appropriate use of specific biomarkers to clarify histologic interpretations and enhance diagnostic accuracy. A plan for disseminating and monitoring recommendation implementation in the practicing community was also developed. The implemented recommendations will facilitate communication between pathologists and their clinical colleagues and improve accuracy of histologic diagnosis with the ultimate goal of providing optimal patient care.**

Key Words.—**squamous intraepithelial lesion, human papillomavirus, superficially invasive carcinoma, p16, terminology**

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The biology of the human papillomavirus (HPV) and its critical role in cancers of the lower anogenital tract (LAT) have been delineated during the last several decades. Human papillomavirus interacts with squamous epithelia in 2 basic ways. In the first, the squamous epithelium supports virion production, but lesions are transient. Historically, these processes have been termed *low-grade lesions*, *grade 1 intraepithelial neoplasia*, *mild dysplasia*, or, in the appropriate architectural background, *condyloma*. Human papillomavirus–infected squamous epithelia produce a morphologic low-grade lesion at some point in the complete life cycle of the virus, although it may be undetected clinically. In contrast, the second form of HPV-epithelial interaction is characterized by lesions that are broadly classified as precancerous. These are lesions in which the coordinate control between viral gene expression and epithelial differentiation is broken. It is postulated that viral oncogene overexpression drives cell proliferation to produce a clonal expansion of relatively undifferentiated cells characterized clinically by persistent viral detection, persistent and growing colposcopic abnormalities, and, over time, a substantial risk of malignant transformation. These precancers are morphologically indistinguishable from each other by routine histologic morphology regardless of the sex of the individual or the site of the lesion (see Figure 1) [1–4].

Despite these 2 well-established patterns of viral-epithelial interaction, the histopathologic terminology of HPV-associated processes in the LAT remains disparate and complex. This is primarily the result of terms evolving from different interest groups, particularly those in the areas of gynecology and gynecologic pathology and dermatology and dermatopathology, but also from specialty groups focused on specific body sites. These differing terminologies, for biologically equivalent lesions, have created the potential for miscommunication as pathologists attempt to reconcile the various terminologies with identified lesions and clinicians guide patient management based on these pathologic diagnoses. To optimize this communication, diagnostic terms should be consistent across body sites that share disease commonalities, and convey meaning, grounded in science, that allows for appropriate patient management.

The field of cytopathology had a similar terminology problem before the Bethesda conferences of 1988, 1991, and 2001. These conferences formulated a new terminology for reporting cytologic abnormalities in gynecologic and anal cytology. This terminology, now commonly known as *The Bethesda System* (TBS), created standard reporting terms and criteria for each interpretive category. It has been widely implemented in the United States and internationally and has led to improved and more reliable communication between pathologists and clinicians and among those in different medical specialties [5]. In addition, TBS was designed to be consistent with the current knowledge of HPV-associated disease. Until the introduction of TBS, morphologic terminologies were tied to older, less accurate understanding of the disease process. The Bethesda System also enabled the development of clinical management guidelines linked to standardized terminology.

The role of colposcopy and biopsy is to identify high-grade disease. Both colposcopic and biopsy interpretation have limited reproducibility and accuracy [6–9]. Biopsies represent potentially limited samples within fields of possible disease that may be of varying grade. Sampling issues may lead to underrepresentation of the actual disease present. Larger biopsies and increased numbers of biopsies more accurately assess each patient's "true" biology or cancer risk [6, 7]. Biopsy interpretation also has inherent issues of reproducibility [10]. Biomarkers are routinely used for histopathologic evaluation and lead to greater diagnostic reproducibility. Although changes to clinical management strategies are not explicitly addressed by the LAST recommendations, the ability to more accurately and

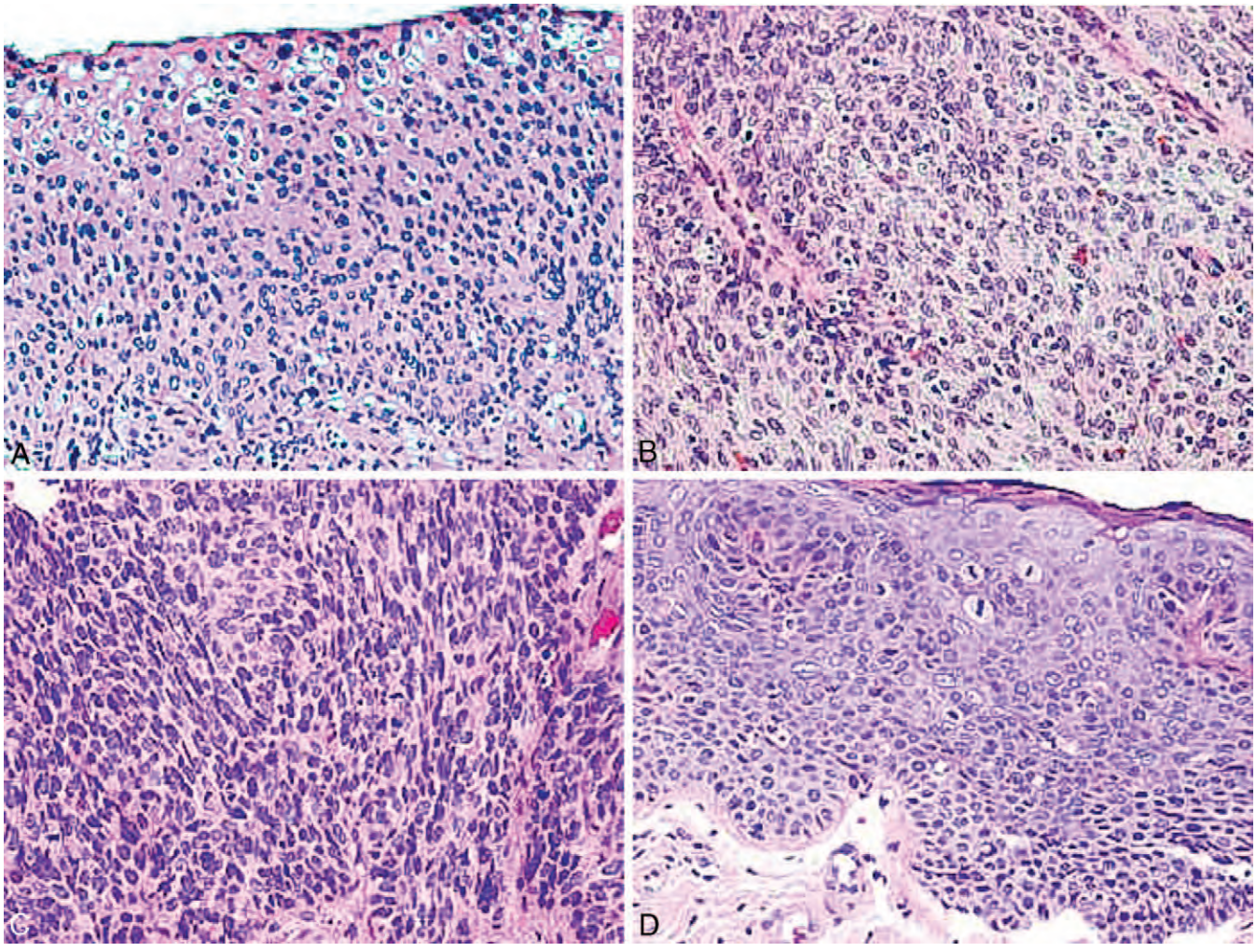

Figure 1. The similarity of morphology between LAT sites and between sexes is shown. Each is an example of a precancerous HSIL. If reviewed without knowledge of biopsy site or sex of the patient, they would be impossible to distinguish from one another. A to D, Medium power, H&E: A, CIN 3 (female); B, AIN 3 (female); C, AIN 3 (male); D, PeIN 3 (male).

reproducibly define patients' cancer risk based on their histopathologic diagnosis will ultimately lead to improved patient care.

The goal of clinical management is to identify and treat high-grade disease to decrease the risk of developing invasive cancer. Not all precancers will progress to cancer. Currently, we cannot predict which lesion would eventually become malignant if not treated. The potential harms of overtreatment of precancer compared with the risk of developing invasive disease if these lesions are not treated need to be balanced. The risks of cancer progression from HPV-associated precancer to invasive cancer are perceived to be different for different body sites. This perception is driven mostly by the relative frequency of LAT cancers and a marked paucity of long-term natural history data. The 30-year progression risk of invasive cancer is 30% to 50% for untreated high-grade cervical disease [11, 12]. Although data are not as robust, similar progression risk is seen for untreated vulvar precancer [13, 14]. Similar long-term data are lacking for anal cancer precursors and other LAT squamous cancers [15]. Long-term prospective studies of outcomes for patients with untreated high-grade precursors will be difficult to achieve.

On the basis of these underlying principles of HPV-associated disease (see Table 1) and issues related to terminology, a consensus process was conceived and sponsored by the College of American Pathologists (CAP) and the American Society for Colposcopy and Cervical Pathology (ASCCP). The Lower Anogenital Squamous Terminology (LAST) Project was designed to comprehensively evaluate the terminology of HPV-associated squamous lesions of the LAT, including the cervix, the vagina, the vulva, the perianus, the anus, the penis, and the scrotum. The project had several specific objectives carried out by 5 work groups (WGs; see Table 2):

1. To develop a historical perspective of the origins of terminologies in the LAT, with an emphasis on how nomenclature has influenced management.
2. To address whether the biology of HPV-associated disease in all of these sites allowed for unification of terminology.
3. To propose terminology for intraepithelial lesions and early invasive carcinoma.
4. To perform a review to determine whether currently available biomarkers support any proposed terminology

Table 1. General Principles Underlying the LAST Project

- There is unified epithelial biology to HPV-related squamous disease.
- Each cytologic or histologic sample is only a statistical representation of the patient's true biology.
- The more samples or data points available, the more accurate the assessment of the patient's true biology.
- The true biology represents the risk for cancer at the current time and, to a lesser extent, the risk for cancer over time.
- Diagnostic variation can be improved by:
  - aligning the number of diagnostic terms with the number of biologically relevant categories and
  - the use of biologic markers.

Table 2. LAST Project WGs

WG1: Historical review of LAT HPV-associated squamous lesion terminology
WG2: Squamous intraepithelial lesions, with subgroups:
Cervix and vagina
Vulva, penis, and scrotum
Anal canal and perianus
WG3: Superficially invasive squamous cell carcinoma (SISCCA), with subgroups:
Cervix and vagina
Vulva, penis, and scrotum
Anal canal and perianus
WG4: Biomarkers in HPV-associated lower anogenital squamous lesions
WG5: Implications and implementation of standardized terminology

recommendations or improve diagnostic reliability and reproducibility of histopathologic interpretation.

5. To facilitate and monitor dissemination and implementation of terminology changes into clinical practice with the goal of optimizing educational, quality assurance, regulatory, and clinical processes.

Final recommendations from the LAST Project are summarized in Table 3.

CAP-ASCCP LAST CONSENSUS PROCESS

A detailed account of the LAST Project is available in the Supplemental Digital Content; http://links.lww.com/LGT/A6. Briefly, the CAP Pathology and Laboratory Quality Center (the CAP Center) and the ASCCP convened a steering committee (SC) and 5 WGs that consisted of experts in the field including surgical pathologists, gynecologic pathologists, dermatopathologists, and medical and surgical specialists including gynecologists, gynecologic oncologists, dermatologists, infectious disease specialists, and surgeons (see A, Supplemental Digital Content; http://links.lww.com/LGT/A6). Work group members and advisors included representatives from both sponsoring organizations and other clinical specialties. Both sponsoring organizations used their respective approval processes for the formal review and appointment of the project chairs and WG members.

MANAGEMENT OF CONFLICTS OF INTEREST

All expert panel members complied with the CAP conflicts of interest policy (in effect, October 2010), which required disclosure of financial or other interests that may have an actual, potential, or apparent conflict (see Appendix, Supplemental Digital Content; http://links.lww.com/LGT/A6). Both ASCCP and the CAP provided the funding for this project; no industry funds were used in the development of the consensus statements and recommendations.

LITERATURE REVIEW AND CONSENSUS PROCESS

A computerized search was conducted for 4 of the 5 WGs using the following electronic databases: OVID MEDLINE, PubMed, Wiley Cochrane Library, and OCLC WorldCat, for English-language articles only. All study designs and publication types were included. Reference lists from identified articles were examined for articles not identified in the searches. The scope, key questions, search terms as defined by the SC, and the literature review results are displayed in the supplemental methodology material (see Appendix, Supplemental Digital Content; http://links.lww.com/LGT/A6). Screening and data extraction were completed using DistillerSR (Evidence Partners, Ottawa, Canada) for WG2, 3, and 4.

Each identified article underwent an inclusion-exclusion process, dual-independent reviews conducted by co-chairs and WG members. On the basis of each WG's inclusion-exclusion criteria, articles were kept for full data extraction, as "indirect background material," or excluded from further review. Articles with 2 differing votes were considered in "conflict." Conflicts were adjudicated by both reviewers for WG2 and WG3 and by co-chair referees when conflicts could not be resolved. Co-chairs alone adjudicated WG4 conflicts. Conflicts included the "uncertain" reviews at the title/abstract level and the "indirect background material" reviews at the full text level. Final data extractions were performed by all WG members. After data extractions, WG members crafted draft summations and recommendations. The drafts were posted on the ASCCP Web site for open comment for 26 days from mid-January to mid-February 2012. After review of the open comments, draft recommendations were revised, if needed, before the consensus conference held immediately preceding the March of 2012 ASCCP Biennial Meeting in San Francisco, CA.

Recommendations for terminology of squamous intraepithelial lesions (WG2) and superficially invasive squamous carcinomas (WG3) were based on the expert opinion of WG members and advisors after their comprehensive review of the literature. The recommendations from WG4, on use of biomarkers, were chiefly driven by the specific data from the comprehensive literature review. For this reason, an independent assessment of the strength of the evidence identified to support WG4's recommendations was performed by an expert in evidence evaluation, Dr Evan Myers (Duke University), following WG4's review and development of recommendations.

At the consensus conference, WG members and advisors, along with representatives from 35 participating organizations (see Table 5, Supplemental Digital Content; http://links.lww.com/LGT/A6) and observers, deliberated on, revised, and voted on the final draft recommendations; observers did not vote. At least a two-thirds majority (67%) was required for passage of each recommendation. The LAST Project writing committee was tasked with adding to the documentation the appropriate supporting detail and explanatory material for the recommendations.

The CAP Independent Review Panel, the CAP Transformation Program Office Steering Committee, and the

ASCCP Executive Committee provided final review and approval of the article.

HISTORICAL REVIEW OF LAT HPV-ASSOCIATED SQUAMOUS LESION TERMINOLOGY—WG1

Work group 1 was in charge of framing the historical development of terminology applied to HPV-associated squamous lesions of the LAT and the influence of terminology on clinical management.

The history of terminology for LAT-associated precancer has developed along 2 separate paths depending on whether the epithelial lesion is mucosal or cutaneous. Terminology of mucosal cervical, vaginal, and anal lesions was largely developed by general pathologists, gynecologic pathologists, and gynecologists. In contrast, terminology for cutaneous vulvar, penile, and perianal lesions was largely developed by dermatologists and dermatopathologists. Terminology for HPV-associated disease of the LAT has changed numerous times during the last 120 years along with our understanding of the disease process and the treatment strategies.

Mucosal Terminology

Cervix: Preinvasive Lesions.—The earliest description of intraepithelial precancer was by Sir John Williams in 1888 [16]. Subsequent descriptions of the "earliest histologic changes of cervical cancer" as *surface carcinoma* or *intraepithelial carcinoma,* and later *carcinoma in situ* (CIS), reflected the histologic descriptions of cells that morphologically looked like cancer but had not invaded below the basement membrane [17–19]. The identification of CIS created a 2-tiered clinical approach that fostered hysterectomy for women with CIS and no treatment for women without it (see Figure 2). By the early 1950s, it was increasingly clear that surface lesions existed on the cervix that had abnormal histologic features that did not fulfill the criteria for CIS. These lesions seemed to have lower risk for progressing to cancer than CIS does. A variety of confusing terms were developed for these surface lesions, including *anaplasia* and *basal cell hyperplasia*. In 1952, Reagan and Hicks [20] coined the term *atypical hyperplasia* for cervical abnormalities with "greater degrees of differentiation than CIS and less risk for subsequent development of cancer." In the following year, they replaced this with "*dysplasia,*" which they graded mild, moderate, or severe [21]. The word "dysplasia" is derived from the Greek word *dys* for "bad" and *plasia* for "molding" and has been used in many areas of medicine, usually to describe a nonmalignant process. As late as the 1950s, some pathologists and clinicians argued that CIS was not the precursor to cervical cancer, but the common finding of CIS adjacent to cervical cancer, and the nearly identical incidence of both lesions eventually sealed this link [22, 23]. Although many acknowledged the difficulty in differentiating severe dysplasia from CIS, women with CIS continued to be treated by hysterectomy, whereas women with severe dysplasia were more often treated by cold knife conization.

In 1956, Koss and Durfee [24] described cells with ballooned cytoplasm, labeling them koilocytes from the Greek word for "empty space," and noted the similarity to descriptions of Reagan's mild dysplasia. In 1976, Meisels and Fortin [25] linked koilocytotic atypia with HPV.

The most profound change in cervical histologic terminology came in 1969 when Richart proposed that cervical carcinogenesis was a continuum of disease ranging from mild dysplasia to cervical cancer [26, 27]. Because of this morphologic spectrum, he coined the term *cervical intraepithelial neoplasia* (CIN) to emphasize its association as a precursor to cancer. Mild dysplasia was now termed CIN 1; moderate dysplasia, CIN 2; and severe dysplasia, CIN 3. Richart found "an absence of objective evidence" to support the arbitrary division of CIN into 2 diseases—dysplasia and CIS—and therefore basing therapy on such a distinction was not valid. Because all grades of CIN were thought to be on a continuum to cancer, treatment of all, based on the size and location of the lesion, became common practice. Treating even minor HPV-induced abnormalities quickly threatened to overburden the capacity of hospital-based surgical treatment of cervical precancer. In response, in-office ablative treatment methods—first, cryotherapy and later, CO_2 laser ablation—were developed. However, tradition and lingering misunderstanding of the precancerous nature of CIS resulted in a slow demise of the term and the use of hysterectomy as primary treatment for women with CIS continued.

By the late 1980s, the biology of HPV and cervical oncogenesis was increasingly understood. In addition, the subjectivity of the differentiation between CIN 2 and CIN 3 became apparent. This led to increasing recognition that a 2-tiered system of low- and high-grade intraepithelial lesions was more biologically relevant and histologically reproducible than the 3-tiered CIN 1, CIN 2, and CIN 3 terminology [28–30]. The creation of the 1988 TBS cytology terminology supported a similar low-grade and high-grade division [31]. However, the promotion of a 2-tiered terminology for histology in the 1990s lacked official support by any professional organizations and was never widely adopted. The 2001 and 2006 ASCCP Consensus Guidelines for the clinical management of cervical histological abnormalities use a 2-tiered terminology for cervix, except in adolescents and young women with CIN 2 and CIN 3 [32, 33]. This exception in the ASCCP Consensus Guidelines perpetuated the clinical reliance on a 3-tiered terminology for cervical histology for managing adolescents and young women.

Two important changes in the management of intraepithelial neoplasia began in the 1990s: expectant management of CIN 1 and in-office excision of high-grade precancer (CIN 2, 3) using the loop electrosurgical excision procedure (LEEP). Unlike prior transitions that paralleled changes in terminology, these were largely driven by a better understanding of the transience of most CIN 1 lesions and to improved excisional technology with LEEP that could be performed safely in an office setting (see Figure 2).

In the new millennium, there has been renewed debate about adopting a 2-tiered low-grade and high-grade terminology for all LAT HPV-associated intraepithelial lesions [34–36]. The primary concern regarding adopting a 2-tiered system for the cervical histology is that guidelines for management of CIN 2, 3 in adolescents and young women promoted expectant management of CIN 2 with the option to follow lesions reported as CIN 2, 3 but not CIN 3 [33, 37, 38]. The counter arguments advanced for adopting a 2-tiered system include that it better reflects the known biology of HPV-associated disease, that diagnostic variability is reduced, and that management based on further divisions in terminology does improve patient outcomes [35]. The CAP-ASCCP LAST Consensus Conference addresses these recent concerns.

Table 3. Summary of Recommendations

Recommendation	Comment
SQUAMOUS INTRAEPITHELIAL LESIONS, WG2	
1. A unified histopathologic nomenclature with a single set of diagnostic terms is recommended for all HPV-associated preinvasive squamous lesions of the LAT.	
2. A 2-tiered nomenclature is recommended for noninvasive HPV-associated squamous proliferations of the LAT, which may be further qualified with the appropriate –IN terminology.	–IN refers to the generic intraepithelial neoplasia terminology, without specifying the location. For a specific location, the appropriate complete term should be used. Thus, for an –IN 3 lesion: cervix = CIN 3, vagina = VaIN 3, vulva = VIN 3, anus = AIN 3, perianus = PAIN 3, and penis = PeIN 3
3. The recommended terminology for HPV-associated squamous lesions of the LAT is LSIL and HSIL, which may be further classified by the applicable –IN subcategorization.	
SUPERFICIALLY INVASIVE SQUAMOUS CELL CARCINOMA, WG3	
1. The term *superficially invasive squamous cell carcinoma* (*SISCCA*) is recommended for minimally invasive SCC of the LAT that has been completely excised and is potentially amenable to conservative surgical therapy.	Note: Lymph-vascular invasion (LVI) and pattern of invasion are not part of the definition of SISCCA, with the exception of penile carcinoma.
2. For cases of invasive squamous carcinoma *with positive biopsy/resection margins*, the pathology report should state whether: The examined invasive tumor exceeds the dimensions for a SISCCA (defined below) OR The examined invasive tumor component is less than or equal to the dimensions for a SISCCA and conclude that the tumor is "*At least a superficially invasive squamous carcinoma*."	
3. In cases of SISCCA, the following parameters should be included in the pathology report: The presence or absence of LVI. The presence, number, and size of independent multifocal carcinomas (after excluding the possibility of a single carcinoma).	
4. CERVIX: SISCCA of the cervix is defined as an invasive squamous carcinoma that: Is not a grossly visible lesion, AND Has an invasive depth of $\leq$3 mm from the basement membrane of the point of origin, AND Has a horizontal spread of $\leq$7 mm in maximal extent, AND Has been completely excised.	
5. VAGINA: No recommendation is offered for early invasive squamous carcinoma of the vagina.	Owing to the rarity of primary SCC of the vagina, there are insufficient data to define early invasive squamous carcinoma in the vagina.
6. ANAL CANAL: The *suggested* definition of superficially invasive squamous cell carcinoma (SISCCA) of the anal canal is an invasive squamous carcinoma that: Has an invasive depth of $\leq$3 mm from the basement membrane of the point of origin, AND Has a horizontal spread of $\leq$7 mm in maximal extent, AND Has been completely excised.	
7. VULVA: Vulvar SISCCA is defined as an AJCC T1a (FIGO IA) vulvar cancer. No change in the current definition of T1a vulvar cancer is recommended.	Current AJCC definition of T1a vulvar carcinoma: Tumor $\leq$2 cm in size, confined to the vulva or perineum AND Stromal invasion $\leq$1 mm Note: The depth of invasion is defined as the measurement of the tumor from the epithelial-stromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion.
8. PENIS: Penile SISCCA is defined as an AJCC T1a. No change in the current definition of T1a penile cancer is recommended.	Current AJCC definition of T1a penile carcinoma: Tumor that invades only the subepithelial connective tissue, AND No LVI AND Is not poorly differentiated (i.e., grade 3–4)
9. SCROTUM: No recommendation is offered for early invasive squamous carcinoma of the scrotum.	Owing to the rarity of primary SCC of the scrotum, there is insufficient literature to make a recommendation regarding the current AJCC staging of early scrotal cancers.

Table 3 Continued	
Recommendation	**Comment**
10. PERIANUS: The *suggested* definition for SISCCA of the perianus is an invasive squamous carcinoma that: Has an invasive depth of ≤3 mm from the basement membrane of the point of origin, AND Has a horizontal spread of ≤7 mm in maximal extent, AND Has been completely excised.	
BIOMARKERS IN HPV-ASSOCIATED LOWER ANOGENITAL SQUAMOUS LESIONS, WG4	
1. p16 IHC is *recommended* when the H&E morphologic differential diagnosis is between precancer (–IN 2 or –IN 3) and a mimic of precancer (e.g., processes known to be not related to neoplastic risk such as immature squamous metaplasia, atrophy, reparative epithelial changes, tangential cutting).	Strong and diffuse block-positive p16 results support a categorization of precancerous disease.
2. If the pathologist is entertaining an H&E morphologic interpretation of –IN 2 (under the old terminology, which is a biologically equivocal lesion falling between the morphologic changes of HPV infection [low-grade lesion] and precancer), p16 IHC is *recommended* to help clarify the situation. Strong and diffuse block-positive p16 results support a categorization of precancer. Negative or non–block-positive staining strongly favors an interpretation of low-grade disease or a non–HPV-associated pathology.	
3. p16 is *recommended* for use as an adjudication tool for cases in which there is a professional disagreement in histologic specimen interpretation, with the caveat that the differential diagnosis includes a precancerous lesion (–IN 2 or –IN 3).	
4. WG4 *recommends against* the use of p16 IHC as a routine adjunct to histologic assessment of biopsy specimens with morphologic interpretations of negative, –IN 1, and –IN 3.	
a. SPECIAL CIRCUMSTANCE: p16 IHC is recommended as an adjunct to morphologic assessment for biopsy specimens interpreted as ≤ –IN 1 that are at high risk for missed high-grade disease, which is defined as a prior cytologic interpretation of HSIL, ASC-H, ASC-US/HPV-16+, or AGC (NOS).	Any identified p16-positive area must meet H&E morphologic criteria for a high-grade lesion to be reinterpreted as such.

Cervix: Early Invasive Lesions.—*Microinvasive* carcinoma is defined as a lesion that is predominantly intraepithelial with a focus of cells invading below the basement membrane into the superficial stroma. The histologic criteria for microinvasive carcinoma, particularly as related to the depth, length, and breadth of the invasive component, has varied greatly over the years, as has the importance of lymph-vascular invasion (LVI), confluence, and tumor volume. Therefore, this term and its definition have remained controversial.

In 1947, Mestwerdt gave the first definition of *microcarcinoma* as a carcinoma with invasion no more than 5 mm in depth [39]. Several other terms have been used, including *microinvasive carcinoma*, *early invasive carcinoma*, *very small carcinoma*, *early invasive preclinical carcinoma*, *pin-point invasion*, and *stage IA cervical carcinoma*. Between 1961 and 1985, the International Federation of Gynecology and Obstetrics (FIGO) changed the definition of stage IA microinvasive carcinoma 6 times, with treatment varying from conization alone, to the opposite extreme of radical hysterectomy with pelvic lymphadenectomy [39]. Concern continues to be expressed about marked interobserver variability in diagnosing microinvasion, with many cases of intraepithelial gland involvement being overinterpreted and the depth of invasion measured by different methods with variable measurement cutoffs.

Vaginal Preinvasive Lesions.—The first description of a vaginal intraepithelial lesion was made at the Mayo Clinic in 1933 more than a century after vaginal cancer was first described by Cruveilhie. For several decades, the lesion was termed vaginal CIS and was felt to be very rare, an impression that continued with Woodruff's [40] 1981 review of all literature on vaginal CIS in which he could find only 300 cases. However, increasing use of cytology and colposcopy soon demonstrated that vaginal HPV-induced squamous lesions were very common, particularly those of lower grades than CIS. By the 1980s, the terminology of vaginal intraepithelial neoplasia (VaIN) came into common use, with VaIN 1 equating to mild dysplasia; VaIN 2, to moderate dysplasia; and VaIN 3, to severe dysplasia/CIS [41].

Anal Preinvasive Lesions.—Early descriptions of anal preinvasive and invasive disease did not separate anal canal from perianus. These were primarily cutaneous lesions variously described as Bowen disease and CIS. It was not until 1962 that the need to separate perianal from anal tumors based on the different biology and behavior of these diseases was proposed [42]. In 1971, Oriel and Whimster [43] suggested the possible viral origin of Bowen disease in a report of CIS adjacent to anal warts. The association of HPV with anal precancer and cancer became plausible after documentation of HPV-16 in cervical cancer. Subsequent

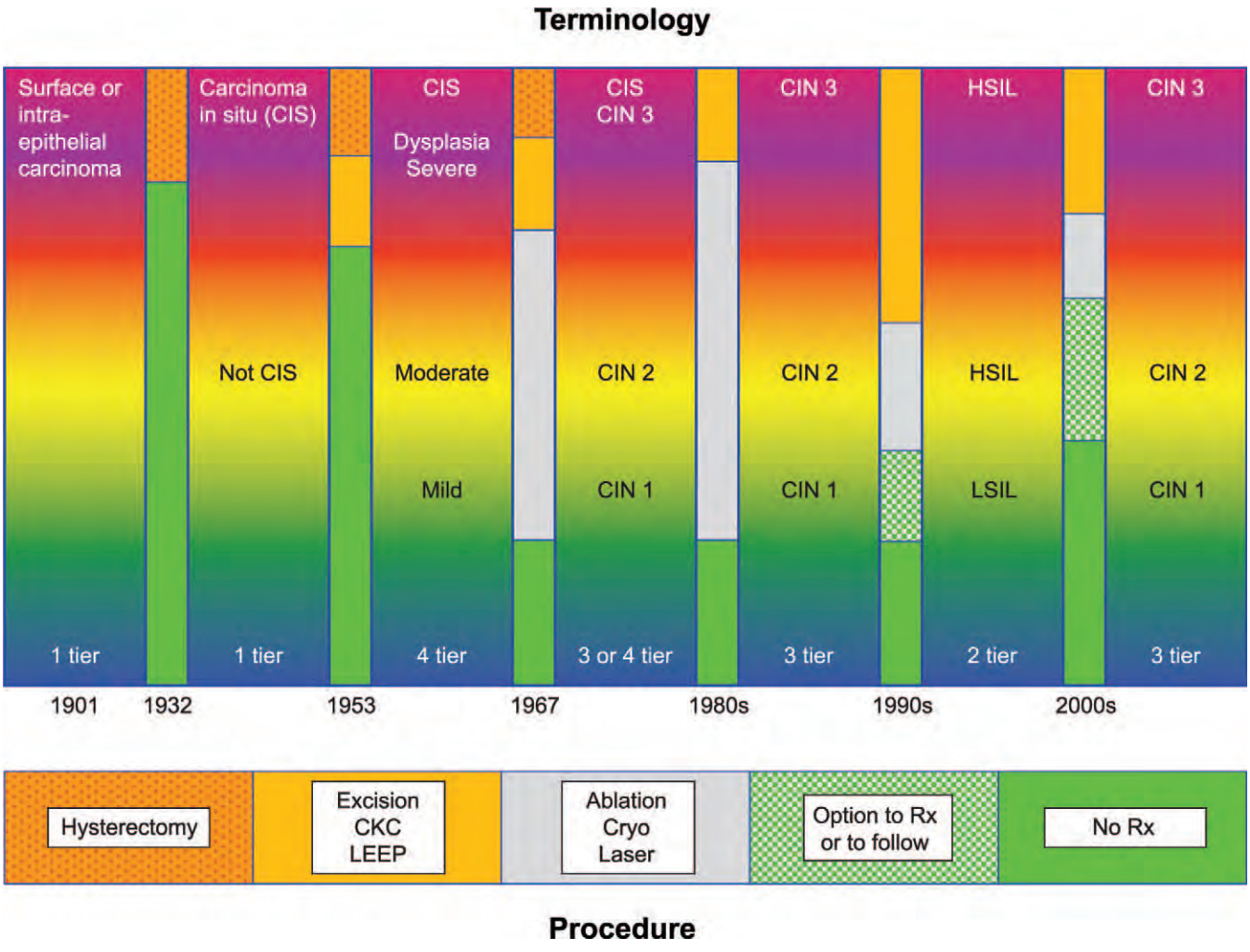

Figure 2. Changes to the terminology and number of tiers used to describe cervical precancer over time with corresponding management options (procedure). See text for additional details. CKC, cold knife conization; Cryo, cryotherapy; RX, treatment. Modified with permission. Courtesy of J. Thomas Cox.

documentation of oncogenic HPV types in both preinvasive and invasive anal cancer confirmed this association, as acknowledged by the International Agency for Research on Cancer in 1995 [44, 45].

In 1981, Fenger and Bichel [46] published the first study of *dysplastic* changes in the anal canal. In 1986, Fenger and Nielsen [47] described the presence of dysplasia and CIS adjacent to most anal canal carcinomas, showing that anal lesions shared the common HPV-associated oncogenic pathway seen in the cervix and other areas of the LAT. In the same year, they introduced the terminology of *intraepithelial neoplasia in the anal canal* (*AIN*). Analogous to CIN, AIN was divided into 3 grades: AIN 1, AIN 2, and AIN 3.

In the mid-1990s, the International Agency for Research on Cancer monograph on the evaluation of carcinogenic risks to humans supported the association of HPV with AIN and anal cancer [45]. In 1996, Northfelt et al [48] introduced the term *anal squamous intraepithelial lesion* as an alternative to AIN, with low-grade anal squamous intraepithelial lesion corresponding to AIN 1 and high-grade anal squamous intraepithelial lesion comparable to AIN 2 or 3. In 2000, the CAP published the cancer protocol for the examination of specimens from patients with carcinoma of the perianus and anal canal exposing the controversies regarding tumor location and anatomic terminology [49]. This controversy in the terms used to describe tumor location was further explored by Wendell-Smith in 2000 [50]. The surgical definition of the anal canal, proposed by the American Joint Committee on Cancer (AJCC), is the most widely accepted [51, 52]. By its definition, the anal canal extends from the apex of the anal sphincter complex to the palpable intersphincteric groove at the distal edge of the internal sphincter muscle.

Cutaneous Terminology

Cutaneous HPV-associated precancers on the vulva, perianus, and penis were all initially named after the 2 clinicians who first described them. In 1911, a dermatologist, Louis Queyrat, described lesions of the glans penis that were subsequently named *erythroplasia of Queyrat*. In 1912, JT Bowen described lesions on the shaft of the penis, buttocks, and thighs that were given the eponym *Bowen disease* [53]. As numerous descriptions of similar lesions on the vulva and the perianus began to appear in the literature, *Bowen disease* became the term applied to cutaneous precancers throughout the LAT.

Vulvar Preinvasive Lesions.—The histological description of Bowen disease was a full-thickness intraepithelial lesion, later termed *carcinoma in situ* by Woodruff and Hildebrandt in 1958 [54]. However, it soon became clear that cutaneous intraepithelial lesions were of 2 types and perhaps of 2 different etiologies. In 1961, Abell and Gosling [55] described 2 distinct histopathologic types as *intraepithelial carcinoma of Bowen's type* and *intraepithelial carcinoma simplex type*. The natural history of these vulvar squamous intraepithelial lesions was not well understood. There was a general consensus that all of these intraepithelial lesions were "premalignant" and required therapy. The 1972 report by Friedrich [56] of a pregnant woman with multifocal papular lesions of the vulva that histologically resembled CIS and resolved spontaneously postpartum questioned the consensus that these lesions required extensive treatment. Friedrich suggested the term *reversible vulva atypia*, but in 1978, Wade, Kopf, and Ackerman coined the term *Bowenoid papulosis* because these lesions looked histologically like Bowen disease but were clinically different in both appearance and in natural history [57].

The divergence in terminology between dermatopathologists and gynecologic pathologists for cutaneous areas of the LAT continued in 1976 with the report from the International Society for the Study of Vulvovaginal Disease (ISSVD) on "New Nomenclature for Vulvar Disease" [58]. The ISSVD recommended the continued use of the term *squamous cell carcinoma in situ*. It provided a classification of atypical changes of the vulvar epithelium less atypical than CIS under the rubric of "hyperplastic dystrophy with atypia." These were subclassified as mild, moderate, or severe atypia depending on the extent of the intraepithelial changes. Terms that were not recommended "because of the confusion associated with the use" included *Bowen disease*, *erythroplasia of Queyrat*, *carcinoma simplex*, and *leukoplakic vulvitis*. In 1982, the term *vulvar intraepithelial neoplasia* (VIN) was first introduced by Crum et al [59], paralleling the CIN nomenclature. The term, *VIN*, eventually gained great acceptance and adoption of similar terminology for the description of penile (PeIN) and perianal (PAIN) HPV-associated intraepithelial neoplasia followed. In 1986, the ISSVD accepted VIN as a general category of intraepithelial neoplasia with the grades of VIN 1, 2, and 3 [60]. The ISSVD added that *condylomatous dysplasia* was not a preferred term.

In 1994, the World Health Organization published a second edition of *Histological Typing of Female Genital Tract Tumours* addressing vulvar tumor terminology [61]. In this work, the term *squamous intraepithelial lesion* was introduced as an encompassing term, including lesions classified as dysplasia and CIS. The term *VIN* (including VIN 1, 2, and 3) was included as an alternate to the dysplasia/CIS terminology.

The intraepithelial neoplasia (–IN) term did not completely dominate LAT cutaneous terminology, and numerous names were proposed that reflected increasing knowledge of the HPV-associated etiology of these lesions. In 1994, Gross et al [62] demonstrated that typical condylomata acuminata and flat condyloma-like lesions were due to HPV-6 or –11, whereas papular and pigmented lesions with severe atypia, referred to as Bowenoid papulosis, were due to HPV-16.

In 2004, the ISSVD proposed a modified terminology for VIN as 2 distinct processes: the "usual type" encompassed high-grade VIN lesions (VIN 2 and 3) and were caused by HPV and the "differentiated type" was not caused by HPV [63]. The classification did not include grading of VIN lesions. Cases formerly interpreted as VIN 1 were designated as a nonneoplastic disorder or as condyloma acuminatum. In the 2010 American Registry of Pathology Fascicle 13, Kurman et al [64] proposed resurrecting the terms *VIN 1* and *VIN 2/3* and further subclassifying these as warty, basaloid, mixed warty-basaloid, pagetoid, and differentiated (simplex) VIN.

This lengthy history of vulvar terminology was paralleled by changes in the management of the disease. Intraepithelial lesions of the vulva were initially all considered to be premalignant and aggressive therapy, usually surgical, was recommended. As late as the mid-1960s, full or deep vulvectomy was the standard treatment [65]. By the late 1970s, less aggressive therapies with vulvar sparing techniques became more common [66]. In addition, treatment based on other factors, such as patient age and the size and extent of the lesion, was implemented.

In the 2011 ACOG-ASCCP Committee Opinion, VIN 1 lesions are considered condyloma and should be managed accordingly [67]. The preferred treatment recommended for high-grade VIN lesions is local excision, with 0.5- to 1.0-cm margins, but modified "…to avoid injury to the clitoris, urethra, anus, or other critical structures." When invasion is suspected, wide local excision is recommended. Laser ablation is considered an acceptable treatment if cancer is not suspected. Topical imiquimod 5% is also an acceptable nonsurgical treatment of HPV-associated VIN 2, 3 [67].

Perianal Preinvasive Lesions.—The demarcation between the perianus and adjacent perineum in both sexes, and the adjacent vulva in women, is not anatomically clear. The terminology of perianal HPV-associated precancer has paralleled the terminology of vulvar lesions. Common terminology for perianal preinvasive lesions includes Bowen disease, CIS, and PAIN grades 1, 2, and 3.

Penile/Scrotal Preinvasive Lesions.—Scrotal cancer was the first cancer determined to have an environmental cause (soot). In 1775, Sir Percival Pott described scrotal cancer as a rare cancer overall but very common in young chimney sweeps. In 1891, Tarnovsky first described a squamous intraepithelial lesion of the penis. Twenty years later, Queyrat and Bowen identified similar penile lesions [53]. As with terminology in other areas of the LAT, full-thickness intraepithelial lesions on the penis or scrotum were variously described as *Bowen disease* if on the shaft of the penis or scrotum, *erythroplasia of Queyrat* if on the glans penis, or *CIS* in any of these areas [57, 68]. Bowen disease was described clinically as typically raised, white, and scaly, whereas erythroplasia of Queyrat was usually a macular-papular, red to violet, velvety lesion. In 1982, the terminology of PeIN was introduced, akin to CIN and other HPV-associated intraepithelial lesions.

In 1992, Della Torre et al [69] reported that HPV-related warty and basaloid types of PeIN were more prevalent than the non-HPV related differentiated type of PeIN. As with squamous carcinoma of the vulva, 2 etiologic pathways to penile cancer were proposed: one HPV related and the other non-HPV related. More recently, the terms *low-grade* (*LSIL*) and *high-grade squamous intraepithelial lesion* (*HSIL*) have been proposed for squamous lesions of the penis [70]. In the 2011 Armed Forces Institute of Pathology Fascicle, the PeIN terminology is used and further subclassified as differenti-

ated or simplex PeIN and undifferentiated PeIN as *warty*, *basaloid*, *mixed warty-basaloid*, with other descriptions including *small cell*, *spindle* (*clear*) *cell*, *pagetoid*, and *pleomorphic* types. It also recognized a mixed differentiated and undifferentiated histology [71]. In this classification, Bowenoid papulosis is considered as a separate lesion and is not included as a PeIN lesion.

As summarized in this historical overview, the disparate terminologies for squamous lesions of the anogenital tract and their clinical management have morphed over time. The next step in this evolutionary process is a common nomenclature reflecting the morphologic and biologic similarities of these lesions and our current understanding of HPV-associated disease.

SQUAMOUS INTRAEPITHELIAL LESIONS—WG2

Work group 2 was in charge of determining whether the current knowledge of HPV-associated biology could be harmonized with histopathologic terminology across all lower anogenital body sites and, if so, to develop appropriate terminology. The ultimate goal of a unified and scientifically based terminology is to optimize clinical management by improving communication between pathologists and clinicians.

Work group 2 reviewed 1,909 articles from the published literature. After exclusions, 186 articles were included for data extraction and analysis. Recent textbooks and professional society documents were also reviewed. The recommendations were based on this comprehensive literature review, expert opinion, and open comment period responses. The current state of clinical management for noninvasive cervical disease is based on guidelines from the ASCCP and ACOG, which use a 2-tiered terminology for cervix, except in adolescents and young women where a 3-tiered scheme is used [33, 72]. The recent ASCCP/ACOG guidelines for treating HPV-related vulvar disease are based on ISSVD nomenclature with 2 tiers—condyloma and VIN [73, 74]. At present, there are no formal guidelines for the management of vaginal, anal, perianal, or penile noninvasive disease. As described previously, there is considerable overlap in the terminology between the body sites, with multiple variations of cytologic, gynecologic, dermatologic, and dermatopathologic terms used in an ad hoc fashion. This situation leads to potential confusion about the meaning of individual terms and complicates the development of appropriate management guidelines. The following recommendations were developed based on the common biology of HPV-associated squamous disease at these sites.

WG2 Recommendation No. 1

A unified histopathologic nomenclature with a single set of diagnostic terms is recommended for all HPV-associated preinvasive squamous lesions of the LAT.

Rationale for Recommendation No. 1.—The comprehensive literature review and expert opinion support the biologic and morphologic equivalence of HPV-associated squamous proliferations across the LAT. Given this equivalence, a unified histopathologic nomenclature is recommended for all HPV-associated preinvasive intraepithelial squamous lesions in the LAT. Biomarker characteristics, as noted by WG4, are also consistent across LAT sites, lending further support to this recommendation.

WG2 Recommendation No. 2

A 2-tiered nomenclature is recommended for noninvasive HPV-associated squamous proliferations of the LAT, which may be further qualified with the appropriate –IN terminology. (–IN refers to the generic intraepithelial neoplasia terminology, without specifying the location. For a specific location, the appropriate complete term should be used. Thus, for an –IN 3 lesion: cervix = CIN 3, vagina = VaIN 3, vulva = VIN 3, anus = AIN 3, perianus = PAIN 3, and penis = PeIN 3.)

Rationale for Recommendation No. 2.—Current understanding of HPV biology does not support a 3-tiered system of mild, moderate, severe dysplasia/CIS or –IN 1, 2, 3. Rather, as stated in the introduction, there is support for a dichotomous separation of morphologic designations that reflect transient active HPV replication and persistent HPV-associated precancer. On the basis of the comprehensive literature review by WG4, no biomarker data supported a 3-tiered system (see below). Instead, data are consistent with a 2-tiered system with low-grade lesions that are generally self-limited HPV infection and high-grade lesions that have the potential to progress to invasive carcinoma. The equivocal nature of the diagnosis of –IN 2, an intermediate category that has no biologic correlate, is thought to represent a mixture of low-grade and precancerous disease that cannot be reliably distinguished based on hematoxylin and eosin (H&E) morphology [10, 75]. The –IN 2 category is not a reproducible histologic category among pathologists. Studies of diagnostic concordance demonstrate considerable interobserver variability reflected in very low κ statistics [10]. As might be expected from this mixture of high- and low-grade lesions, the risk of progression for lesions classified as –IN 2 is intermediate between –IN 1 and –IN 3. In addition, a substantial proportion of CIN 2 is found to represent CIN 3 on follow-up [6]. The recommendation for a 2-tiered system also harmonizes LAT terminology with other published systems, including those of recent textbooks and professional societies [64, 73, 74, 76, 77].

As expected, classification agreement with lower variability between observers can be improved in a 2-tiered versus a 3-tiered system [10, 28, 78–87]. Improved agreement among pathologists leads to a more consistent and reproducible diagnosis, which may lead to more valid clinical outcome data. Further methods for more precise classification of identified lesions using biomarkers are discussed in the recommendations from WG4. There is evidence to show that using certain biomarkers significantly increases interobserver agreement [88–91].

Considerable discussion occurred at the LAST consensus meeting and during the open comment period regarding the utility of maintaining an intermediate or equivocal category (i.e., –IN 2). The most frequently raised rationale for retaining this category was that current management guidelines for the cervix recommend conservative management of this intermediate category in young reproductive-aged women. Hence, there was concern for overtreatment should the –IN 2 category be merged into a high-grade tier. Given this concern, it was decided that qualifying the 2-tiered diagnosis with the relevant –IN category in parentheses is appropriate. This qualified 2-tiered stratification is similar to the recommendation for the initial, transitional TBS terminology from 1989 and 1991 that proposed a 2-tiered cytologic squamous intraepithelial lesion classification

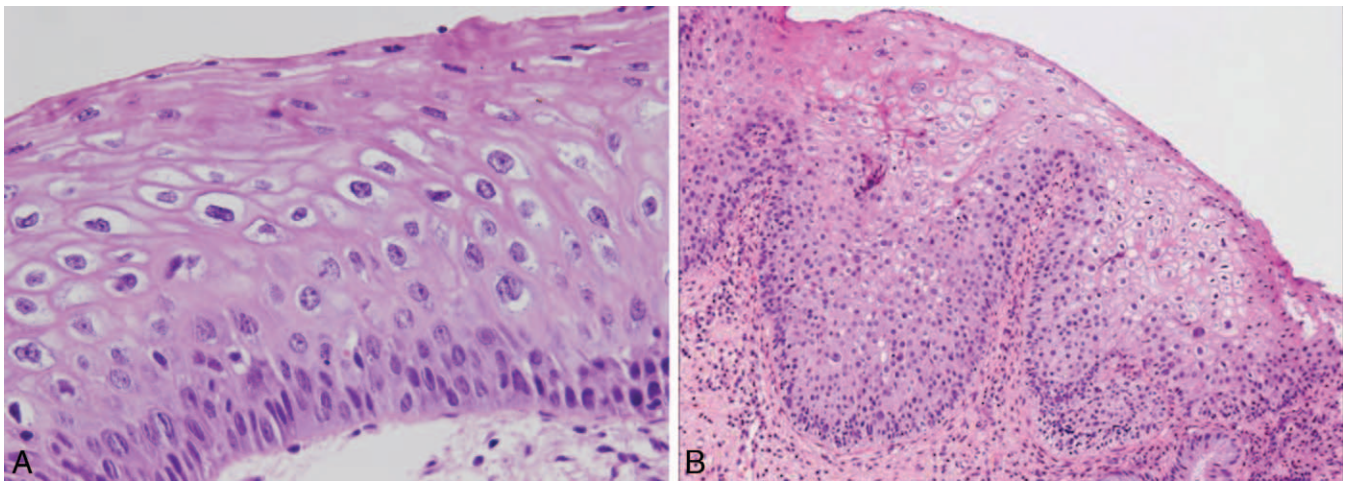

Figure 3. A, Vagina: LSIL (VaIN 1). B, Cervix: LSIL (CIN 1). In both images, the nuclei in the lower one third of the epithelium are enlarged with variable size and increased nuclear-to-cytoplasmic ratios. Cells in the upper layers show changes associated with HPV infection including nuclear size variability, multinucleation or binucleation, and cytoplasmic koilocytic change. Abnormal mitoses and marked nuclear atypia are not present. A, High power, H&E. B, Medium power, H&E.

with the option for further subclassification such as mild, moderate, or severe dysplasia (CIN 1, 2, or 3) [92].

WG2 Recommendation No. 3

The recommended terminology for HPV-associated squamous lesions of the LAT is *low-grade squamous intraepithelial lesion* (*LSIL*) and *high-grade squamous intraepithelial lesion* (*HSIL*), which may be further classified by the applicable –IN subcategorization.

Rationale for Recommendation No. 3.—This recommendation harmonizes the descriptive terminology for cytology and histopathology for biologically similar HPV-associated squamous lesions of the LAT. This terminology is also the one used for 2-tiered histologic systems in recent textbooks published in the field [64, 76, 77]. In addition, this terminology was the most widely supported by responses during the open comment period and at least a 67% supermajority of the participants at the consensus conference.

Concern was expressed that using the same terminology for cytology and histomorphology would not allow for distinction as to whether the diagnosis was associated with a cytologic or histologic specimen. On a written pathology report, the specimen type is clearly stated, so this confusion is minimized. However, in short-hand verbal communication, it may be important to designate reports as associated with cytology or histology specimens. The option of adding the specific –IN terminology with the basic 2-tiered classification would also help to identify these samples as histopathology.

The hallmark of SIL is an abnormal cellular proliferation with nuclear atypia that includes enlargement, pleomorphism, change in chromatin texture, and irregular nuclear borders. With increasing severity of SIL, the nuclear-to-cytoplasmic ratios increase, mitotic activity increases, and, in most cases, the cells appear more immature. It is important to note that nuclear changes are usually present throughout the full thickness of the epithelium, irrespective of the severity of the lesion. For that reason, cytologic sampling of the superficial layers can detect both low- and high-grade lesions. In general, it is the relative maturation or lack of maturation of the cytoplasm in the superficial layers, coupled with persistent mitotic activity, that defines the severity of the process.

Criteria that define the 2-tiered classification system:

LSIL:

- Proliferation of squamous or metaplastic cells with abnormal nuclear features including increased nuclear size, irregular nuclear membranes, and increased nuclear-to-cytoplasmic ratios. There is little cytoplasmic maturation in the lower third of the epithelium, but maturation begins in the middle third and is relatively normal in the upper third. Mitotic figures are limited to the lower one third of the epithelium (see Figure 3A).

And/or

- The presence of diagnostic cytopathic effect of HPV (koilocytosis) including multinucleation, nuclear enlargement, and pleomorphism accompanied by perinuclear halos without the features of a high-grade lesion (see Figure 3B).

HSIL:

- Proliferation of squamous or metaplastic squamous cells with abnormal nuclear features including increased nuclear size, irregular nuclear membranes, and increased nuclear-to-cytoplasmic ratios accompanied by mitotic figures. There is little or no cytoplasmic differentiation in the middle third and superficial thirds of the epithelium. Mitotic figures are not confined to the lower third of the epithelium and may be found in the middle and/or superficial thirds of the epithelium (see Figure 4).

It is important to NOT overcall LSIL as HSIL. Low-grade SIL is a common finding, especially on cervical biopsies. These are typically self-limited HPV infections that will resolve spontaneously.

Special circumstances:

Abnormal mitosis or significant nuclear atypia (see Figure 5): Abnormal mitoses and substantial nuclear atypia are more commonly seen in high-grade lesions. Some consider lesions with the overall morphology of LSIL, with either marked nuclear atypia in the lower third of the epithelium or atypical mitoses at any level, to be consistent with HSIL. As noted in WG4's recommendations, positive p16

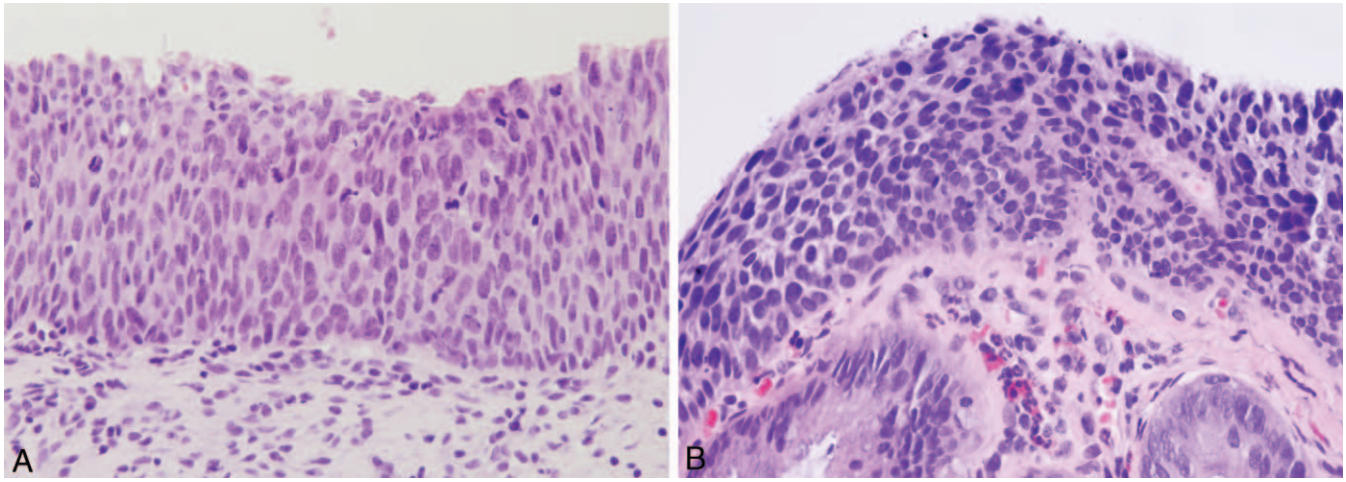

Figure 4. A, Cervix: HSIL (CIN 3). B, Anal: HSIL (AIN 3). These mucosal lesions have a full-thickness proliferation of abnormal immature or parabasal-like cells. There is loss of nuclear polarity, anisonucleosis, and increased nuclear-to-cytoplasmic ratios. Mitoses are seen in the upper two thirds of the epithelium. A and B, High power, H&E.

staining in this circumstance supports the diagnosis of HSIL.

Thin SIL (historically called thin dysplasia; see Figure 6): Morphologically, these are immature intraepithelial lesions less than 10 cells thick. If a lesion is unequivocally SIL with significant immature abnormal basal proliferation or mitosis above the basal cells, it is designated as HSIL. If there is doubt about the nature of the proliferation (e.g., immature metaplasia versus SIL) then p16 staining can be used as per WG4 Recommendation No. 1.

Keratinizing SIL (see Figure 7): A markedly atypical keratinizing proliferation is high grade. These lesions are defined by an abnormal keratinizing layer on the surface. The epithelium has dyskeratotic cells with markedly atypical, often pleomorphic nuclei. There is an abnormal proliferation of basal-type cells, but these often have more eosinophilic cytoplasm than is seen in mucosal high-grade lesions. These changes are most often seen in cutaneous sites with keratinizing epithelium such as vulva or perianus, although these changes may occasionally be seen in a mucosal epithelium such as cervix and vagina.

Dysplasia extending into the endocervical glands (see Figure 8): In general, grading of lesions extending into the endocervical glands can be performed as with surface lesions. If the abnormal basal proliferation fills the gland with no or minimal evidence of maturation, this should be classified as high grade. However, it is important to be aware of the possibility of tangential sectioning of epithelial basal layers that may make accurate grading difficult or impossible.

Condyloma acuminatum (see Figure 9): Condyloma acuminatum is, by definition, a papillary proliferation with low-grade cytopathic features of HPV infection. The majority are caused by low-risk HPV types 6 and 11. Lesions within this spectrum are designated as LSIL, with the additional optional designation of condyloma in parentheses. Condylomas are common in external anogenital areas and less frequent in the cervix and vagina.

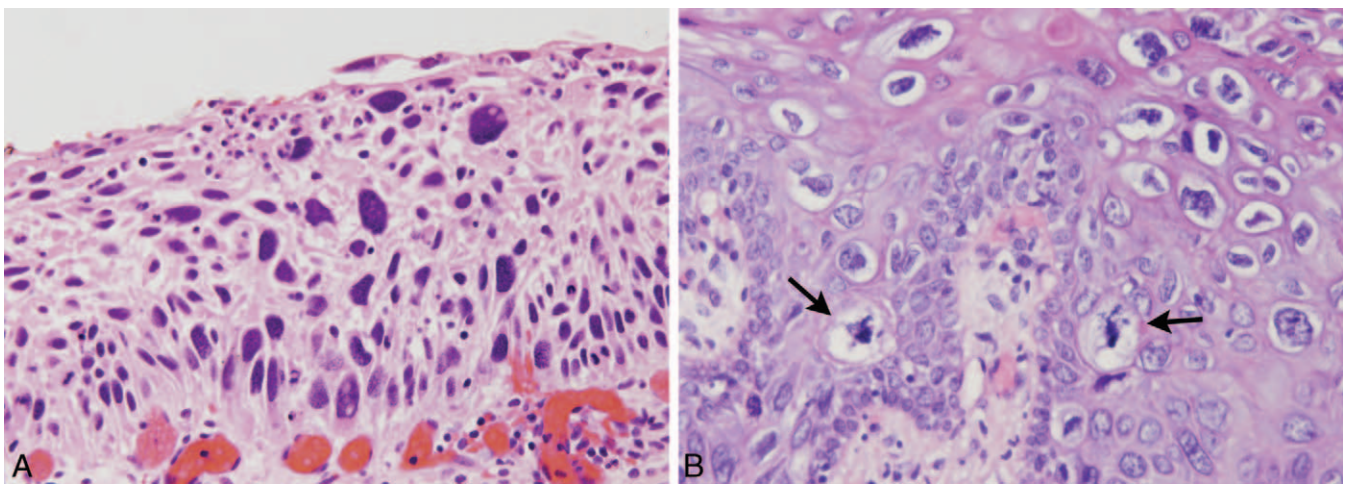

Figure 5. A and B, Cervical HSIL (CIN 2). A, Marked nuclear atypia is seen extending throughout the full thickness of the epithelium. Unlike classic –IN 3, these cells have more abundant cytoplasm. However, this degree of nuclear change is considered to be high grade. B, In this biopsy, there are abnormal mitoses (arrows) that are in the lower one third of the epithelium. The overlying cells show maturation and koilocytic change. The presence of these abnormal mitoses suggests HSIL and, in the presence of block-positive p16 staining, the diagnosis is HSIL (CIN 2). A and B, High power, H&E.

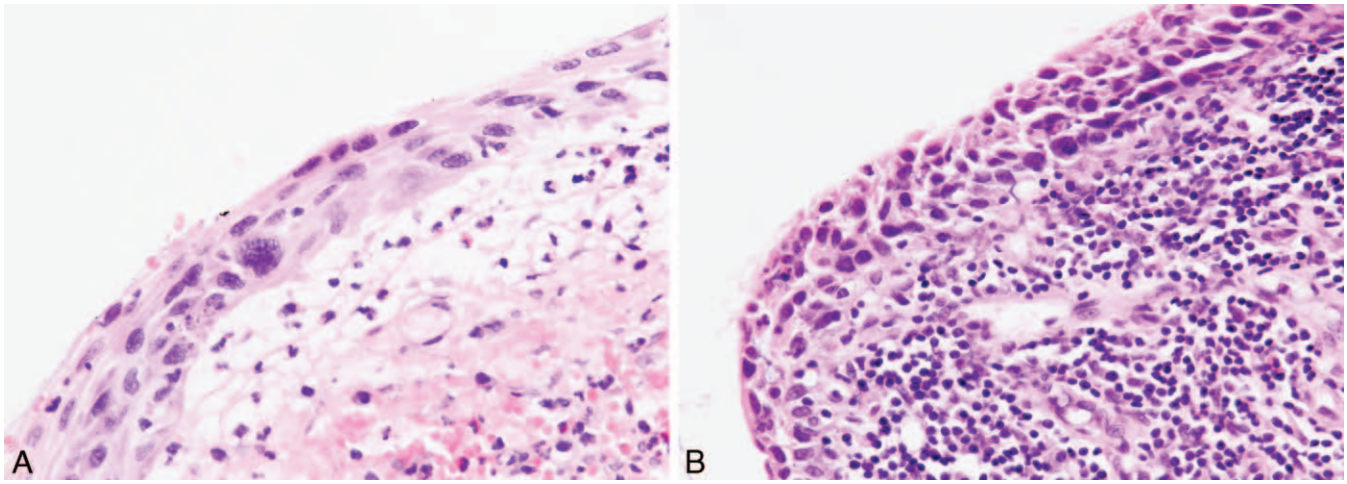

Figure 6. A and B, Cervix: HSIL (CIN 3). Both A and B demonstrate a thin SIL. The epithelium is less than 10 cells in thickness but shows marked nuclear atypia with anisonucleosis, mitotic activity above the basal layer, and loss of nuclear polarity consistent with a high-grade lesion. A and B, High power, H&E.

Bowenoid papulosis (see Figure 10): The clinical morphology of Bowenoid papulosis consists of small cutaneous papules that have high-grade histomorphology indistinguishable from –IN 3. In small or partial biopsies, an unequivocal diagnosis of Bowenoid papulosis is not possible based solely on microscopic findings. In the appropriate clinical setting of a patient with small, cutaneous anogenital papules, a note stating that the differential diagnosis includes Bowenoid papulosis may be warranted. If the lesion is excised and its small size can be identified, it can be diagnosed as HSIL with an additional designation of Bowenoid papulosis in parentheses. Bowenoid papulosis may have a lower risk of progression to cancer than cutaneous HSIL found in larger plaques (Bowen disease).

Use of LAST Terminology in a Pathology Report

The recommended terminology for squamous intraepithelial lesions should be used as with any other diagnostic terms in a routine surgical pathology report. In general, when an –IN qualifier is used in parentheses, the lesion grade should be based on the H&E histomorphology of the lesion. However, if a biomarker is used to evaluate the specimen, as specifically recommended by WG4, the results may override the original H&E interpretation. For example, if a putative –IN 2 lesion is negative for p16, the lesion represents either LSIL or a non–HPV-associated mimic, and should be reported as such (see Figures 16–18).

SUPERFICIALLY INVASIVE SQUAMOUS CELL CARCINOMA—WG3

Work group 3's charge was to review data across LAT sites to recommend specific terminology for minimally invasive squamous cell carcinoma (SCC), especially where minimal invasion is not well defined (i.e., anus). If possible, unification of terminology across sites was favored. Such terminology should be designed to provide clear and relevant communication between pathologists and clini-

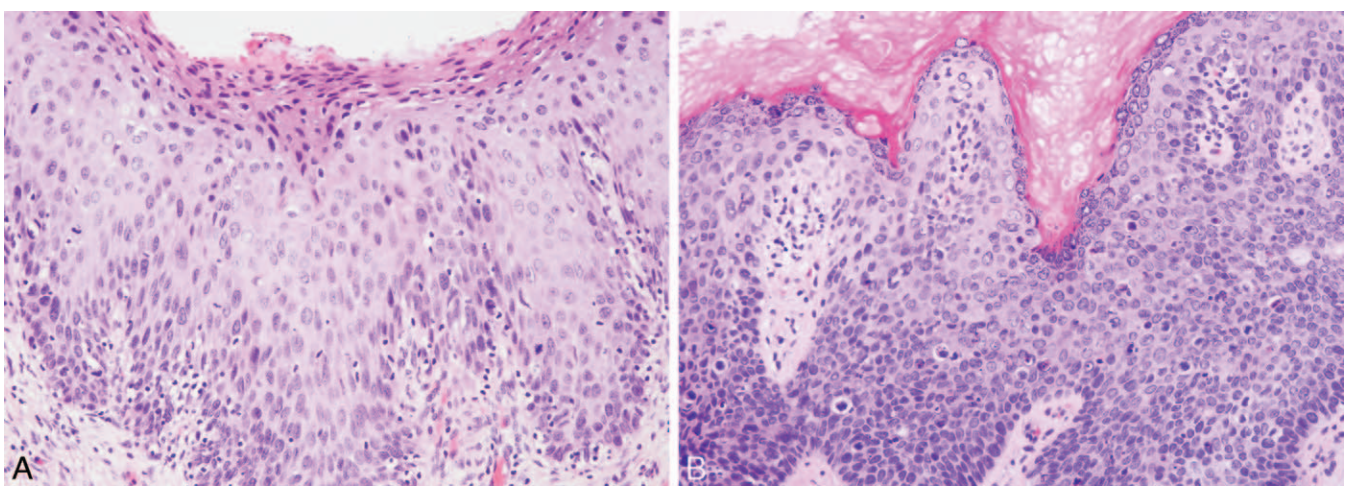

Figure 7. A, Cervix: HSIL (CIN 3). B, Perianus: HSIL (PAIN 3). High-grade keratinizing SIL often shows more cellular maturation in the middle layers of the epithelium as is seen in A. In both panels, there is an abnormal keratinizing surface, and mitoses are seen throughout the epithelium. Although keratinizing dysplastic change is most commonly seen in cutaneous anogenital sites, (B) they may be seen in the mucosal areas such as the cervix or anal canal. A and B, High power, H&E.

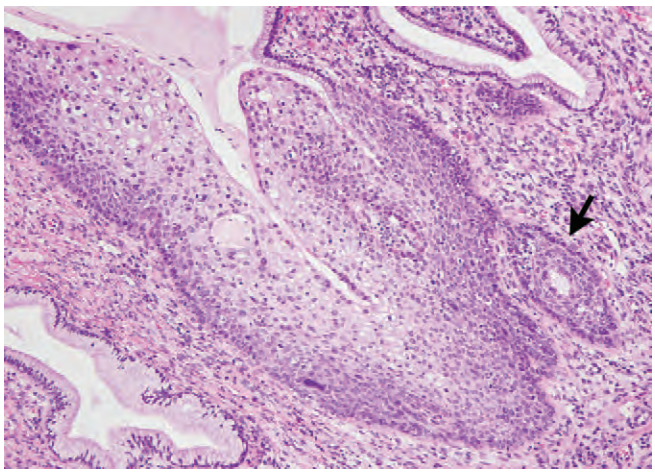

Figure 8. Cervical LSIL (CIN 1). Low-grade squamous intraepithelial lesion extends into an endocervical gland neck. When the full thickness of the abnormal epithelium is seen, the interpretation is straightforward. In areas with tangential sectioning (arrow), care must be taken not to overcall HSIL. Medium power, H&E.

cians, with a specific focus on reconciling histopathologic diagnoses with current clinical management. Work group 3 identified 1863 articles in its comprehensive literature search and extracted data from 194. Most articles dealt with cervical disease, but some articles did address vulvar, penile, anal, and perianal diseases. This literature review was supplemented with background information, the current *AJCC Cancer Staging Manual* (*7th edition*) and errata, and other current pathology textbook resources [52]. The recommendations are based on this comprehensive literature review, expert opinion, open comment period responses, and consensus conference discussion.

The literature review highlighted a widespread but inconsistent use of "microinvasive" terminology. There are a variety of definitions, per site and between sites. Different sites use different defining parameters. There are outstanding methodological issues such as multifocality and precision in measurement. The use of some potential prognostic parameters, for example, LVI, varies among systems and sites. There is lack of clarity in reporting margin involvement by invasive carcinoma or intraepithelial neoplasia. There is no current definition identified for minimally invasive cancers of the anal canal and perianus. Cancer of the perianus is staged as skin cancer, not as anal cancer or vulvar cancer, and the vulvar and perianal regions anatomically overlap in women. The central conclusion of the literature review was that adopting a category of superficially invasive squamous cell carcinoma (SISCCA) based on clinical outcome for these sites would have several potential benefits: clear identification of groups that might be amenable to conservative treatment (e.g., cervix), permit comparison of results for management of identical stage disease across body sites, and eliminate confusion in defining early invasive disease across body sites.

Superficially invasive squamous cell carcinoma is defined based largely on depth and width of invasion. The diagnostic criteria proposed for SISCCA recognize that the risks for metastasis differ across body sites. In addition, biopsy reports should include consistent terminology for lesions that have been completely excised and those that have positive margins.

Reports on minimally invasive squamous carcinomas could merely state the diagnosis and list all objective findings of potential prognostic importance, such as depth and width of invasion and any LVI, rather than define a category of SISCCA for invasive carcinomas that might be amenable to local excisional (conservative) treatment only. However, defining the features of a SISCCA category for each LAT site would have 3 major advantages. First, although a listing of prognostic parameters alone might be sufficient for the oncologic subspecialist's management of patients, it is not optimal reporting for all health professionals managing LAT neoplasia who may only occasionally deal with SISCCA. The role of the modern pathologist is to integrate objective parameters into a definitive diagnostic report based on evidence-based outcomes. Using this approach, the surgical pathology report delivers synthesized information relevant to clinical management rather than just data points. A clearly defined category of SISCCA identifies those patients who can be potentially managed by local treatment only. Second, a well-defined category of SISCCA will permit comparative

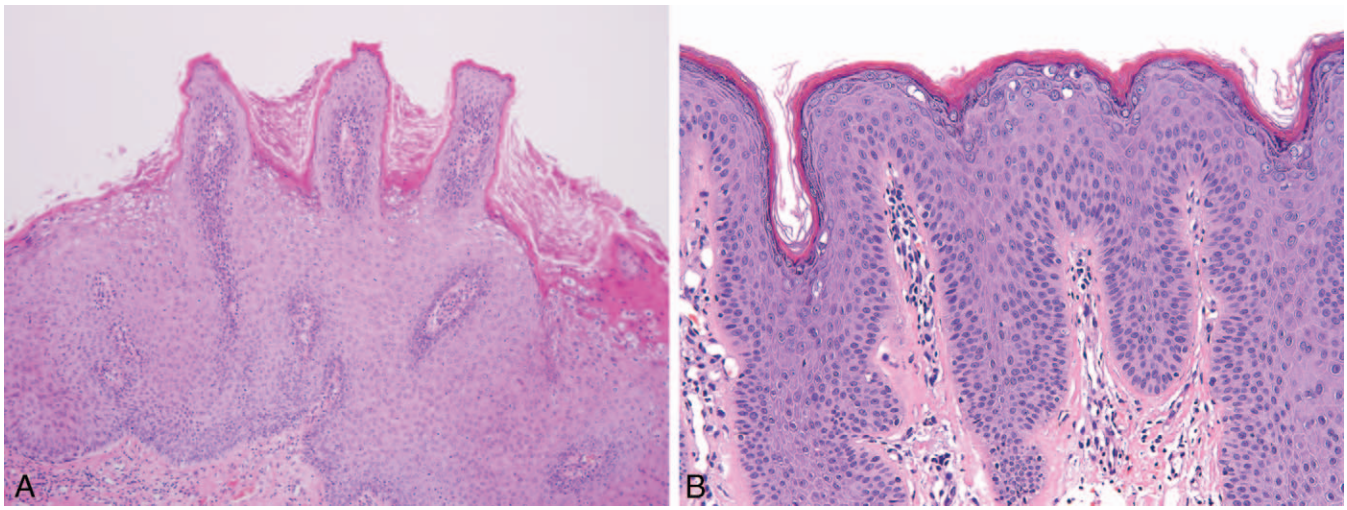

Figure 9. A, Perianus: LSIL (condyloma). B, Vulva: LSIL (condyloma). Low-grade lesions with a papillary growth pattern may be designated as condylomas in the proper clinical setting. These lesions should not demonstrate high-grade features. A, Low power, H&E. B, Medium power, H&E.

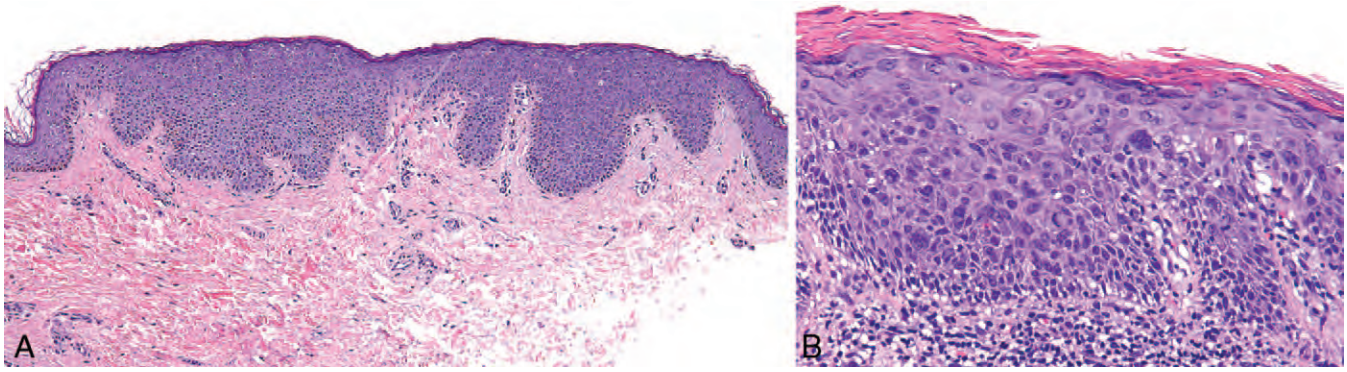

Figure 10. A, Vulva: HSIL (Bowenoid papulosis). B, Penis: HSIL (PeIN 3). In A, the entire extent of the high-grade lesion can be seen, and given the small size and location, Bowenoid papulosis can be included in parentheses in the diagnoses. In B, only a portion of the lesion can be seen and, although Bowenoid papulosis may be suggested in a comment, it should not be part of the diagnostic line. A, Low power, H&E. B, High power, H&E.

research in the management of identical groups of patients, which is not assured if only prognostic parameters are listed. Third, defining SISCCA would eliminate confusion in dealing with the parameters of early invasive disease that exists in some anogenital sites, such as the cervix.

The first 3 recommendations from WG3 are general and are to be applied across all LAT sites. These are followed by an additional 7 site-specific recommendations that include measurement recommendations where these have been shown to have prognostic significance. A subsequent paper with detailed methods of measurement is planned for future publication.

WG3 Recommendation No. 1

The term *superficially invasive squamous cell carcinoma* (SISCCA) is recommended for minimally invasive squamous cell carcinoma of the LAT that has been completely excised and is potentially amenable to conservative surgical therapy. Note: Lymph-vascular invasion (LVI) and pattern of invasion are not part of the definition of SISCCA, with the exception of penile carcinoma.

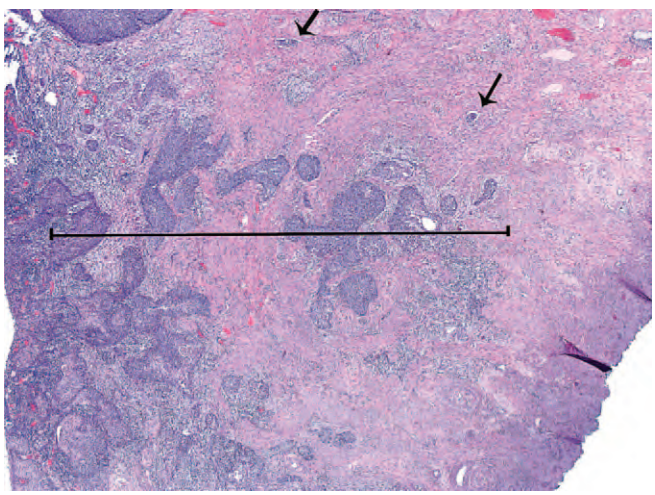

Figure 11. Cervical SISCCA with less than 3 mm (line); LVI is present (arrows). It was completely excised. Low power, H&E. Reprinted with permission from *Journal of Lower Genital Tract Disease* (2011;15:146–57). Copyright 2011, American Society for Colposcopy and Cervical Pathology.

Explanatory Notes: Recommendation No. 1.—Resection margin status is best determined from a single marked or inked surgical excisional biopsy. In the cervix, for example, this will usually mean a LEEP or cone specimen. Punch biopsies may identify invasive carcinoma, but their size is usually suboptimal to definitively identify SISCCA. In the setting of multiple specimens from the same lesion, the final diagnosis must be based on the consideration of all the findings. For example, if a 3-mm punch cervical biopsy shows invasive squamous carcinoma 2 mm in depth and a subsequent LEEP specimen shows only a healing biopsy site without residual carcinoma, then SISCCA is present.

WG3 Recommendation No. 2

For cases of invasive squamous carcinoma with positive biopsy/resection margins, the pathology report should state whether:

The examined invasive tumor exceeds the dimensions for a SISCCA (defined below)

OR

The examined invasive tumor component is less than or equal to the dimensions for a SISCCA and conclude that the tumor is "*at least a superficially invasive squamous carcinoma*."

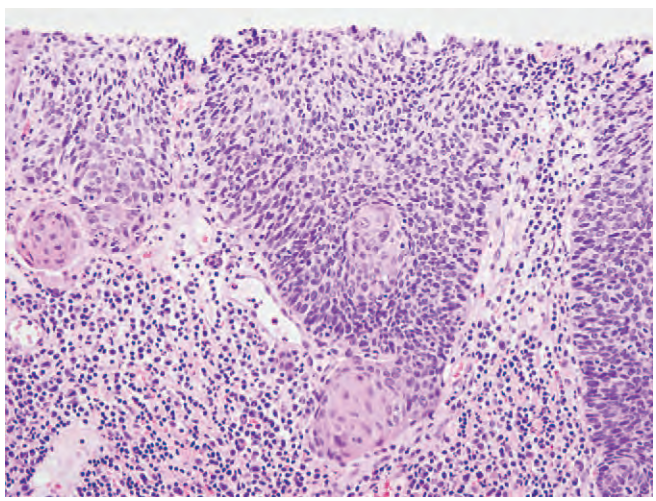

Figure 12. Superficially invasive squamous cell carcinoma of the anal canal with a nest of malignant squamous cells invading into the stroma. Note overlying HSIL. Medium power, H&E.

Explanatory Notes: Recommendation No. 2.—Anogenital tract biopsies may show invasive squamous carcinoma with invasive disease at the margins. In this clinical situation, it is important to clearly indicate whether the current specimen qualifies for SISCCA (if no more invasive disease is identified) or whether more advanced disease is already evident.

In this recommendation, positive biopsy or resection margins refers to invasive carcinoma at the surgical resection margin. The presence of HSIL at the surgical margins does not negate the diagnosis of SISCCA; however, its presence should be reported.

WG3 Recommendation No. 3

In cases of SISCCA, the following parameters should be included in the pathology report:

The presence or absence of LVI.

The presence, number, and size of independent multifocal carcinomas (after excluding the possibility of a single carcinoma).

Explanatory Notes: Recommendation No. 3.—Lymph-vascular invasion and tumor multifocality may play a role in the management of LAT squamous carcinomas but are not usually criteria in the diagnosis of SISCCA. However, these 2 parameters should also be reported.

Lymph-vascular invasion is most reliably defined when the following features are identified in an H&E histologic section: a tumor island is present within a space, the space has an apparent endothelial lining, the tumor is adherent to the lining, the space is not due to retraction artifact, and the finding is beyond the invasive front. Frequently, however, LVI is only identified within the invasive tumor front and the latter criterion cannot be met. Immunohistochemical (IHC) staining for vascular and lymphatic endothelium may be used to confirm the presence of LVI. The absence of IHC staining, however, does not exclude the presence of LVI because a variety of preanalytic and technical factors can lead to negative IHC staining of the endothelium.

Site-Specific Recommendations

After establishing the primary general recommendations for SISCCA, the current terminology systems and evidence for each specific anogenital site were reviewed, and recommendations were adopted.

Cervix.—It is thought that all SCCs of the cervix are attributable to HPV [93]. There are abundant data that early invasive squamous carcinoma (SCC) of the cervix can safely be treated conservatively. Historically, a variety of terms, including *microinvasive carcinoma*, have been used to label this group. Criteria for defining patients amenable to conservative management have changed over the years.

Initially, invasive squamous carcinomas as deep as 5 mm, regardless of LVI, were considered to be amenable to conservative therapy, but evidence accumulated that metastatic lymph node disease and/or local recurrence occurred in a small, but significant proportion of these patients [94–97]. Consequently, more restrictive definitions of minimally invasive squamous carcinoma were proposed.

Currently, 2 principal systems are used: the first, developed by the Society of Gynecologic Oncologists (SGO), is more commonly used in the United States and the second, developed by FIGO, is used in other parts of the world. Staging of minimally invasive squamous carcinoma differs between these 2 systems, making comparisons difficult.

In 1973, SGO defined microinvasive cervical carcinoma as any lesion in which neoplastic cells invade the stroma, in 1 or more sites, to a depth of 3 mm or less below the base of the epithelium, without lymphatic or blood vessel involvement [98, 99]. The margins of the specimen must be clear of the lesion [76]. The SGO definition does not comment on the width of the lesion. Clinical studies and expert opinion have generally concluded that "microinvasive" SCC can be managed conservatively by cervical conization, LEEP excision, or simple hysterectomy, although more restrictive depth criteria of 2 mm or even 1 mm have been proposed or used [98, 100–113].

In the last 40 years, accumulated evidence indicates that there are significant deficiencies in the SGO criteria for "microinvasive" disease. No lateral or horizontal criteria are used in the SGO definition of "microinvasive" carcinoma, although tumor volume has been shown to be a major predictor of lymph nodal metastases [114, 115]. Occasional cases have been reported with extensive lateral spread and tumor volume, but with less than 3 mm depth of invasion that still meets the criteria for SGO "microinvasive" carcinomas [116]. The 2009 revised CAP protocol for cervical carcinoma introduced a 7-mm maximal lateral extent for "microinvasive" carcinoma [117]. Moreover, the prognostic significance of LVI in minimally invasive carcinomas remains unclear [105]. The presence of LVI strongly correlates with the depth of invasion and tumor volume, and this correlation is a major confounding variable [110, 111, 118]. Clinical studies have shown LVI to be an inconsistent predictor of lymph node metastases in cases of invasive carcinoma 3 mm or less in depth [105, 119–123]. Consequently, it is unclear whether LVI should remain an unequivocal exclusion criterion to preclude conservative management among cases in which the depth of invasion is 3 mm or less. Although the SGO definition of "microinvasion" requires that the lesion be entirely excised, it is unclear whether this requires the margin to be free of invasive squamous carcinoma, HSIL (CIN 3), or any SIL (CIN). Finally, perpetuation of the use of the SGO microinvasive carcinoma concept may continue to impair the international comparability of cervical carcinoma management.

The AJCC (TNM) and FIGO staging classifications are concordant albeit with minor nomenclature discrepancies. For example, AJCC T1a is labeled as FIGO IA. Large cervical carcinomas are staged clinically, but early-stage carcinomas are defined by pathologic examination of a biopsy specimen. FIGO stage I is a carcinoma strictly confined to the cervix (extension to the corpus is disregarded) [124]. Any grossly or clinically identified carcinoma is staged as IB. Colposcopic suspicion or identification of an invasive carcinoma alone does not lead to a diagnosis of stage IB. Stage IA carcinoma is present when the invasive disease is only identified microscopically, and stromal invasion is limited to 5 mm or less and to a lateral or horizontal width of 7 mm or less [125]. The depth of invasion is measured from the base of the epithelium of the presumptive point of origin, whether squamous or glandular. Vascular space involvement, either venous or lymphatic, does not alter the staging. Stage IA1 lesions, a subset of IA, has a depth of invasion of 3 mm or less, whereas stage IA2 carcinomas have invasion of greater than 3 mm. These 2 subsets of disease reflect an increasing risk of metastatic lymph node disease secondary to increasing tumor volume.

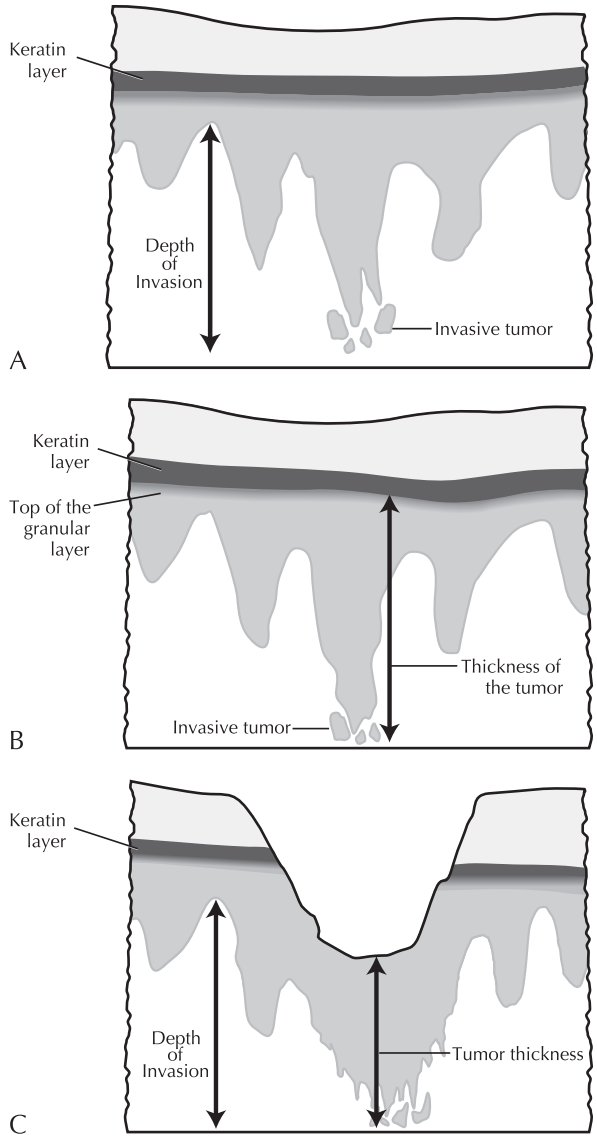

Figure 13. Cutaneous anogenital SISCCA: measurement of the depth of invasion. A, The depth of invasion is measured from the epithelial-dermal junction of the adjacent-most superficial dermal papillae to the deepest point of invasion. This measurement is applicable whether the surface epithelium is ulcerated or keratinized. This is the AJCC-recommended method of measuring vulvar squamous cell carcinomas in determining whether a tumor is stage T1a or T1b. B, Measurement for the thickness of the tumor when the epithelial surface is intact. If the tumor is keratinized, the thickness of the tumor is measured from the granular cell layer to the deepest point of invasion. For squamous cell carcinomas, the convention is to measure from the bottom of the granular cell layer. If the epithelium is not keratinized, the thickness of the tumor is measured from the surface of the tumor to the deepest point of invasion. C, Measurement for tumor thickness when the tumor is ulcerated. The tumor thickness is measured from the surface of the ulcerated tumor to the deepest point of invasion. For SCC, the depth of invasion is a more accurate measurement of the true depth of the tumor, as measured from the epithelial dermal junction of the adjacent dermal papillae to the deepest point of invasion. Reprinted with permission. Figure © E.J. Wilkinson, 2007 From *AJCC Cancer Staging Manual*, 6th ed. New York, NY: Lippincott, Williams & Wilkins; 2002.

Since the adoption of FIGO IA staging methods more than 15 years ago, evidence has accumulated and confirmed the clinical utility of the FIGO IA1 and IA2 subsets. The proportion of patients with lymph node metastases in FIGO IA1 or invasive carcinomas 3 mm or less in depth is negligible, and many authors have concluded that local excision is adequate management [97, 121, 126–133]. Nevertheless, some have adopted the presence of LVI, or "extensive" LVI, as an exclusion criterion for conservative management [105, 110, 111, 134]. In contrast, there is an increased prevalence of both lymph node metastases and recurrence after local excision in FIGO IA2, and many studies conclude that local excision alone is inadequate for this group of patients [39, 103, 118, 126, 128, 130, 134–138].

In summary, the comprehensive literature review and expert opinion supports that a unifying terminology for invasive squamous carcinoma of the cervix be based on the widely adopted FIGO system and that cervical SISCCA is equivalent to a FIGO IA1.

WG3 Recommendation No. 4.—Cervix.—Superficially invasive squamous cell carcinoma of the cervix is defined as an invasive squamous carcinoma that:

Is not a grossly visible lesion, AND
Has an invasive depth of ≤3 mm from the basement membrane of the point of origin, AND
Has a horizontal spread of ≤7 mm in maximal extent, AND
Has been completely excised.

Rationale for Recommendation No. 4.—Patients with SISCCA of the cervix may have SIL (CIN) at margins of excision (see Figure 11). The diagnosis of SISCCA is not excluded based on this parameter. Persistent or recurrent cervical disease may occur in women with negative margins or those involved by SIL, and both groups remain at risk for persistent or recurrent SIL [98]. Women with involved margins are at increased risk for both the presence of multifocal invasive squamous carcinoma and persistent SIL [96, 137, 139–143]. Clinical follow-up or immediate reexcision may be chosen in the management of women with SIL at the surgical margins.

Vagina.—Vaginal cancers are rare. Approximately 40% to 60% of SCCs of the vagina are attributable to HPV [93]. In addition, vaginal squamous carcinomas are, in general, not amenable to local resection. FIGO uses clinical staging for cancer of the vagina. All available data before the first definitive treatment should be used, including the results of biopsy or fine needle aspiration of regional lymph nodes. Pathologic staging of vaginal cancer focuses on examination of the resected specimen, including pelvic and retroperitoneal lymph nodes. The current AJCC definition of a T1 (FIGO stage I) tumor is one confined to the vagina. T1 tumors are not further subdivided. Scant literature on the behavior of minimally invasive squamous carcinoma is available [144–146]. On the basis of the lack of evidence on early vaginal carcinoma and the general absence of a local resection option, no recommendation could be made to define SISCCA of the vagina.

WG3 Recommendation No. 5—Vagina.—No recommendation is offered for early invasive squamous carcinoma of the vagina. Owing to the rarity of primary SCC of the vagina, there are insufficient data to define early invasive squamous carcinoma in the vagina.

Rationale for Recommendation No. 5.—The literature review yielded no data to recommend changes to the current staging for vaginal SCC. It is staged clinically and uses all available data including biopsy results and regional lymph

node fine needle aspiration to determine definitive treatment. Squamous cell carcinoma confined to the vagina is an AJCC T1 tumor (FIGO stage I). T1 tumors are not further subdivided.

Anal Canal.—Approximately 90% to 93% of anal canal SCC is attributable to HPV [93]. Historically, abdominoperineal resection was the primary management for anal canal cancer [52, 147, 148]. In the 1980s, primary surgical therapy was supplanted by combined modality therapy with radiation and chemotherapy. Combined modality therapy has achieved superior survival rates and reduced recurrence rates while preserving the anal sphincter [149]. Surgical therapy was reserved for those with poor performance status, those who declined a colostomy, and those with small, well-differentiated tumors [150]. Local surgical excision can provide excellent outcomes for patients with tumors that are small (<1 cm) and do not infiltrate the sphincter [150, 151]. The significance for the diagnosis of "microinvasive squamous cell carcinoma" in the anal canal is undetermined [152].

WG3 Recommendation No. 6.—Anal Canal.—The *suggested* definition of superficially invasive squamous cell carcinoma (SISCCA) of the anal canal is an invasive squamous carcinoma that:

Has an invasive depth of ≤3 mm from the basement membrane of the point of origin, AND
Has a horizontal spread of ≤7 mm in maximal extent, AND
Has been completely excised.

Rationale for Recommendation No. 6.—The current AJCC definition of a T1 anal tumor is 2 cm or less in greatest dimension (see Figure 12) [52, 147, 148]. T1 tumors of the anal canal are not subdivided further. Combined modality therapy is the current primary therapy and standard of care for anal SCC but also has associated morbidity [153]. Historically, patients with small cancers excised with clean margins have had good outcomes [150, 151]. As more early invasive anal cancers are diagnosed (owing to increased awareness and screening), highlighting minimally invasive cancers that are potentially amenable to conservative sphincter-sparing surgical therapy with lower morbidity than combined modality therapy is imperative. The suggested definition of anal canal SISCCA, albeit arbitrary, is similar to that for the cervix. It will allow capturing of consistent, prospective data for this potentially important category. In addition, it is our opinion that the conservative management of a patient with anal SISCCA should include an evaluation by an expert experienced with high-resolution anoscopy and anal canal cancer.

Vulva.—Approximately 40% to 50% of SCCs of the vulva are attributable to HPV [93]. Current staging for SCCA of the vulva is the same regardless of the etiology. The AJCC definition of a T1a (FIGO IA) vulvar squamous carcinoma is a lesion 2 cm or less in size, confined to the vulva or perineum, and with stromal invasion of 1 mm or less. T1b (FIGO IB) lesions are those more than 2.0 cm in size or any size with stromal invasion of more than 1.0 mm. FIGO adds that stage I lesions are node-negative.

WG3 Recommendation No. 7—Vulva.—Vulvar SISCCA is defined as an AJCC T1a (FIGO IA) vulvar cancer. No change in the current definition of T1a vulvar cancer is recommended. The current AJCC definition of T1a vulvar carcinoma is:

Tumor 2 cm or less size, confined to the vulva or perineum AND Stromal invasion of 1 mm or less.

Note: The depth of invasion is defined as the measurement of the tumor from the epithelial-stromal junction of the adjacent-most superficial dermal papilla to the deepest point of invasion.

Rationale for Recommendation No. 7.—The depth of invasion is defined as the measurement of the tumor from the epithelial-stromal junction of the adjacent-most superficial dermal papilla to the deepest point of invasion (see Figure 13). Measurement of depth can be problematic in the vulva (e.g., in an ulcerated lesion). Measurement is less likely to be an issue on excisional than on punch biopsy specimens. The current prognostic literature uses depth as the most important measurement. Prospective collection of thickness data may provide prognostication in the future. On the basis of the literature review, no changes to the current AJCC definition are suggested.

The purpose of defining a separate category of superficially invasive lesions is that these lesions have an extremely low risk of lymph node metastases and hence may be treated less aggressively than larger tumors [154]. Vulvar stage IA lesions can be managed by wide local tumor excision without inguinofemoral node dissection [155, 156]. Lymph node dissection can then be performed if final pathology shows a lesion exceeding "superficially invasive" criteria. For the vulva, the definition is well established and in use by the AJCC, as well as CAP and ISSVD.

Penis.—Cancers of the penis are rare in the United States. Approximately 40% of SCCs of the penis are attributable to HPV [93]. The AJCC definition of a T1a penile squamous carcinoma is a tumor that invades subepithelial connective tissue without LVI and is not poorly differentiated (i.e., not grade 3–4). If LVI is identified or the tumor is poorly differentiated, the lesion is classified as T1b. Both parameters are independent predictors of inguinal lymph node involvement in patients with SCC of the penis and should prompt more aggressive care. For the penis, AJCC does not provide a specific measurement but limits the definition to invasion of no more than the subepithelial connective tissue. Measurement of depth of invasion for penile cases will provide data for future studies as to whether the measurement of depth of invasion is significant.

There are fewer studies available on SISCCA of the penis than of the vulva. The current AJCC TNM staging defines stage T1 penile cancer as a tumor that invades the subepithelial connective tissue without LVI and is not poorly differentiated. Specific measurements of depth of invasion are not included in the definition [157]. Some authors stratify T1 tumors by grade into low-, intermediate-, and high-risk categories, recommending lymphadenectomy for high-risk (T1G3) lesions, surveillance for low-risk (T1G1) lesions, and consideration of lymphadenectomy for intermediate-risk (T1G2) lesions, potentially including growth pattern and presence of LVI as points of consideration in the decision [158].

WG3 Recommendation No. 8—Penis.—Penile SISCCA is defined as an AJCC T1a. No change in the current definition of T1a penile cancer is recommended.

Current AJCC definition of T1a penile carcinoma:
Tumor that invades only the subepithelial connective tissue, AND No LVI
AND Is not poorly differentiated (i.e., grade 3–4).

Rationale for Recommendation No. 8.—On the basis of the literature review, no changes to the current AJCC definition are suggested.

Scrotum.—Squamous cell carcinoma of the scrotum is now very rare. Although some are HPV-associated, historically its development is linked to occupational exposure in chimney sweeps [159]. The current AJCC staging system for scrotal cancer is as per cutaneous SCC. There are no subdivisions of T1 skin cancers, defined as 2 cm or less with fewer than 2 high-risk features (>2 mm thickness, Clark level ≥ IV, perineural invasion, poorly differentiated, or undifferentiated).

WG3 Recommendation No. 9—Scrotum.—No recommendation is offered for early invasive squamous carcinoma of the scrotum.

Owing to the rarity of primary SCC of the scrotum, there is insufficient literature to make a recommendation regarding the current AJCC staging of early scrotal cancers.

Rationale for Recommendation No. 9.—On the basis of the literature review, no changes to the current AJCC definition are suggested.

Perianus.—The proportion of SCC of the perianus attributable to HPV are different between women and men, with 80% of female and 29% of male perianal cancers associated with HPV [160]. The perianus is currently defined as the region extending 5 cm from the anal opening or verge as visualized by gentle retraction on the buttocks [161]. This region overlaps anatomically with the vulvar perineum. In women, the perineum should be considered part of the vulva for staging and management purposes [52]. The distinction between anal canal and perianal malignancies is important because anal canal lesions have different natural histories [148].

WG3 Recommendation No. 10—Perianus.—The *suggested* definition for SISCCA of the perianus is an invasive squamous carcinoma that:
Has an invasive depth of ≤3 mm from the basement membrane of the point of origin, AND
Has a horizontal spread of ≤7 mm in maximal extent, AND
Has been completely excised.

Rationale for Recommendation No. 10.—In the current AJCC staging system, perianal cancers are staged as cutaneous SCC. T1 skin cancers are defined as those measuring 2 cm or less with fewer than 2 high-risk features (>2 mm thickness, Clark level ≥IV, perineural invasion, poorly differentiated, or undifferentiated). There are no subdivisions of T1 skin cancers [49, 52]. Historically, anal canal and perianal cancers have often been grouped together in studies of anal cancer. The suggested measurements of depth and horizontal spread for anal canal and perianal SISCCA are the same. Similar to the situation for the anal canal, defining a minimally invasive cancer of the perianus will allow for meaningful and consistent prospective data collection.

WG3 Outstanding Issues

The major outstanding issue for SISCCA is the methodology for measurement. Specific details on methodology for measurements of depth, definitions of horizontal/lateral extent, and measurements in the presence of multifocality of carcinoma are planned for a future publication.

BIOMARKERS IN HPV-ASSOCIATED LOWER ANOGENITAL SQUAMOUS LESIONS—WG4

Work group 4 was tasked with evaluating the use of molecular markers in conjunction with H&E morphology for the assessment of specimens from the LAT. In doing so, 2,291 articles were identified from the literature search. Using prespecified criteria and following a systematic title/abstract and full-text review process, this number was culled to 72 from which complete data extraction was performed. Fifty-three of these articles dealt with the biomarker p16. Most articles focused on cervical disease; however, some articles did address lesions in vulvar, penile, and anal sites. Of the selected literature, prospective studies and those having histologic adjudication as a criterion standard were given more emphasis.

The literature and expert review process was directed toward evaluating and selecting the best science for the best possible patient care, regardless of costs. In this regard, WG4 was highly cognizant of the interplay between medicine and industry in the published literature. Just as the utility of HPV testing for cervical cytology screening and triage was critically tied to the performance characteristics of HPV DNA tests, similar concepts must be applied for biomarker-based tests [162]. On the basis of these considerations, the clinical utility of p16 immunohistochemistry as proposed by WG4 is directly related to the performance characteristics of a particular clone described in the literature and, in some cases, to specific immunohistochemistry (IHC) kits as reported in the literature. These tests have defined characteristic staining patterns in consensus adjudicated diagnostic categories. For example, the test kits used in peer-reviewed publication show that more than 99% of histologic CIN 3 are p16-positive [163]. In contrast, less than 5% of histologically negative biopsies are p16-positive, and many of such cases, in retrospect, contain small missed lesional areas of high-grade disease [163, 164]. Clinical use of alternative clones, kits, or systems requires equivalent data to ensure similar clinical performance. Similar concepts would apply to any other potential biomarker (e.g., ProEx C [Becton Dickinson, Franklin Lakes, NJ] or Ki-67) with similarly developed criteria, albeit with some marker-specific nuances. Use of test kits with different test characteristics raises the possibility of causing harm by overcalling or undercalling severity of lesions.

Work group 4's recommendations, and the evidence used to support them, were evaluated by an independent reviewer with experience in the development of evidence-based guidelines (Evan R. Myers, MD, MPH, Department of Obstetrics and Gynecology, Duke University) before the consensus conference; articles excluded during the initial search and review phase were not reviewed again. On the basis of the reviewer's overall assessment of the quality of the evidence for test characteristics and observer variability, WG4's recommendations were framed using "recommend" if the recommendations are unlikely to change based on further evidence and "suggest" if the recommendation is

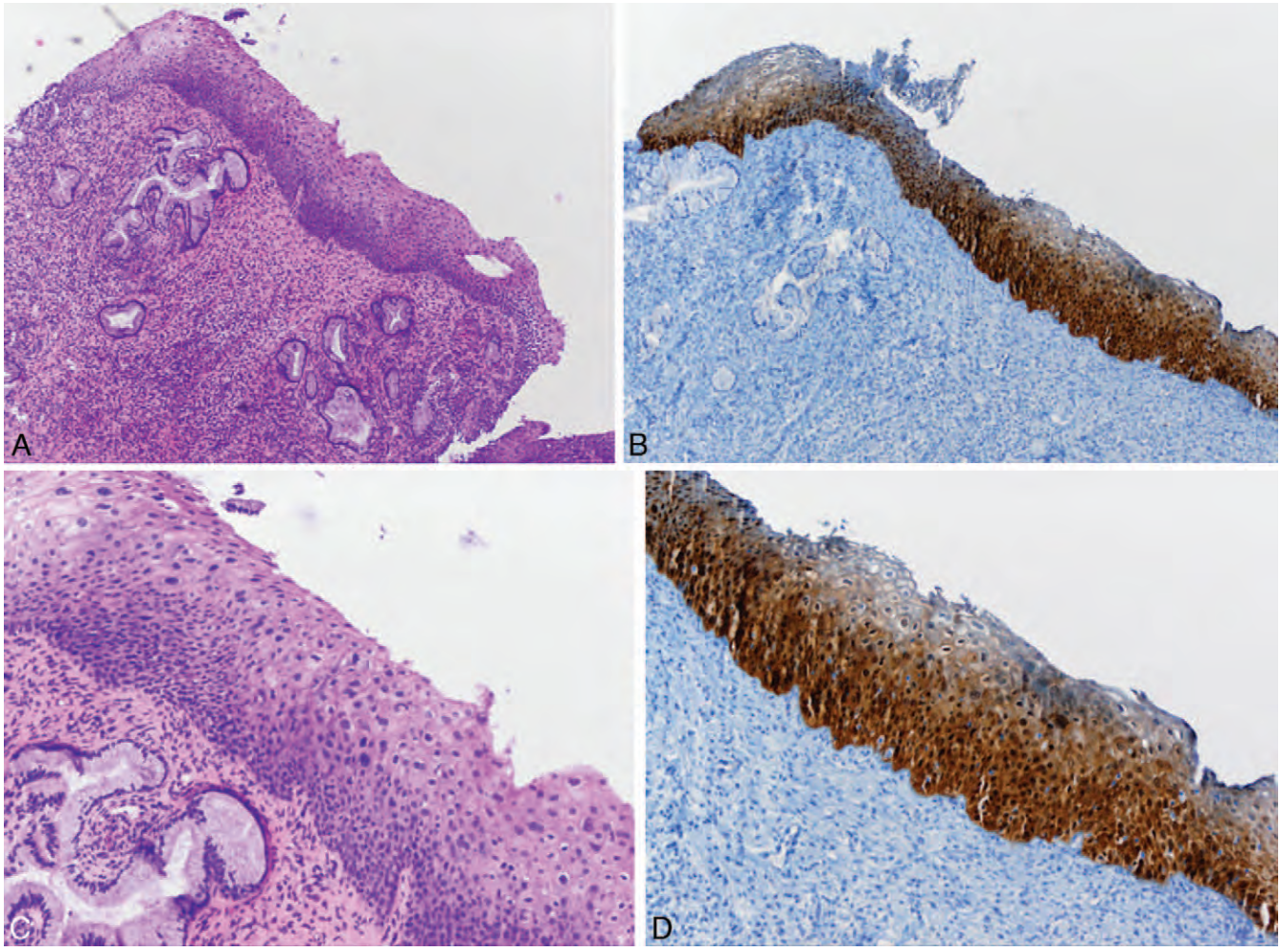

Figure 14. A cervical biopsy with SIL showing partial maturation; some might question the lesion grade (? CIN 2). A and C, H&E morphology at low and medium power with atypical parabasal-like cells extending into the middle third of the epithelium (C). B and D, Corresponding p16 IHC stains with diffuse strong staining meeting the definition of p16 strong diffuse block-positive described in the text. Therefore, this case is best interpreted as HSIL.

most likely correct but could be better supported by additional data.

Work group 4 was tasked with evaluating which, if any, biomarkers (broadly defined as any molecular or immunochemical assay) would be useful in better defining HPV-associated lesions of the LAT and would reduce interobserver variability in diagnosis. On the basis of this, recommendations were made regarding their optimal use. Key to WG4's recommendation decisions was the need to discourage and prevent inappropriate use or overuse of any biomarker(s).

After completion of the initial tier of literature review, WG4 evaluated data associated with the following biomarkers: p16, Ki-67 (Mib1), ProEx C, L1, HPV 16/18 mRNA, telomerase/TERC, and HPV genotyping.

On the basis of final literature review and data extractions, we concluded that only p16, a biomarker that is recognized in the context of HPV biology to reflect the activation of E6/E7–driven cell proliferation, had sufficient evidence on which to make recommendations regarding use in LAT squamous lesions. ProEx C and Ki-67 (Mib1) had similar trending data, but the literature was insufficient to make an independent recommendation for use, alone or in combination. Individual institutions might opt to use these other markers in cases with equivocal p16 IHC staining or as an adjunct, given that both have cleaner nuclear staining. However, the accumulated evidence was insufficient to make an independent recommendation for use of any additional biomarker, alone or in combination.

Although only a few studies that focused on body sites other than cervix were available, all showed results similar to cervix. Given the underlying similarities in HPV-associated biology in all LAT sites, we concluded that the recommendations below are applicable across all LAT sites. It should be noted, however, that these data and recommendations do not apply to non–HPV-associated precancerous lesions, such as simplex or differentiated VIN.

WG4 Recommendation No. 1

p16 IHC is *recommended* when the H&E morphologic differential diagnosis is between precancer (–IN 2 or –IN 3) and a mimic of precancer (e.g., processes known to be not related to neoplastic risk such as immature squamous metaplasia, atrophy, reparative epithelial changes, tangen-

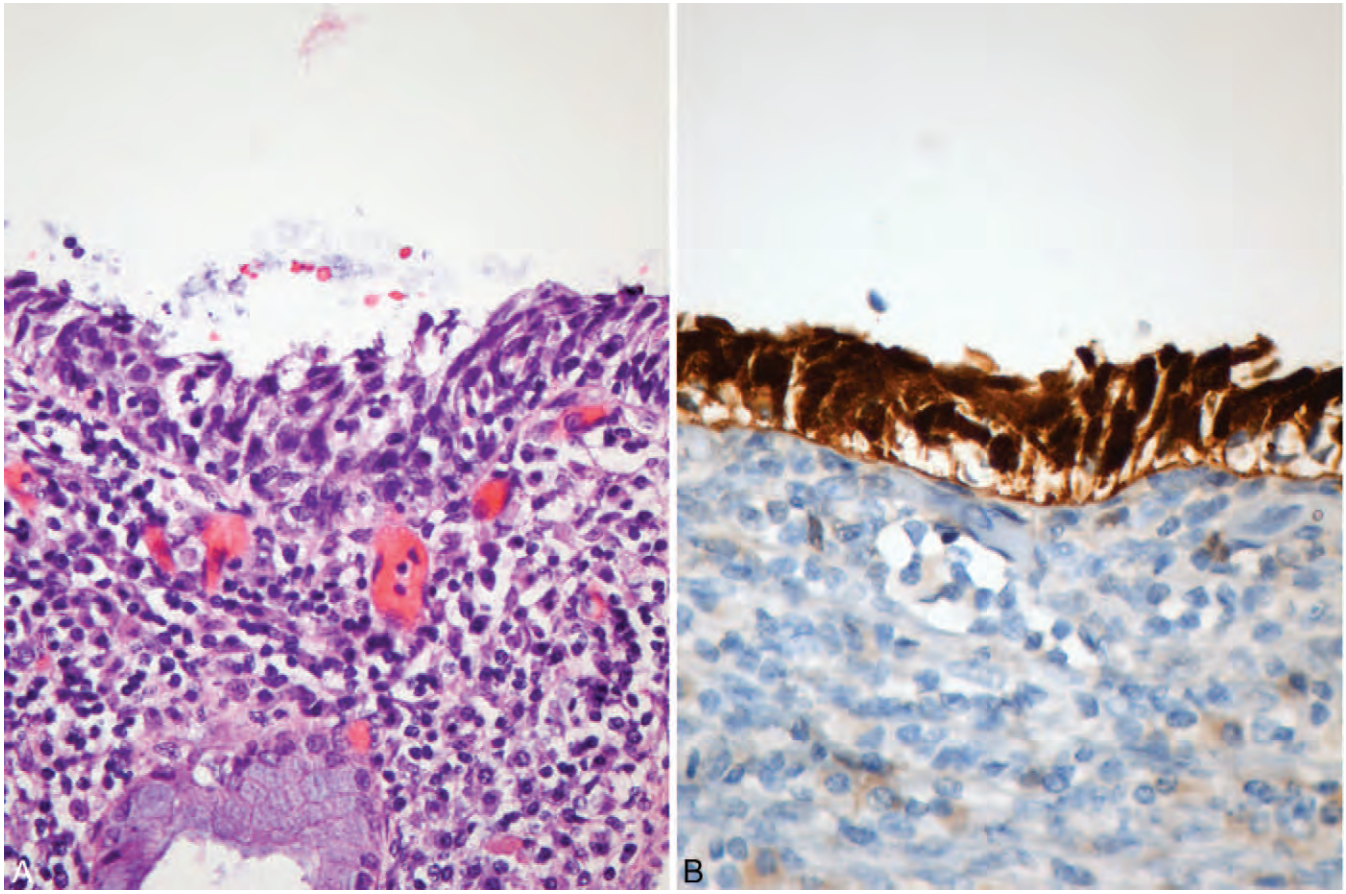

Figure 15. Some cases of HSIL, especially in the zone of immature metaplasia where the epithelium may be thin, can be diagnostically problematic. In this cervical biopsy (A), the differential diagnosis includes inflamed immature squamous metaplasia and HSIL. Strong diffuse block-positive p16 staining (B) strongly favors the interpretation of this biopsy as precancer (HSIL). A, High power, H&E. B, High power, p16.

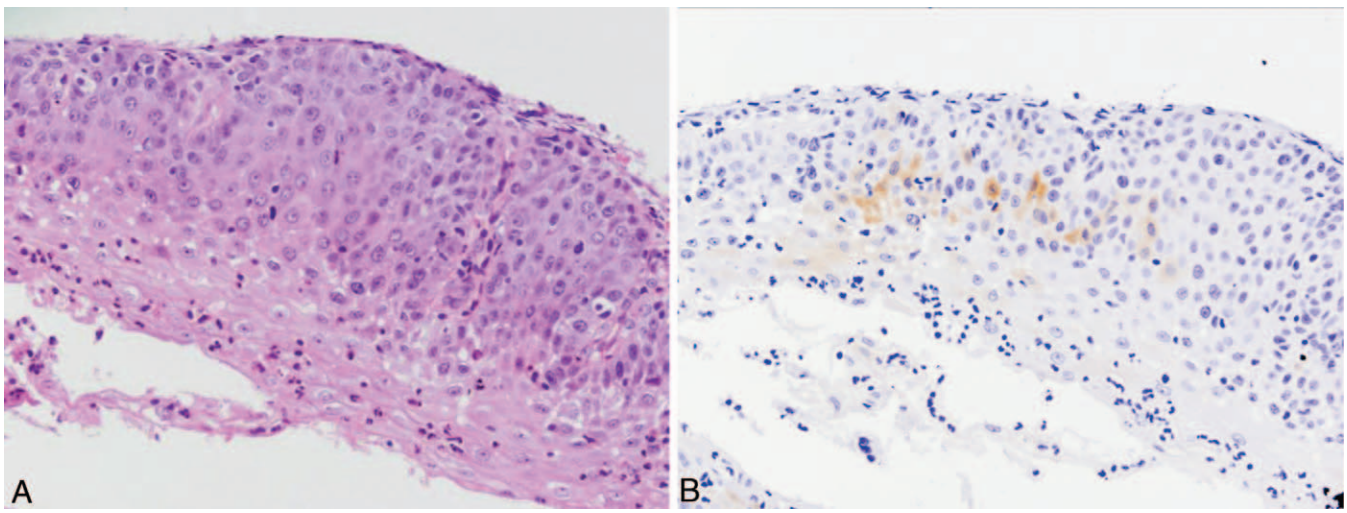

Figure 16. A, A cervical biopsy with a differential diagnosis on H&E of HSIL (CIN 2) versus reparative atypia owing to the relative lack of maturation and koilocytosis. B, The weak, patchy and irregular staining with p16 IHC (p16-negative) supports the interpretation of a reactive process rather than an HSIL. This pattern of blotchy or patchy p16 staining should be interpreted as negative (non–block-positive staining). A, Medium power, H&E. B, Medium power, p16.

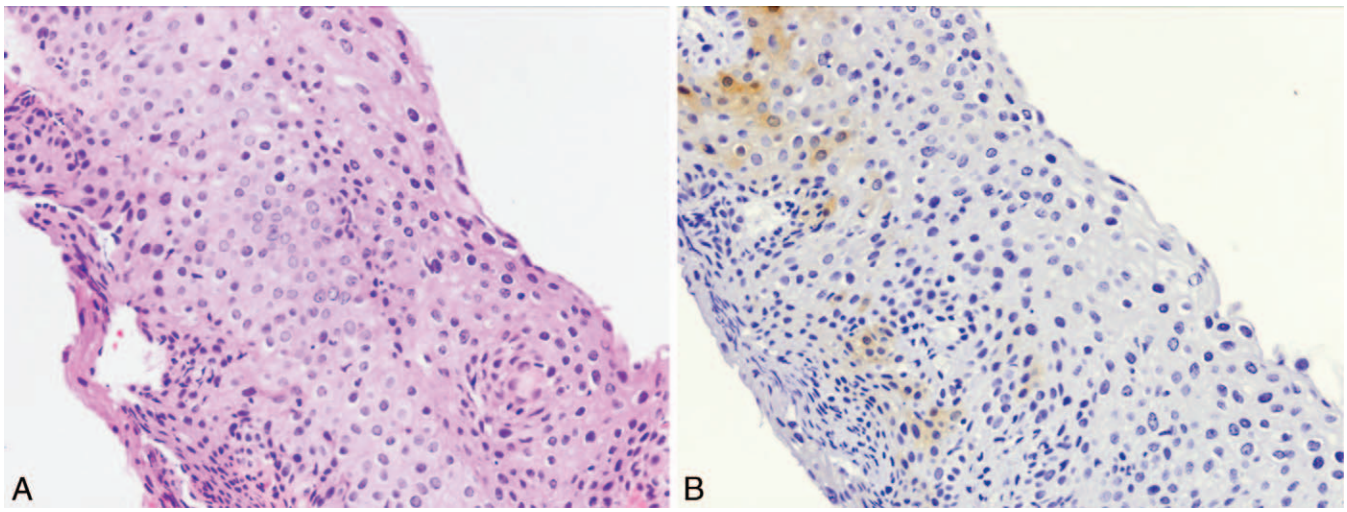

Figure 17. A, Cervical biopsy with unequivocal SIL that is tangentially cut, raising the differential diagnosis of LSIL versus HSIL. B, Immunohistochemical stain demonstrating weak, patchy p16 reactivity that starts above the basal layer, a pattern that should be interpreted as negative, which, in this case, supports the final combined interpretation as LSIL. A, High power, H&E. B, High power, p16.

tial cutting). Strong and diffuse block-positive p16 results support a categorization of precancerous disease.

Strong and diffuse block staining for p16 = p16-positive.—*In squamous epithelia, this is defined as continuous strong nuclear or nuclear plus cytoplasmic staining of the basal cell layer with extension upward involving at least one third of the epithelial thickness. The latter height restriction is somewhat arbitrary but adds specificity. Note that full-thickness staining or extension into the upper third or upper half is specifically not required to call a specimen positive (see Figures 14 and 15).*

Focal or patchy nuclear staining is nonspecific and can be seen with reactive squamous metaplasia, as well as low-grade disease (LSIL, –IN 1). All other staining patterns, described as cytoplasmic only, wispy, blob-like, puddled, scattered, single cells, and others, are defined as negative (see Figures 16–18).

Clearly, the concept of continuous block staining requires "adequate" tissue size and orientation and should correlate with the area of morphologic concern. Small fragments, tangential cuts, free-floating single cells, and others may lead to more subjective and variable interpretations, but in such cases, the minimum would be that all cells in question are strongly stained and morphologically are already under consideration in the differential diagnosis of a precancerous lesion (see Figure 19).

WG4 Recommendation No. 2

If the pathologist is entertaining an H&E morphologic interpretation of –IN 2 (under the old terminology), which is a biologically equivocal lesion falling between the morphologic changes of HPV infection (low-grade lesion) and precancer, p16 IHC is *recommended* to help clarify the diagnosis. Strong and diffuse block-positive p16 results support a categorization of precancer. Negative or non–block-positive staining strongly favors an interpretation of

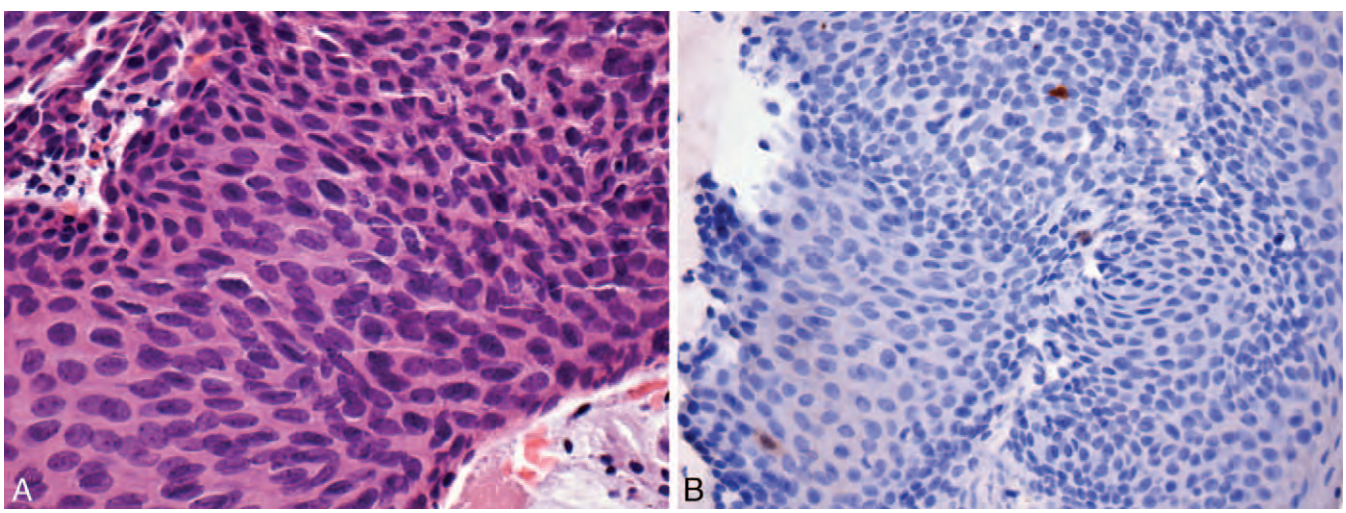

Figure 18. Some immature squamous metaplastic lesions can be hyperplastic rather than thin (A, contrast with Figure 15A). In this case, the cervical epithelium mimics bladder mucosa with somewhat elongate nuclei and some nuclear grooves (transitional metaplasia). Note the absence of mitotic figures and relative nuclear uniformity. B, The near total absence of p16 reactivity strongly supports the interpretation that this is a HSIL mimic rather than precancer. A, High power, H&E. B, High power, p16.

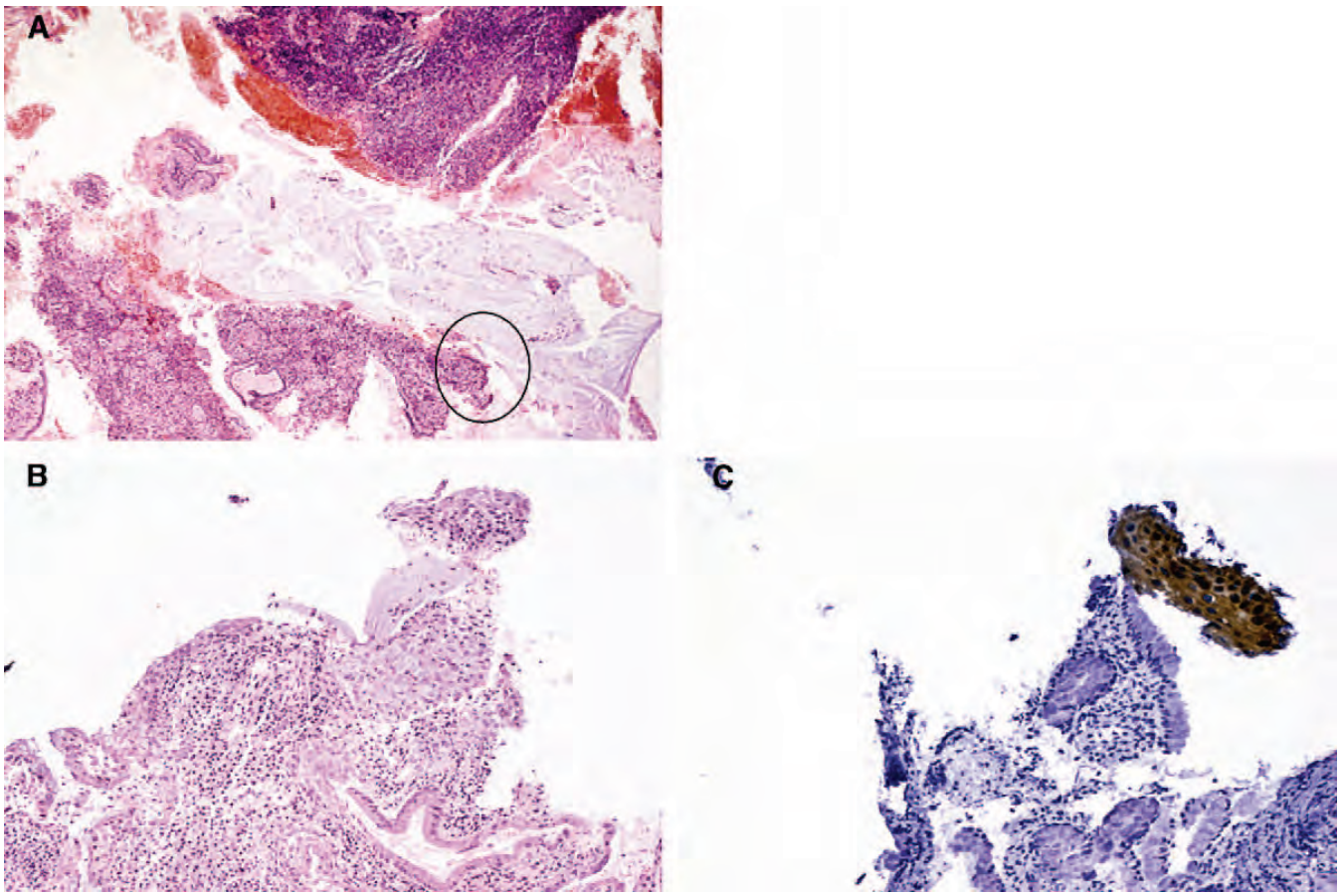

Figure 19. A, Low-power H&E of the colposcopic biopsy from a patient referred for an HSIL on her Pap test. The biopsy was initially read as negative, but because of the lack of correlation between the cytology and histology, a p16 stain was performed. The small fragment seen in C was reinterpreted as HSIL (B), based on strong diffuse block-positive p16 staining and abnormal underlying histologic appearance. The same small area is circled in A. A, Low power, H&E. B, High power, H&E. C, High power, p16.

low-grade disease or a non–HPV-associated pathology (see Figures 14 and 17).

Note: Unlike Recommendation No. 1, Recommendation No. 2 deals with a specimen that already has the morphology of SIL, not its benign mimics. p16 immunohistochemistry should be used to clarify a H&E diagnosis of –IN 2. If the pathologist's histologic diagnosis is unequivocal –IN 1, p16 immunohistochemistry is NOT recommended (see Recommendation No. 4). There is insufficient evidence to determine whether there is an actionable difference in patient management between p16-positive and p16-negative –IN 1. Hence, now, it is recommended that clinical management of –IN 1 be based on the H&E histologic diagnosis alone; p16 IHC is not indicated.

Note: p16 should not be used if the H&E morphologic differential diagnosis is between low-grade disease (–IN 1) and negative because –IN 1 can be p16-negative and p16 positivity is not a definition for –IN (of any level).

Rationale for Recommendation Nos. 1 and 2.—In the largest prospective, adjudicated study using p16, Galgano et al [163] showed that diffuse strong staining with p16 showed similar accuracy for high-grade disease when compared with an adjudicated histology result. Given that –IN 2 has been consistently proven to be a poorly reproducible diagnosis, p16 immunostaining improves the accuracy of single-pathologist interpretations of high-grade versus low-grade disease relative to adjudicated pathology panel interpretations, which are the best surrogate available for biologic accuracy. This is with the caveat that the pathologist is already entertaining an interpretation of –IN 2. Hence, adding a p16 result to the H&E morphologic assessment leads to a more accurate prediction of the risk of the patient for having a precancerous lesion. Additional studies have demonstrated a strong positive correlation between p16 block staining and precancerous disease [89, 164–168]. p16 immunostaining substantially reduces interobserver variability in the diagnosis of precancerous disease (see next paragraphs) [88–91, 163]. Studies also show that diffuse strong p16 staining is highly associated with a positive test result for HPV-16 (or other high-risk HPVs) [169–171].

WG4 Recommendation No. 3

p16 is *recommended* for use as an adjudication tool for cases in which there is a professional disagreement in histologic specimen interpretation, with the caveat that the differential diagnosis includes a precancerous lesion (–IN 2 or –IN 3).

Rationale for Recommendation No. 3.—A number of studies address the issue of interobserver variability in interpretation of LAT squamous lesions [88–91, 163]. These studies all show that there is substantial improvement in

correlation between observers when p16 immunostaining is used. Therefore, in association with Recommendation No. 1 above, the addition of p16 provides a more objective adjudication of the differential diagnosis than does H&E histologic assessment alone.

Quality of Evidence for WG4 Recommendation Nos. 1, 2, and 3.—Review of the 18 articles cited for Recommendations 1 to 3 found 2 studies directly comparing the performance of H&E alone versus H&E/p16 for cervical disease using consensus histology as the reference standard and 4 reporting test characteristics for H&E/p16–positive alone (see C2 for additional details, Supplemental Digital Content; http://links.lww.com/LGT/A6). For each of these studies, sensitivity, specificity, and 95% confidence intervals could be directly calculated from the data. In addition, 5 studies provided data on interobserver variability as measured by κ statistics, for H&E alone versus H&E/p16. The quality of the evidence for the test characteristics of H&E/p16, based on the studies identified through the review process, is moderate to high. Both of the direct comparisons showed statistically significant increases in sensitivity for a consensus diagnosis of CIN 2+ and increases in sensitivity for CIN 3+ (statistically significant in the study of Galgano et al [163], although not significant in that of Bergeron et al [90]). Specificity was decreased with the addition of p16; the absolute decrease was much larger in the study of Galgano et al than in that of Bergeron et al. In studies without a comparator, sensitivities were all 95% or higher at both thresholds. Factors contributing to the high quality of evidence included (1) consistency of results across multiple studies and settings, (2) precision of results, and (3) low risk of bias in the study designs. Factors decreasing the quality of evidence included (1) relative indirectness in terms of specific clinical outcomes—in particular, the association of CIN 2 lesions, even if based on consensus histology, with cancer; and (2) indirectness in terms of setting. The 2 studies involving direct comparisons were both performed in settings outside general US practice, either in Europe or in a single academic institution where institutional bias in terms of histologic thresholds may have lowered sensitivity and raised specificity for histology alone [90, 163].

The quality of the evidence for improved consistency of readings with p16 is high. All 5 studies measuring interobserver variability found significant or close-to-significant improvement in consistency of readings with the addition of p16 to H&E assessment alone. The clinical significance of this finding is supported by the data on sensitivity and specificity for individual pathologists presented in Galgano et al [163].

On the basis of the quality of the reviewed evidence, there is a high degree of certainty that use of p16 leads to improved sensitivity but decreased specificity compared with H&E alone, with substantially improved consistency between observers. This suggests that use of p16, in accordance with WG4 Recommendation Nos. 1 to 3, would result in improved clinical outcomes, but there is lack of direct evidence about the impact of implementing these recommendations in a general US population. This especially raises concern about the potential for overtreatment if the recommendations are not followed; this concern specifically led to the development of WG4 Recommendation No. 4.

WG4 Recommendation No. 4

WG4 *recommends against* the use of p16 IHC as a routine adjunct to histologic assessment of biopsy specimens with morphologic interpretations of negative, –IN 1 and –IN 3.

Rationale for Recommendation No. 4.—At the consensus conference, there was considerable concern about the potential for overuse of p16 IHC by pathologists as an assessment tool for cases of morphologic –IN 1. Overuse in unequivocal cases of –IN 1 might lead some pathologists to inappropriately overinterpret such cases as high-grade (–IN 2), leading to the potential for overtreatment. As noted above, the natural history of p16-positive –IN 1 is not well known, and although some evidence exists to support it as a higher risk category, the evidence is insufficient at this time to alter clinical management from that based on the histologic assessment alone [172–174]. In addition, the natural history of p16-negative –IN 3 is uncertain, and hence, the use of p16 to downgrade an unequivocal example of –IN 3 is not recommended. p16 IHC should not be performed when these morphologic diagnoses are unequivocal. In these circumstances, p16 IHC should only be used when the differential diagnosis contains mimics of high-grade lesions (see WG4 Recommendation No. 1), when –IN 2 is in the differential diagnosis with a low-grade lesion (see WG4 Recommendation No. 2), or when there is a difference of opinion to be resolved in these areas (see WG4 Recommendation No. 3).

WG4 Recommendation No. 4a

Special Circumstance.—p16 IHC is recommended as an adjunct to morphologic assessment for biopsy specimens interpreted as ≤–IN 1 that are at high risk for missed high-grade disease, which is defined as a prior cytologic interpretation of HSIL, ASC-H, ASC-US/HPV-16 +, or AGC (NOS).

Any identified p16-positive area must meet H&E morphologic criteria for a high-grade lesion to be reinterpreted as such.

Rationale for Recommendation 4a.—This recommendation addresses a special situation in which use of p16 IHC is recommended to maximize the sensitivity for detecting high-grade lesion foci that might have been missed on initial H&E examination of tissue biopsies in very specific high-risk situations (see Figure 19). Data using p16 IHC show that areas of small or equivocal high-grade disease have been identified on histologic specimens using p16 that were not initially recognized on H&E sections alone in a significant proportion of high-risk cases [175]. Specific high-risk situations are those in which the patient is at substantial risk for prevalent precancer (at least 30%), such as when preceding cervical cytology specimens have been interpreted as HSIL, ASC-H, ASC-US positive for HPV-16, or AGC [176–178]. In such circumstances, p16 block-positive areas identified are most likely to represent precancerous disease. However, p16-positive foci identified in such cases must, on review of H&E slides, also have morphologic features diagnostic of HSIL to make the diagnosis.

p16 IHC should NOT be used in circumstances other than those special high-risk situations as stipulated in this recommendation or other circumstances with equivalent or higher risk of precancer. In other lower-risk situations, the likelihood of false-positive results not indicative of high-grade disease is increased, which could lead to overtreatment. In the future, as the use of HPV genotyping becomes

Table 4. Estimated Percentage (%) of Total Cervical Biopsies for Which IHC Is Recommended [6, 10, 163, 178–180]		
LAST WG4 recommendation	Comment	Estimated % of biopsies for IHC
No. 1: HSIL vs mimics	CIN 3 accounts for <10% of biopsies and we estimate that approximately 10% of these may be problematic or have mimics	1
No. 2: Possible CIN 2	CIN 2 currently accounts for no more than 10% of biopsies	10
No. 3: Professional disagreement	An uncommon situation	1
No. 4: Cautions against use in LSIL (CIN 1)	LSIL (CIN 1) accounts for up to 40% of diagnoses for cervical biopsies. If an estimated 10% of those are problematic (i.e., the pathologist is considering LSIL versus HSIL [CIN 2]), the impact is low	4
No. 4a: High-risk colposcopic referral situations with H&E biopsies initially ≤LSIL	Most referrals for colposcopy are for Pap tests interpreted as LSIL or ASC-US and high-risk HPV-positive (not genotyped). Reported rates for these results are HSIL 1%, ASC-H 0.5%, AGC 0.5%, and ASC-US, HPV-16–positive at 1%	3
Total	Conservative estimate of overall utilization of IHC is <20% of all cervical biopsies	19

more common, additional high-risk situations, such as LSIL with HPV-16 positivity, may be considered as an additional high-risk category.

Quality of Evidence for WG4 Recommendation No. 4.—The quality of the evidence for superior sensitivity of H&E/p16 is high to moderate (see C2 for additional details, Supplemental Digital Content; http://links.lww.com/LGT/A6). In the clinical setting described above, where there is a higher pretest probability of precancer, the likelihood of a false-positive is reduced, and the importance of detecting true disease is increased. Therefore, the balance of benefit versus harm is toward the higher sensitivity but lower specificity of adding p16, and given the overall quality of the evidence, the use of "recommend" is warranted.

Additional Findings From WG4

On the basis of the evidence reviewed, we could make no recommendation for or against a 2-tiered or 3-tiered nomenclature system based on histologic evaluation alone. However, we noted that, although all the marker studies examined were neutral or supportive of a 2-tiered system/biology, no positive marker-based studies to support a distinct 3-tiered biology were identified. Because of the lack of evidence for a biologically defined intermediate category, p16, as noted above, is recommended to clarify any considered intermediate category (–IN 2) into either a low-grade or precancerous lesion (WG4 Recommendation No. 2). Therefore, use of p16 may effectively support the use of a 2-tiered classification system in this particular circumstance.

We concluded that there is insufficient evidence to prospectively determine high-grade versus low-grade disease based solely on a p16 result. In particular, the natural history of –IN 1 adjudicated by p16 is uncertain and critically needs further study. Hence, at present, no recommendation can be made for or against the use of p16 for this purpose. In addition, we concluded that there is insufficient evidence to prospectively make a determination of –IN 1 versus no –IN based solely on the use of p16. Strong and diffuse block-positive p16 staining, in the appropriate morphologic context, strongly supports a diagnosis of high-grade –IN. The majority (80%–90%) of –IN 2 and approximately 99% of –IN 3 cases are p16-positive. A positive p16 stain does not exclude CIN 1; at least 30% of adjudicated CIN 1 cases are p16-positive. At present, no recommendation could be made for or against the use of p16 for this purpose. Hence, p16 should not be used to initially assess biopsies that, on H&E alone, would otherwise be interpreted as morphologically negative or CIN 1.

We concluded that no recommendation could be made regarding any differences in –IN 1 management (based on the addition of a p16 stain) at this time. There are 3 studies that provide data regarding this question [172–174]. In these studies, the presence of strong and diffuse block-positive p16 immunostaining in CIN 1 was associated with increased "progression" or precancer outcomes on follow-up. Conversely, those cases testing negative for p16 were far more likely to "regress." However, this association was not absolute because there were cases having precancer outcomes that were p16-negative. Therefore, at this time, although p16-positive –IN 1 lesions may represent a subgroup of cases that are at higher risk of progression, no management recommendation can be made based solely on a p16 result.

We concluded that no recommendation could be made regarding any management differences in morphologically determined high-grade dysplasia (–IN 3) based solely on the addition of a p16 result. However, it was noted that most adjudicated CIN 3 lesions are p16-positive (>99%), which strongly argues against its utility in this diagnostic category [163].

We also concluded that the evidence does not support any combination of markers to substantially improve performance when compared with the use of p16 alone. A number of studies addressed the use of p16 in combination with Ki-67. The overall improvement of performance (sensitivity and specificity) was minimal when compared with the p16 result alone [163]. Hence, the routine addition of Ki-67 to p16 IHC is not recommended. Other studies detail the use of ProEx C, which performs in a similar manner to p16; however, currently, there is insufficient evidence to make an independent recommendation for use. In cases for which p16 IHC is inconclusive or technically inadequate, use of Ki-67 and/or ProEx C IHC may be considered.

Considerations on Practice Impact—Cervical Biopsies

The most common concern expressed during the open comment period and at the consensus conference was the

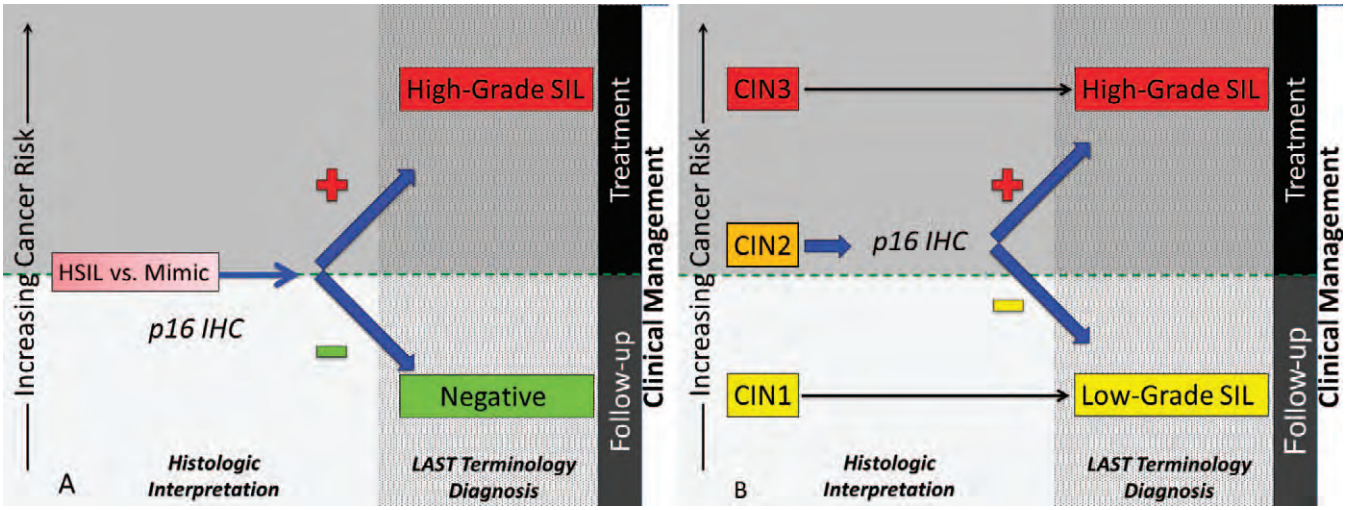

Figure 20. Pathologic diagnoses using p16 and potential clinical management options for cervical biopsies. A, Use of p16 to evaluate the differential diagnosis of HSIL versus a mimic, such as immature squamous metaplasia and atrophy. B, Use of p16 to evaluate morphologic CIN 2. The choice of clinical management for HSIL depends on the entire clinical scenario including patient's age, colposcopic findings, and biopsy diagnosis. Management options include excisional therapy (cold knife conization, LEEP), ablative therapy (cryotherapy, laser vaporization), and close observation, as during pregnancy. Modified with permission. Courtesy of Philip E. Castle.

impact of biomarker use, especially overutilization leading to potential overtreatment. As noted above, the recommended use of the biomarker p16 will result in both downgrading and upgrading of H&E diagnoses. The estimated magnitude of p16 IHC utilization when used according to WG4 recommendations is for fewer than 25% of all cervical biopsy specimens, and in these specimens, it will improve sensitivity and consistency of diagnoses (see Table 4). The statistics used to generate these estimates were based on published data from large surveys, population-based studies, and clinical trials and the conservative data available from several very large clinical studies [6, 10, 163, 178–180].

IMPLICATIONS AND IMPLEMENTATION OF STANDARDIZED TERMINOLOGY—WG5

The overall scope and purpose of WG5 was to address the potential implications of the LAST Project recommendations and to develop and initiate action plans for implementation of the recommendations.

Effective communication is absolutely necessary for widespread acceptance and adoption to occur. As with the Bethesda System terminology for gynecologic cytology, widespread communication of the benefits of changing and unifying terminology was necessary before adoption occurred. Likewise, we identified communities of interest for the LAST Project recommendations to include patients and patient advocacy groups; pathologists; treating physicians including gynecologists, primary care providers, dermatologists, gynecologic oncologists, infectious disease specialists, colorectal surgeons, urologists, and others; and nurse practitioners and other allied health professionals; government, regulatory, and nomenclature agencies including CMS, Joint Commission, AJCC, FIGO, SGO, World Health Organization, and others; public health, research, and surveillance organizations such as the Centers for Disease Control and Prevention, Surveillance Epidemiology and End Results (SEER), and tumor registries; educational, training, and testing organizations including specialty societies, training facilities, examination boards, publications and scientific literature; and payers and *Current Procedural Terminology* and *International Classification of Disease* coding organizations.

To communicate to these communities of interest, we recommended sustained organizational support to aid in the dissemination of the LAST recommendations. Specific actions include support for guideline publication; promote editorial commentaries for journals in related fields; present summary recommendations at scientific meetings; produce educational materials for professionals and patients; and develop a Web site that will include reference images, sample reports, and a self-test.

One of the major concerns raised by the clinical community regards management of cervical lesions in young women. The ASCCP will address specific issues related to its clinical management guidelines in the near future. A potential reconciliation of the LAST terminology and the 3-tiered CIN system with current clinical management is represented in Figure 20.

Many of these recommendations have already been initiated and will continue to be developed further. It is also imperative to have liaison with professional organizations to assess current practice regarding use of LAST terminology for squamous HPV-associated lesions and associated biomarker usage and to monitor adoption of the LAST recommendations.

CONCLUSIONS

The LAST Project was conceived to align terminology for HPV-associated squamous lesions of the LAT with current knowledge to improve communication between pathologists making diagnoses and clinicians using these diagnoses to optimally manage patients. In doing so, the project found ample justification to recommend a unified terminology across all LAT sites. For intraepithelial lesions, a 2-tiered terminology (LSIL and HSIL) reflects the biology of transient, productive HPV infections and persistent precancerous lesions. For superficially invasive squamous carcinomas of these sites, a uniform terminology and criteria for diagnosis brings order to similar entities. As a corollary to

the process, the use of biomarkers was addressed, to aid in the accurate and reproducible classification of intraepithelial lesions and strong recommendations for appropriate use were made. The LAST Project recommendations were made after a rigorous process that included comprehensive literature reviews with grading of evidence where appropriate, formulation of the recommendations by experts in the field, solicitation of public comment, and a final consensus conference with recommendation ballot that included representatives from professional societies, government agencies, and interested observers. The LAST Project recommendations reflect the participants' consensus judgment for best evidence-based pathology practice and nomenclature for HPV-associated squamous lesions of the LAT.

The work is not yet done. Integrating the LAST recommendations into the standard practice of pathologists and clinicians is an ongoing task. Plans to implement educational programs detailing the recommendations and their appropriate incorporation into practice are underway. Assessments of both the uptake and effects of the recommendations are being planned. All the members of the LAST Project anticipate the results of this implementation and its beneficial effects on providing optimal patient care.

CAP-ASCCP CONSENSUS STATEMENT

The CAP developed the Pathology and Laboratory Quality Center as a forum to create and maintain evidence-based practice guidelines and consensus statements. Practice guidelines and consensus statements reflect the best available evidence and expert consensus supported in practice. They are intended to assist physicians and patients in clinical decision making and to identify questions and settings for further research. With the rapid flow of scientific information, new evidence may emerge between the time a practice guideline or consensus statement is developed and when it is published or read. Guidelines and statements are not continually updated and may not reflect the most recent evidence. Guidelines and statements address only the topics specifically identified therein and are not applicable to other interventions, diseases, or stages of diseases. Furthermore, guidelines and statements cannot account for individual variation among patients and cannot be considered inclusive of all proper methods of care or exclusive of other treatments. It is the responsibility of the treating physician or other health care provider, relying on independent experience and knowledge, to determine the best course of treatment for the patient. Accordingly, adherence to any practice guideline or consensus statement is voluntary, with the ultimate determination regarding its application to be made by the physician in light of each patient's individual circumstances and preferences. CAP and ASCCP assume no responsibility for any injury or damage to persons or property arising out of or related to any use of this statement or for any errors or omissions.

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Erratum

A word was omitted from an article that appeared in the October 2012 issue of the *Archives* (Darragh TM, Colgan TJ, Cox JT, Heller DS, Henry MR, Luff RD, et al, for members of the LAST Project Work Groups. The lower anogenital squamous terminology standardization project for HPV-associated lesions: background and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. *Arch Pathol Lab Med*. 2012;136(10):1266-1297). On page 1291 of the article, a sentence appears that currently states, "A positive p16 stain does exclude CIN 1; at least 30% of adjudicated CIN 1 cases are p16-positive." This sentence should have read as, "A positive p16 stain does not exclude CIN 1; at least 30% of adjudicated CIN 1 cases are p-16 positive."

Novi izzivi v presejanju za raka materničnega vratu: izhodišča za presojo prenove presejalne politike DP ZORA

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Povzetek

Podobno kot v drugih državah z organiziranimi presejalnimi programi za zgodnje odkrivanje predrakavih sprememb materničnega vratu tudi v Sloveniji načrtujemo presojo obstoječe presejalne politike Državnega presejalnega programa ZORA. Spoznanje, da je dolgotrajna okužba z nevarnejšimi HPV nujen, vendar ne zadosten dejavnik za nastanek raka materničnega vratu, je spodbudilo razvoj s HPV-povezanih tehnologij, ki omogočajo tako boljšo zaščito pred okužbo s HPV (cepljenje proti HPV) kot tudi boljšo prepoznavo žensk s povečanim tveganjem za predrakave spremembe materničnega vratu visoke stopnje (testi HPV). Namen presoje je zagotoviti, da bo slovenski presejalni program ostal v koraku s sodobnimi znanstvenimi spoznanji in slovenskim ženskam še naprej zagotavljal najboljšo možno obravnavo. Cilja presoje sta odločiti se, ali bomo presejalno politiko spremenili ali ne, in če da, izbrati presejalno politiko, ki bo ženskam prinašala največ koristi, ki bo prilagojena na posebnosti slovenskega zdravstvenega varstva in obstoječega presejalnega programa ter bo finančno vzdržna. V nadaljevanju so opisani vzroki in izhodišča za presojo, med katerimi so zagotovo najpomembnejša dopolnjena Evropska priporočila za zagotavljanje kakovosti v presejanju za raka materničnega vratu iz leta 2015.

Ključne besede: presejanje za raka materničnega vratu, test PAP, test HPV, evropske smernice, presejalna politika, DP ZORA

Uvod

Spoznanje, da je dolgotrajna okužba z nevarnejšimi človeškimi papilomavirusi (angl. *human papillomaviruses*, HPV) nujen, vendar ne zadosten dejavnik za nastanek raka materničnega vratu (RMV), je relativno novo in dovolj revolucionarno, da je bila leta 2008 zanj podeljena Nobelova nagrada. To spoznanje je spodbudilo razvoj s HPV-povezanih tehnologij, ki omogočajo tako boljšo zaščito pred okužbo s HPV (cepljenje proti HPV) kot boljšo prepoznavo žensk s povečanim tveganjem za predrakave spremembe materničnega vratu visoke stopnje (testi HPV). V Sloveniji je bilo cepljenje proti HPV leta 2009 umeščeno v nacionalni program cepljenja, leta 2011 pa smo v državnem presejalnem programu (DP) ZORA začeli uporabljati test HPV za triažo žensk s spremembami materničnega vratu nizke stopnje in kasneje še za spremljanje žensk po zdravljenju predrakavih sprememb. Z namenom, da bo slovenski presejalni program sledil sodobnim spoznanjem ter slovenskim ženskam zagotavljal najboljšo možno zaščito, smo si na sedežu DP ZORA na Onkološkem inštitutu Ljubljana za cilj zadali preveriti, ali bi sprememba presejalne politike, v skladu z novimi spoznanji in priporočili, vodila v še boljše obvladovanje bremena predrakavih in rakavih sprememb materničnega vratu v Sloveniji. Presoja presejalne politike mora biti skrbno premišljena, saj vsak poseg v že učinkovito presejalno politiko, poleg priložnosti za izboljšavo, pomeni tudi nevarnost, da bi se učinkovitost zaradi različnih, včasih težko predvidljivih vzrokov, zmanjšala. To je v Sloveniji še posebej pomembno, saj se je po vzpostavitvi obstoječega presejalnega programa ZORA incidenca RMV prepolovila, zaradi česar se v zadnjih letih po ocenah mednarodne podatkovne zbirke GLOBOCAN umeščamo med evropske države z manjšo incidenco RMV (1). V prispevku so pomembne informacije o cepljenju proti HPV in o testih HPV, povzeta so strokovna izhodišča za morebitno spremembo presejalne politike, ki temeljijo na priporočilih dopolnjenih Evropskih smernic za zagotavljanje kakovost v presejanju za RMV iz leta 2015 (2), na koncu pa so navedene nekatere slovenske posebnosti, ki jih moramo poznati in upoštevati pri presoji glede morebitne spremembe presejalne politike DP ZORA.

Cepljenje proti HPV

Cepivo proti HPV je zelo učinkovito in varno cepivo, ki spodbudi tvorbo genotipsko specifičnih protiteles, kar pomeni, da je cepljena oseba zaščitena predvsem proti okužbam s tistimi genotipi, ki jih pokriva cepivo. V letu 2017 so v svetu in Sloveniji registrirana tri cepiva proti okužbi s HPV:

- 2-valentno cepivo vsebuje virusom podobne delce HPV 16 in 18,
- 4-valentno cepivo vsebuje virusom podobne delce HPV 6, 11, 16 in 18,
- 9-valentno cepivo vsebuje virusom podobne delce enakih genotipov kot 4-valentno cepivo in še petih dodatnih HPV 31, 33, 45, 52 in 58.

Cepljenje deklic proti HPV lahko prepreči nove okužbe, ne zdravi pa že obstoječih. Ker je okužba s HPV izjemno pogosta in se večina spolno aktivnih žensk in moških prvič okuži že v prvem letu spolnega življenja, je najbolj učinkovito cepljenje pred začetkom spolne aktivnosti. Pričakujemo, da bodo deklice, cepljene po nacionalnem programu, v primerjavi z necepljenimi, imele za okoli (3, 4):

- 70–90 % manj raka materničnega vratu,
- 50–85 % manj predrakavih sprememb materničnega vratu visoke stopnje, tako ploščatoceličnih kot žleznih,
- 50 % manj predrakavih sprememb materničnega vratu nizke stopnje, PIL-NS,
- 40 % manj raka zunanjega spolovila,
- 70 % manj raka nožnice,
- 90 % manj raka zadnjika,
- 20 % manj raka ustnega dela žrela vključno z bazo jezika in tonzilami,
- pri cepljenih s 4- in 9-valentnim cepivom, ki preprečujeta okužbo z manj nevarnima HPV 6 in 11, pa bo manj tudi anogenitalnih bradavic (do 90 %) in ponavljajoče se respiratorne papilomatoze (papilomi grla).

Programi cepljenja proti okužbam s HPV že dajejo prve javnozdravstvene rezultate. V državah z visoko precepljenostjo se zmanjšuje prevalenca okužb s HPV ter tudi že incidenca predrakavih sprememb materničnega vratu in anogenitalnih bradavic. Za zmanjšanje incidence s HPV-povezanih rakov bomo morali počakati več let, da bodo prve cepljene generacije deklic dosegle starost, v kateri bi začele zbolevati. V Avstraliji, ki je cepljenje proti HPV uvedla med prvimi in dosegla okoli 60–80 % precepljenost deklet pri vsaj 20 generacijah, se je incidenca predrakavih sprememb materničnega vratu pri mladih dekletih prepolovila, anogenitalne bradavice pa se skoraj ne pojavljajo več (4). Avstralci so prvi dokazali tudi, da cepljenje proti HPV omogoča kolektivno imunost. Ko so dosegli visoko precepljenost deklet, se je pomembno zmanjšala pojavnost genitalnih bradavic tudi pri necepljenih moških ter pri necepljenih dekletih/ženskah.

Slovenski nacionalni program cepljenja proti HPV poteka od leta 2009. Vanj so vključene deklice v 6. razredu osnovne šole in šolajoče se zamudnice, ki se niso cepile po programu. Cepljenje je brezplačno, ni pa obvezno. Pred cepljenjem morajo starši podpisati izjavo, v kateri se opredelijo za ali proti temu, da bo njihov otrok cepljen. Z razvojem cepiv in novimi spoznanji se prilagajajo tudi priporočila za cepljenje, ki gredo v smer uporabe več-valentnih cepiv in manjšega števila odmerkov. Program cepljenja vsako leto na spletni strani objavi Nacionalni inštitut za javno zdravje. Cepljenje je dostopno tudi starejšim ženskam in dečkom, vendar za njih ni brezplačno. V razvitem svetu in tudi v Sloveniji se vse bolj pogosto srečujemo s paradoksom, da ljudje opuščajo dokazano učinkovite javnozdravstvene ukrepe. Predvsem je v ospredju opuščanje cepljenja, ki se med drugim kaže tudi v premajhni precepljenosti slovenskih deklic proti okužbi s HPV. Podatki Nacionalnega inštituta za javno zdravje kažejo, da je po nacionalnem programu cepljenih manj kot polovica vseh deklic, precepljenost pa se je od uvedbe cepljenja do šolskega leta 2014/2015 zmanjšala za vsaj 10-odstotnih točk. Zdi se, da smo v Sloveniji pri določenih boleznih z učinkovitimi preventivnimi ukrepi breme bolezni tako zmanjšali, da je postalo še tako majhno tveganje, ki ga ukrep predstavlja, nesprejemljivo. Nasprotniki cepljenja zelo prepričljivo, vztrajno in entuziastično preko svetovnega spleta in drugih komunikacijskih kanalov širijo napačne informacije glede (ne)varnosti in (ne)učinkovitosti cepiv in cepljenja, kar vodi v škodljivo opuščanje cepljenja. Zato je treba z ustrezno komunikacijsko strategijo opolnomočiti tiste, ki so jim programi namenjeni, in s tem doseči njihovo čim večjo udeležbo v teh programih. Pri tem je izredno pomembna vloga ginekologa, še posebej je za ženske pomembno njegovo mnenje in priporočilo glede cepljenja proti HPV. Na podlagi kratkega pogovora med obiskom v ambulanti se lahko mati odloči, da bo svojega otroka cepila ali pa ne. Dolžnost ginekologa je, da je ustrezno informiran o z dokazi podprtih priporočilih glede cepljenja in da tista cepljenja, za katere ima stroka dokaze o učinkovitosti in varnosti, suvereno priporoča.

V DP ZORA bodo v naslednjih letih začela vstopati dekleta, cepljena proti HPV v okviru nacionalnega programa cepljenja. Ta dekleta bodo imela pomembno manjšo verjetnost, da bodo zbolela za predrakavo spremembo materničnega vratu visoke stopnje ali RMV kot necepljene vrstnice. Čeprav bodo cepljena dekleta imela manjše tveganje, pa bodo še vedno zbolevala – predvsem zaradi okužb z nevarnejšimi HPV, ki jih cepiva ne pokrivajo. Zaradi povezave med naravnim potekom bolezni in genotipom HPV, ki bolezen povzroča, pričakujemo, da bodo predrakave spremembe pri cepljenih dekletih v primerjavi z necepljenimi imele večjo verjetnost za nazadovanje ter manjšo verjetnost za napredovanje v RMV, zaradi česar se lahko ob neustrezni presejalni politiki posebno pri mladih ženskah poveča odkrivanje in zdravljenje klinično

nepomembnih predrakavih sprememb (tudi visoke stopnje) in s tem povezani neželeni učinki zdravljenja, kot je na primer povečano tveganje za prezgodnji porod. Vse to bo spremenilo razmerje med koristmi in škodo, ki jo lahko povzročimo s presejanjem. Pričakujemo, da bo pri cepljenih dekletih bolj učinkovito presejanje s testom HPV z daljšimi presejalnimi intervali in če bodo dekleta ob začetku presejanja starejša.

Testi HPV

Klinično preverjeni testi HPV so v primerjavi s testom PAP bolj občutljivi za predrakave spremembe visoke stopnje in imajo večjo negativno napovedno vrednost. Presejanje s testom HPV omogoča 60–70 % večjo zaščito pred RMV kot presejanje s testom PAP, pri čemer se presejalni interval lahko varno podaljša na 5 let ali tudi več (5). Dopolnjene Evropske smernice iz leta 2015 zato državam z dobro organiziranimi presejalnimi programi priporočajo razmislek o spremembi presejalne politike, in sicer zamenjavi presejanja s testom PAP za presejanje s testom HPV, vendar le ob upoštevanju priporočil za uporabo testa HPV (2). Kljub nedvomnim prednostim testa HPV lahko namreč nekritična uporaba tega testa povzroči več škode kot koristi. Testiranje mladih žensk z visoko prevalenco klinično nepomembnih, prehodnih okužb prepogosto testiranje ali testiranje s klinično nepreverjenimi testi HPV lahko vodi v prekomerno odkrivanje in posledično zdravljenje predrakavih sprememb, ki bi sicer spontano nazadovale in ženskam nikoli ne bi povzročale težav. To je za ženske lahko škodljivo, saj se po zdravljenju predrakavih sprememb materničnega vratu lahko pojavijo neželeni učinki, med katere sodi tudi povečano tveganje za prezgodnji porod. Ko ženska izve, da je okužena z nevarnejšimi HPV, je pogosto v stiski – skrbi jo za lastno in partnerjevo zdravje, porajajo se vprašanja o partnerjevi zvestobi, spremenjeno je lahko njeno spolno življenje. Če okužba ne povzroča sprememb, ki potrebujejo zdravljenje, je čakanje na izid (ali bo okužba izzvenela ali ne) lahko mučno in dolgotrajno. Za že tako obremenjene ginekološke ambulante to pomeni še dodatne, nepotrebne obremenitve, za državo pa nepotrebne stroške. Dodatne informacije o testu HPV in uporabi tega testa v presejalnih programih so predstavljene v drugem prispevku v tem zborniku z naslovom Presejanje s testom HPV: kateri testi izpolnjujejo merila za uporabo v presejalnih programih (Poljak in Oštrbenk) in tudi v zborniku 6. izobraževalnega dne programa ZORA v prispevku z naslovom HPV v Sloveniji: rezultati slovenskih raziskav (2012–2015) in uporaba s HPV-povezane tehnologije (6).

Strokovna izhodišča za presojo prenove presejalne politike

Presejalne politike se med državami razlikujejo, najpogosteje zaradi prilagajanja znanstvenih in strokovnih izhodišč nacionalnim posebnostim; pogosto se razlikujejo tudi priporočila ameriških in evropskih strokovnih združenj. V Sloveniji sledimo priporočilom Evropskih smernic za zagotavljanje kakovosti v presejanju za RMV 2008, ki jih je izdala Mednarodna agencija za raziskovanje raka (angl. *International Agency for Reserach on Cancer*, IARC) pri Svetovni zdravstveni organizaciji (7). Smernice so bile leta 2015 dopolnjene s tremi poglavji (2):

- Presejanje s testom HPV,
- Organizacija presejanja s testom PAP in testom HPV,
- Implementacija cepljenja proti HPV.

Dopolnjene smernice vsebujejo 62 novih priporočil, ki jih je smiselno proučiti in implementirati ob upoštevanju osnovnih strokovnih izhodišč za presejalne programe, ki so navedena že v Evropskih smernicah iz leta 2008 in Priporočilu Sveta Evropske Zveze iz leta 2003 ter se nanašajo tako na organizacijo, načrtovanje sprememb, spremljanje in ocenjevanje presejalnega programa kot na komunikacijo ter zagotavljanje in nadzor kakovosti na vseh ravneh programa, od presejanja, do nadaljnje obravnave žensk vključno s kakovostjo citologije, molekularne diagnostike, kolposkopije in histologije (7, 8).

Državam z učinkovitimi populacijskimi, organiziranimi presejalnimi programi prenovljene Evropske smernice priporočajo, da proučijo obstoječo presejalno politiko in razmislijo, ali bi uvedba presejanja s testom HPV izboljšala razmerje med koristmi in škodo, ki jo povzroča presejanje. Pri tem je ključno, da ima koordinator programa na voljo kadrovske, finančne in tehnološke vire ter dovolj avtonomnosti, da lahko zagotovi izpolnjevanje priporočil smernic. Smernice namreč še posebej poudarjajo, da se presejanje s testom HPV priporoča le v dobro organiziranih presejalnih programih z dobrim sistemom za spremljanje in nadzor kakovosti dela in učinkovitosti programa, saj je tveganje za neželene stranske učinke in visoke stroške ob neustrezni uporabi presejalnega testa ali pri neustreznih nadaljnjih postopkih pri presejanju s testom HPV večje kot pri presejanju s testom PAP (2). Pred uvedbo presejanja s testom HPV je treba temeljito proučiti pričakovane zdravstvene koristi spremenjene presejalne politike v primerjavi s stroški pa tudi, ali je program sposoben zagotoviti pravilno uporabo testa HPV v skladu z navodili proizvajalca in priporočili strokovnih smernic. Povzetek priporočil povezanih s presejanjem, ki so navedena v dopolnjenih Evropskih smernic iz leta 2015:

Presejalni test:

- Presejanje s testom HPV se lahko uporablja samo v organiziranih presejalnih programih, ki upoštevajo priporočila dopolnjenih Evropskih smernic. Presejanje s testom HPV se odsvetuje, če je presejanje priložnostno, oportunistično.
- Presejanje z dvema testoma (test HPV in test PAP) hkrati nima dodane vrednosti. Ne glede na starost ženske in presejalni test se na enem presejalnem pregledu vedno priporoča uporaba samo enega presejalnega testa.
- Pri ženskah, za katere presejanje s testom HPV ni priporočeno (ženske mlajše od 30–35 let), se še naprej priporoča presejanje s testom PAP, ob upoštevanju priporočil Evropskih smernic iz leta 2008.
- Če ženska zavrača presejanje s testom HPV, se ji lahko omogoči presejanje s testom PAP.
- Če je rezultat presejalnega testa HPV nezadosten (ni mogoče izdati pozitivnega ali negativnega izvida), se lahko žensko povabi na ponoven pregled in odvzem vzorca za test HPV ali pa se opravi test PAP na istem tekočinskem vzorcu brez dodatnega pregleda.
- Za presejanje se sme uporabiti samo klinično preverjene teste HPV z dobro ponovljivimi rezultati, veliko občutljivostjo za CIN2+ in CIN3+ in čim manjšim odkrivanjem klinično nepomembnih, prehodnih okužb.

Starost žensk:

- Presejanje s testom HPV se lahko začne po 35. letu in ne pred 30. letom. Za starostno skupino 30–34 let dokazi niso enotni, zato ni priporočila.
- Dokazi glede zgornje starostne meje, pri kateri se presejanje lahko zaključi, so pomanjkljivi. Zaenkrat so priporočila enaka kot pri presejanju s testom PAP: presejanje se lahko zaključi med 60–65 letom, če ima ženska pred tem negativen izvid presejalnega testa.

Presejalni interval:

- Presejalni interval po negativnem testu HPV naj bo vsaj 5-letni. Lahko se tudi podaljša na do 10 let, ob upoštevanju starosti ženske in njene presejalne zgodovine.

Smernice za obravnavo žensk s pozitivnim presejalnim izvidom testa HPV:

- Presejalni program, ki uporablja presejanje s testom HPV, mora sprejeti tudi priporočila glede nadaljnje obravnave žensk s pozitivnim izvidom presejalnega testa HPV, vključno z navodilom, kdaj se lahko ženska po pozitivnem presejalnem testu HPV vrne nazaj v presejanje.
- Program mora smernice redno revidirati glede na rezultate spremljanja žensk s pozitivnim izvidom presejalnega testa HPV in glede na nove dokaze.
- Protokoli za zagotavljanje in nadzor kakovosti v vseh laboratorijih in kolposkopskih ambulantah, ki sodelujejo presejalnem programu, morajo ustrezati priporočilom smernic.
- Pri ženskah s pozitivnim presejalnim testom HPV se priporoča takojšnja triaža s testom PAP; brez zamude, najbolje iz istega tekočinskega vzorca (refleksna triaža). Napotitev na kolposkopijo brez predhodne triaže ni priporočena.
- Ženske s triažnim izvidom testa PAP visoke stopnje morajo biti napotene na kolposkopijo brez dodatnih pregledov ali testov. Ženske s triažnim izvidom testa PAP nizke stopnje so lahko napotene na predčasno ponovno testiranje ali na kolposkopijo. Ženske z negativnim triažnim izvidom testa PAP morajo biti napotene na predčasno ponovno testiranje, pri njih se kolposkopije ne priporoča.
- Priporočila za predčasno ponovno testiranje mora presejalni program redno posodabljati. Povezana so s prevalenco okužb s HPV in kakovostjo in organizacijo citologije. Predčasno ponovno testiranje se lahko opravi 6–12 mesecev po prvem testiranju s testom HPV ali testom PAP in lahko vključuje (ali tudi ne) triažni test. Bolj podrobna priporočila glede nadaljnje obravnave žensk glede na izvide ponovnega testiranja so opisana v dopolnjenih smernicah (priporočila 1.23–1.31).

Vabljenje in neodzivnice:

- Če se ženska na odzove na prvo vabilo na presejalni pregled, se priporoča ponovno vabljenje z enim ali dvema vabiloma, ki se lahko opravi tudi telefonsko. Vsa vabila naj bodo personalizirana in naj vključujejo termin pregleda ter navodila, kako ga lahko ženska spremeni.
- Organizirani programi naj s pilotnim programom preverijo presejanje s testom HPV doma pri tistih ženskah, ki se ne odzovejo na vabilo in opomnik. Če so rezultati pilotnega programa primerljivi rezultatom rednega programa (primerljiv odstotek žensk s pozitivnim presejalnim testom, pozitivna napovedna vrednost testa in stroškovna učinkovitost) in je možno umestiti test HPV doma v obstoječ organiziran presejalni program tudi z vseh ostalih vidikov, se priporoča nadgradnja programa s testom HPV doma za neodzivnice.
- Presejanje naj bo za ženske brezplačno ne glede na vrsto presejalnega testa; če to ni možno, pa naj bo strošek minimalen.

Spremljanje žensk in rezultatov programa – centralni presejalni register:

- Presejalni program mora skrbno spremljati obravnavo posamezne žensk s pozitivnim pre-

sejalnim izvidom testa HPV. Spremljati je treba, kako ženske upoštevajo priporočila glede nadaljnje obravnave, izvide dodatnih testov, kolposkopije, histopatologje in zdravljenja predrakavih sprememb.
- Zbrani podatki morajo omogočati izračun evropskih kazalnikov za spremljanje kakovosti presejalnega programa, ki so navedeni v smernicah iz leta 2008 in dopolnjeni leta 2015.

Presejanje in cepljenje:
- Cepilni status ženske s podatki o cepljenju proti HPV mora biti dostopen tako cepilnemu kot presejalnemu registru.
- Priporočeno je načrtovati in raziskovati nove pristope za presejanje cepljenih generacij/žensk, z namenom identifikacije in implementacije take presejalne politike, ki bo dosegla največjo možno sinergijo med cepljenjem in presejanjem ter bo zato tudi najbolj učinkovita.

Dopolnjene Evropske smernice še posebej poudarjajo, da je pri presoji učinkovitih presejalnih politik, kot je tudi slovenska, veliko pozornosti potrebno posvetiti načrtovanju in preverjanju novih priporočil v okviru pilotni raziskav, najbolje randomiziranih. Presoja mora biti dobro koordinirana. Poleg učinkovitosti posameznega presejalnega modela je pri načrtovanju in preverjanju potrebno upoštevati tudi druge organizacijske dejavnike, kot so spremembe v obstoječi mreži laboratorijev, integracija presejanja z obstoječim sistemom zdravstvenega varstva, spremembe zakonskih določil, virov podatkov, spremembe v presejalnem registru in podobno. Presejalnemu modelu je potrebno dodati ustrezen model za nadaljnjo diagnostiko, spremljanje in zdravljenje žensk. Ključno je zagotoviti vzdržnost novega sistema tako z vidika človeških kot finančnih in tehnoloških virov pa tudi, da bodo izvajalci in ciljna populacija novo presejalno politiko sprejeli in upoštevali priporočila, saj je to nujen predpogoj za učinkovito delovanje presejalnega programa.

Tuje raziskave, ki primerjajo zdravstvene koristi in stroške presejanja s testom PAP in testom HPV kažejo, da je v organiziranem populacijskem presejalnem programu, kjer je zagotovljena in nadzorovana uporaba testa HPV v skladu s priporočili, presejanje s testom HPV bolj stroškovno učinkovito kot presejanje s testom PAP. V državah, ki se bodo odločile in zamenjale presejalni test, se bodo ob ustrezni uporabi testa HPV zaradi večje občutljivosti testa HPV v primerjavi s testom PAP in večje negativne napovedne vrednosti, povečale zdravstvene koristi, ki jih bodo od presejanja imele ženske. Obenem se bo zmanjšalo število testov PAP, spremenila pa se bo tudi vloga citologije v presejalnem programu – pri ženskah s pozitivnim presejalnim testom HPV bo citologija postala diagnostična metoda. Če bo presejalna politika priporočala različen presejalni test glede na starost žensk in/ali njen cepilni status, bo vloga citologije deljena – pri nekaterih ženskah bo test PAP še vedno presejalni test, in bo test HPV služil le kot triažni test. Število testov HPV se bo povečalo, vendar zaradi daljšega presejalnega intervala predvidoma manj, kot se bo zmanjšalo število testov PAP (2).

Med državami, ki so se po večletnem razmisleku in številnih raziskavah in preračunih odločile za spremembo presejalne politike, sta tudi Avstralija in Nova Zelandija. V Avstraliji so do sedaj presejali s testom PAP ženske v starosti 18–69 let vsaki dve leti, na Novi Zelandiji pa ženske stare 20–69 let vsake tri leta. Tako Avstralija kot Nova Zelandija načrtujeta prehod na 5-letno presejanje s testom HPV v starosti 25–69 let ter izstopni test HPV v starosti 70–74 let. V triaži je predvidena delna genotipizacija (HPV-16 in HPV-18) in refleksna triaža s testom PAP. Ženske, okužene s HPV-16 in HPV-18, ter ženske, okužene z drugimi nevarnejšimi HPV, ki imajo ob tem citološke spremembe visoke stopnje, bodo napotene na kolposkopijo. Ženske, okužene z drugimi nevarnejšimi HPV (ne s HPV-16 ali HPV-18), in pri katerih refleksna triaža ne bo pokazala patoloških sprememb ali bodo le-te nizke stopnje, bodo napotene na ponoven test HPV čez eno leto. Razlogi za odločitev za tako presejalno politiko, vključno s simuliranimi preračuni, kako bo sprememba presejalne politike vplivala na zdravstvene koristi in stroške, so podrobno opisani v Prilogah 2 in 3 (9, 10). Kratek povzetek ugotovitev je, da nova avstralska in novozelandska presejalna politika v primerjavi z obstoječo zagotavlja dodatno zmanjšanje incidence in umrljivosti zaradi RMV pa tudi manjše število presejalnih testov v življenju ene ženske, in sicer ne glede na to, ali bi v državi uvedli cepljenje proti HPV ali ne. Zaradi visoke precepljenosti v Avstraliji pričakujejo, da se bo v novem presejalnem programu v primerjavi z obstoječim zmanjšalo tudi število kolposkopij in zdravljenj. V odsotnosti cepljenja bi se ob uvedbi izbrane nove presejalne politike število kolpoksopij in zdravljenj v primerjavi z obstoječo presejalno politiko povečalo. Ne glede na ocene spremenjenega števila kolposkopij in zdravljenj pa preračuni kažejo, da bi bila nova presejalna politika tako v Avstraliji kot na Novi Zelandiji cenejša od obstoječe tako sedaj, ko je v državi implementiran uspešen cepilni program, kot v primeru, če cepilnega programa ne bi bilo. Teh ocen in izračunov ne moremo neposredno prenesti na Slovenijo. Z njihovim modelom si sicer lahko pomagamo, vendar moramo pri presoji slovenske presejalne politike upoštevati slovenske posebnosti.

Slovenske posebnosti, ki jih bo potrebno upoštevati pri presoji prenove presejalne politike

Pri presoji, ali spremeniti dokazano učinkovito obstoječo presejalno politiko in če da, kako, bomo tudi v Sloveniji morali upoštevati veliko dejavnikov. Le tako bomo lahko za naše ženske in državo izbrali kar najboljši model za presejanje in nadaljnjo obravnavo v presejanju pozitivnih žensk, ki bo ženskam zagotavljal kar najboljše razmerje med koristmi in škodo, ter bo finančno, tehnološko in kadrovsko vzdržen.

Glavna vprašanja bodo povezana z vrsto presejalnega testa in triažo, presejalnim intervalom, starostjo žensk ob vstopu in izstopu iz presejalnega programa ter nadaljnjo obravnavo žensk glede na izvid presejalnega in triažnega testa – vse to ob upoštevanju razlik v izhodiščnem tveganju med cepljenimi in necepljenimi dekleti zaradi okoli (trenutno) 50-odstotne precepljenosti v okviru nacionalnega programa cepljenja. Dodatno bomo presojali o pomenu tekočinske citologije in refleksne triaže, testa HPV doma za neodzivnice ter izstopnega testa HPV. Zanimale nas bodo dodatne zdravstvene koristi, ki bi jih lahko dosegli s spremembo presejalne politike, v primerjavi s stroški in morebitno zdravstveno škodo. Pri tem bomo v izračune vključili podatke o prevalenci HPV med slovenskimi ženskami, oceno števila presejalnih in predčasnih ponovnih testov, oceno števila kolposkopij, histopatoloških preiskav, zdravljenja predrakavih sprememb ter podatke o kakovosti in dosedanji učinkovitosti slovenske citologije. Poleg organizacijskih, pravnih, finančnih in drugih vidikov bomo morali med drugim upoštevati tudi naslednje slovenske posebnosti:

- Slovenija je ena od evropskih držav z zgodovinsko največjo zabeleženo incidenco RMV in hkrati ena od evropskih držav s populacijskim organiziranim presejalnim programom, ki je uspela najbolj zmanjšati incidenco RMV (11). To sovpada z rezultati nedavne slovenske presečne raziskave na vzorcu žensk, ustreznih za presejanje, ki kaže na dokaj visoko prevalenco okužb z nevarnejšimi HPV, predvsem pri mladih ženskah (12). V starostni skupini 20–25 let je z nevarnejšimi HPV okuženih okoli 25 % deklet, pri starejših pa se prevalenca pričakovano manjša. To kaže, da sprememba v incidenci RMV v Sloveniji najverjetneje ni posledica zmanjšanja izhodiščne ogroženosti, ampak učinka presejalnega programa, ki učinkovito odkriva in zdravi predrakave spremembe, ki bi brez tega napredovale v raka. Vsakršna sprememba presejalne politike, ki bi vodila v zmanjšanje pregledanosti ciljne populacije ali zmanjšanje učinkovitosti odkrivanja in zdravljenja predrakavih sprememb materničnega vratu visoke stopnje, bi lahko ogrozila uspešno obvladovanje bremena raka materničnega vratu v Sloveniji.
- Visoko prevalenco okužb z nevarnejšimi HPV pri mladih dekletih in razmeroma majhno precepljenost bo treba upoštevati tudi pri izračunu zdravstvenih koristi in stroškov morebitne nove presejalne sheme. Ta dva dejavnika bosta lahko omejevala uporabo testa HPV pri mladih ženskah, predvsem na račun prevelikega deleža HPV-pozitivnih žensk, premajhne pozitivne napovedne vrednosti testa HPV in tudi odkrivanja sprememb, ki bi spontano nazadovale – to bo sicer potrebno še podrobneje proučiti. Pri tem bo treba upoštevati tudi precepljenost starejših žensk, ki so se cepile na lastno pobudo. Pomembno je, kdaj bodo cepljene generacije začele vstopati v DP ZORA in kolikšno zaščito lahko pričakujemo ob 50-odstotni precepljenosti (ki se še zmanjšuje), glede na cepiva, s katerimi cepimo, in pričakovano raven kolektivne imunosti.
- Upoštevati bo potrebno tudi obstoječo mrežo citoloških laboratorijev, ki sodelujejo v programu in z visoko izobraženim in usposobljenim kadrom zagotavljajo visoko kakovost slovenske citologije, ki učinkovito manjša incidenco RMV kljub razmeroma majhnem (5-odstotnem) deležu žensk s patološkim izvidom presejalnega testa in minimalnim številom neuporabnih presejalnih testov PAP (v zadnjih letih < 1 %) (13). Poseben izziv bo predstavljala presoja o številu citoloških in molekularnih laboratorijev, prehod na tekočinsko citologijo ter obravnava žensk s pozitivnim presejalnim testom glede na izhodiščno tveganje, tudi v povezavi s cepilnim statusom ženske.
- Pri presoji glede starostne meje za začetek in zaključek presejanja bo potrebno med drugim upoštevati spremembe v starostno-specifični incidenci predrakavih in rakavih sprememb visoke stopnje po uvedbi DP ZORA. Oceniti bo potrebno predvideno zmanjšanje incidence teh sprememb v generacijah žensk, cepljenih proti HPV v nacionalnem programu cepljenja. Smiselno se bo opredeliti glede starosti ob izstopnem testu HPV.
- Pri presoji glede vključitve testa HPV doma za neodzivnice rednega presejalnega programa in presoji glede triažnih metod bomo lahko upoštevali tako mednarodna priporočila kot rezultate nacionalne randomizirane nadzorovane raziskave, opisane v drugem prispevku v tem zborniku z naslovom Raziskovalni projekt sprejemljivosti testa HPV doma med neodzivnicami DP ZORA in učinkovitosti novih triažnih testov: opis raziskav DP ZORA, izvedenih v letih 2013–2016 (Ivanuš in sodelavci). Ob morebitni odločitvi za nadgradnjo programa s testom

HPV doma za neodzivnice bomo lahko upoštevali dragocene izkušnje pridobljene v času trajanja raziskovalnega projekta, ki so opisane v Prilogi 1 z naslovom Raziskovalni projekt sprejemljivosti testa HPV doma med neodzivnicami DP ZORA in novih triažnih testov: opis nalog koordinacijskega centra (Ivanuš in sod.).

- Nadgraditi bo potrebno informacijski sistem programa ZORA, in sicer tako, da bo mogoče sproti spremljati, kako izvajalci upoštevajo priporočila glede presejanja in nadaljnje obravnave žensk. Predvsem bo nujno spremljati, ali morebitna nova presejalna politika res zagotavlja boljše razmerje med koristjo in škodo. Preprečiti bo treba prekomerno uporabo testa HPV zaradi velikega povpraševanja žensk ali zaslužkarstva pa tudi premajhno uporabo testa HPV zaradi morebitnega nezaupanja izvajalcev ali ciljne populacije. Koncept prenove informacijskega sistema DP ZORA je bil izdelan v letu 2016 in je predstavljen v več prispevkih v tem zborniku z naslovi Koncept in tehnične rešitve prenovljenega informacijskega sistema DP ZORA (Muster), Časovnica prenove in vključevanje izvajalcev v projekt prenove informacijskega sistema DP ZORA (Pavlič) in Nove funkcionalnosti prenovljenega informacijskega sistema DP ZORA v prihodnosti (Ivanuš in sod.)
- Prav tako bo treba prevetriti zakonska določila ter zagotoviti finančno, kadrovsko in tehnološko vzdržnost morebitne nove presejalne sheme v obstoječem sistemu zdravstvenega varstva.

Zaključek

Projekt presoje presejalne politike DP ZORA je umeščen v strateški načrt Državnega programa obvladovanja raka 2017–2021. Namen presoje je zagotoviti, da bo slovenski presejalni program ostal v koraku s sodobnimi znanstvenimi spoznanji in slovenskim ženskam še naprej zagotavljal najboljšo možno obravnavo. Cilja presoje sta (1) odločiti se, ali bomo presejalno politiko spremenili ali ne in (2) če da, izbrati tako presejalno politiko, ki bo ženskam prinašala največ koristi, ki bo prilagojena na posebnosti slovenskega zdravstvenega varstva in obstoječega presejalnega programa ter bo finančno vzdržna. Projekt bomo vodili s sedeža DP ZORA na OIL, zaključili ga bomo do leta 2021, ko naj bi vložili predlog za spremembo presejalne politike na Zdravstveni svet, če se bomo odločili za spremembo. K sodelovanju bomo povabili tako odločevalce kot ključne slovenske strokovnjake s področja cervikalne ginekologije, citopatologije, histopatologije in molekularne diagnostike.

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Presejalni register DP ZORA danes

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Povzetek

Za nemoteno delovanje presejalnega programa in nadziranje njegove kakovosti je odločilen ustrezen informacijski sistem. V okviru dejavnosti Epidemiologija in register raka na Onkološkem inštitutu Ljubljana deluje enota Program in register ZORA. Tu vodimo Register ZORA, informacijski sistem, ki omogoča upravljanje s številnimi podatki in vrsto aktivnosti, potrebnih v organiziranem presejalnem programu. V Registru hranimo in obnavljamo podatke o osebah iz Centralnega registra prebivalcev; evidentiramo izvide citoloških brisov iz vseh slovenskih laboratorijev, ki se elektronsko zbirajo v registru v skladu s standardiziranim zapisom; izvide histoloških preiskav, ki jih zbiramo v papirni obliki, kodiramo in ročno vnašamo ter izvide triažnega testa HPV, opravljenega v skladu s strokovnimi smernicami; pripravljamo sezname izbranih skupin žensk za vabila na presejalni pregled; iščemo ženske, ki niso opravile kontrolnega pregleda po patološkem izvidu, in nanje opozarjamo ginekologe ter dodatno izbiramo izvide bolnic z rakom materničnega vratu.

Informacijski sistem je po 15 letih tehnološko zastarel. Moramo in želimo ga kar najhitreje posodobiti in izpopolniti, vendar bo to – glede na možnosti – uresničljivo šele v nekaj letih. Prispevek prikazuje sedanje procese, ki jih omogoča Register ZORA, v naslednjih pa bo prikazana njegova vizija in predvidena prenova.

Ključne besede: informacijski sistem, presejalni program za raka materničnega vratu, Register ZORA, Evropske smernice za zagotavljanje in nadziranje kakovosti v presejanju

Uvod

Že v prvih Evropskih smernicah za zagotavljanje in nadziranje kakovosti v presejanju za raka materničnega vratu (RMV) iz leta 1993, kasneje pa v obeh posodobljenih izdajah iz let 2008 in 2015, je bilo zelo pomembno priporočilo, da je za vodenje organiziranih presejalnih programov za raka materničnega vratu (RMV) (pa tudi drugih bolezni) treba zagotoviti centraliziran informacijski sistem, ki mora poskrbeti, da so vse osebe iz ciljne skupine povabljene na presejalni pregled in da je njihova odzivnost čim večja. Zbrati in obdelati mora vse podatke iz presejalnih in diagnostičnih preiskav, in to v skladu z zakonskimi predpisi o varovanju osebnih podatkov.

Potem ko je predlog, da v Sloveniji vzpostavimo organiziran presejalni program za odkrivanje pred/rakavih sprememb materničnega vratu leta 1995 podprl Zdravstveni svet, smo začeli pripravljati informacijski sistem Register ZORA (RZ). Najprej je bilo treba zagotoviti zbiranje najpomembnejših podatkov o opravljeni presejalni preiskavi, pregledu celic v brisu materničnega vratu (BMV) v laboratorijih za citologijo in izvidu tega pregleda. Izvide je mogoče zbirati v informacijskem sistemu samo, če so strukturirani; na začetku žal nismo imeli niti enotnega, na ravni države dogovorjenega izvida, kaj šele, da bi bil strukturiran. Različni strokovnjaki, tako epidemiologi kot citologi in ginekologi, smo na začetku porabili veliko časa, da smo dorekli enoten, strukturiran izvid z napotnico in računalniški program za vnos podatkov v laboratorijih. Izhajali smo namreč iz znanega dejstva, da se morajo podatki vnašati v informacijski sistem tam, kjer nastajajo, saj je le tako mogoče zagotoviti njihovo kakovost in popolnost. Z osebnimi računalniki s programom za vnos podatkov s citoloških izvidov smo opremili 3 laboratorije, ki so pregledovali BMV žensk iz ljubljanske zdravstvene regije, kjer se je leta 1997 začelo pilotno preverjanje programa.

V organiziranem presejalnem programu je treba zagotoviti čim večjo udeležbo tistega dela prebivalstva, ki mu je program namenjen. Izkušnje kažejo, da je to mogoče doseči le z osebnimi vabili, za kar pa je seveda treba imeti čim popolnejši seznam imen in naslovov ciljne skupine ljudi. V Sloveniji nam ga zagotavlja Centralni register prebivalstva (CRP), v katerem je po enotni matični številki občana (EMŠO) mogoče povezati tudi podatke različnih podatkovnih zbirk. Podatki v tem registru so zaupni, dostop do njih pa drugim uporabnikom zagotavljajo posebni zakoni. V začetku smo dobili posebno dovoljene za dostop do podatkov o ženskah

iz pilotne študije s stalnim bivališčem v ljubljanski in kasneje primorski zdravstveni regiji. Leta 2000 je Zakon o zbirkah podatkov s področja zdravstvenega varstva (ZZPPZ) že vključil zbirko RZ med zbirke, za katere je mogoče v skladu z določili tega predpisa dostopati do osebnih in zdravstvenih podatkov, ki so našteti v tem zakonu.

V pilotni raziskavi smo na ginekološki pregled z odvzemom BMV vabili naključno izbrane ženske stare med 24 in 64 let (s stalnim bivališčem v ljubljanski in kasneje še primorski regiji) ne glede na to, kdaj so nazadnje opravile presejalni pregled, saj zgodovina prejšnjih še ni bila zbrana v sistemu. Informacijski sistem je omogočal tiskanje enotnega obrazca z vabilom, v katerega so se posebej vpisovali le osebni podatki. Z ginekologi smo se dogovorili za dan in eno uro, ko so sprejemali k njim napotene ženske. Predvidevali smo, da odziv ne bo 100-odstoten, zato smo na uro naročali po 6 žensk. Odziv je bil bistveno manjši od predvidenega, saj mnoge naročene ženske niso odpovedale obiska. Zato smo se kasneje v DP ZORA odločili, da pošiljamo iz centra samo priporočilo/vabilo za pregled s seznamom ambulant v regiji stalnega prebivališča ženske. Dodatno je bil razlog tudi v tem, da so si ženske morale na primarni zdravstveni ravni izbrati osebnega ginekologa, ki naj bi poskrbeli za preventivne preglede svojih opredeljenih žensk; seznama ginekologov z njihovimi opredeljenimi ženskami pa v RZ nismo imeli.

Seveda zbrani podatki nimajo pomena, če niso analizirani. Problem tedanjega sistema je bil, da informatikom zaradi njihove preobremenjenosti ni uspelo pripravljati osnov za redne sprotne analize. Zanje smo morali nemalokrat poskrbeti sami, za kar nismo bili dovolj usposobljeni.

Konec leta 2002 smo prekinili pogodbo s podjetjem, ki je izdelalo informacijski sistem za pilotno raziskavo, z novim izvajalcem pa pripravili tehnične pogoje, da smo lahko leta 2003 presejalni program razširili na vso državo (DP ZORA) in vzpostavili državni register (RZ).

Zgradba in aktivnosti Registra ZORA

Register ZORA ima več vsebinskih sklopov, ki omogočajo upravljanje s podatki in aktivnosti, ki so naloga koordinacijskega centra DP ZORA. V njem hranimo in redno posodabljamo podatke o vseh prebivalkah RS, zbiramo podatke o izvidih BMV, histopatoloških preiskavah materničnega vratu in triažnega testa HPV in jih povezujemo s podatki o novih primerih RMV iz Registra raka RS.

Vsi podatki v RZ imajo svoje šifrante, ki jih je treba redno posodabljati. Uporabljamo 3 večje skupine šifrantov: geografskih območij, ki opredeljujejo naslove, izvajalcev zdravstvenega varstva žensk in šifrante vsebine izvidov (BMV, histopatološke preiskave in HPV). Če se šifranti spremenijo, je treba iskati primerne rešitve. Tako je npr. sprememba klasifikacije citološkega izvida leta 2006 in 2011 pomenila za RZ poseben izziv, saj je treba ob zapisovanju sprememb z navzkrižnimi šifranti še vseeno omogočiti, da so rezultati v daljšem časovnem obdobju primerljivi.

Zbrane podatke redno analiziramo in laboratorijem pošiljamo poročila o njihovem delu, uporabljamo pa jih tudi za aktivnosti, ki so sestavni del organiziranega presejalnega programa, kot je npr. pošiljanje vabil na presejalni pregled, spremljanje obravnave žensk po ugotovitvi, da BMV ni normalen ali za preverjanje kakovosti postopkov z udeleženkami programa.

Zbirke podatkov v RZ

Podatki o osebah iz Centralnega registra prebivalcev

Podatki v CRP se nenehno spreminjajo, saj se ljudje rojevajo, spreminjajo priimke, se selijo in umirajo. Zato za DP ZORA še zdaleč ne bi bilo dovolj samo enkrat letno prenesti podatke iz CRP. Treba jih je redno posodabljati. V začetku smo jih posodabljali mesečno, ko smo jih sprejemali na zgoščenki, od leta 2013 pa smo s CRP povezani po zavarovanem omrežju HKOM; tako se podatki o osebah osvežujejo in dopolnjujejo vsako noč.

V RZ za vsako žensko evidentiramo EMŠO, ime in priimek, mesto, občino, naselje in državo rojstva, državljanstvo, naslov stalnega in začasnega bivališča (ulico, hišno številko, naselje, občino), spol, zakonski stan, generalni status (ali je živa, mrtva, odseljena ali o tem ni podatka), geokodo X in Y ter MID (s temi podatki lahko za vsako žensko prenesemo njen naslov na zemljevid) in datum, ko je nastala sprememba kakega od naštetih podatkov.

Na osnovi teh podatkov smo določili administrativne pogoje za vključitev v sistem vabljenja v presejalni program (starost 20 do izpolnjenih 65 let, stalno ali tudi začasno prebivališče v Sloveniji); vse druge ženske ne dobivajo vabil, seveda pa spremljamo njihove izvide, če jih k nam pošljejo iz laboratorijev.

Izvidi citološke preiskave brisa materničnega vratu

Trenutno BMV pregledujejo v devetih citopatoloških laboratorijih. Podatke s strukturiranih izvidov

v skladu z Metodološkimi navodili za informacijski sistem citoloških izvidov BMV vnašajo bodisi v svoj lokalni informacijski sistem, bodisi preko spletne povezave v spletno aplikacijo ZOCI. Iz lokalnih informacijskih sistemov štirih laboratorijev se podatki mesečno prenašajo in zbirajo v RZ preko računalniških pomnilniških sredstev (z zgoščenkami ali ključki USB) ali preko spletnega portala (dva laboratorija). Trije laboratoriji za vnos izvidov uporabljajo posebej v ta namen izdelano aplikacijo, poimenovano »ZOCI«, ki jim omogoča iskanje ustreznih oseb neposredno iz portala RZ in vpogled v prejšnje izvide. Ti laboratoriji po portalu lahko dostopajo do podatkov o osebah v RZ, izvide po vnosu avtorizirajo in sinhronizirajo, prenos podatkov pa poteka avtomatsko vsako noč.

Izvide, ki prihajajo na novo v RZ, je treba pripisati pravi osebi. Ta povezava poteka avtomatično po EMŠO. Če je EMŠO napačen, netočen ali ga sploh ni, je zanj treba v RZ poiskati ustrezno osebo ročno po vnaprej določenih merilih. Ugotavljamo, ali se s podatki v RZ ujemajo priimek, ime, datum rojstva in naslov; če v RZ ni ustrezne osebe, podatke shranjujemo v posebni datoteki. V začetku je bil to najzamudnejši postopek, saj na izvidih nismo našli EMŠO v več kot 90 %; z delovanjem programa in večjo pozornostjo ginekologov pri vpisovanju podatkov na napotnici se je ta delež z leti bistveno zmanjšal (okrog 2 %).

Povprečno letno število izvidov BMV v RZ je 240.000; trenutno imamo evidentiranih preko 3.600.000 izvidov BMV.

Ena od pomembnih nalog osebja RZ je skrb za popolnost in kakovost podatkov. Na manjkajoče podatke o izvidih BMV nas opozorijo ženske ali ginekologi, saj ženske prejmejo nepotrebno vabilo na pregled, ki so ga opravile nedavno. Napake pri analizi podatkov najdejo v laboratorijih ali jih ugotovimo v RZ. V RZ imamo vgrajene tudi logične preverbe, ki nas opozorijo na napake ali pomanjkljivosti v izvidih.

Ne glede na vrsto napake iz RZ redno pošiljamo laboratorijem prošnje, da podatke dopolnijo oz. popravijo. Popravke vnesejo v laboratorijih ali v RZ. Vsi postopki v zvezi s popravljanjem in zapisovanjem napak so standardizirani, vsi popravki pri vnosu izvida se shranjujejo v arhivu.

Izvid histopatološke preiskave

Leta 2004 smo poleg BMV v RZ začeli zbirati tudi izvide histopatoloških preiskav materničnega vratu in maternice (po histerektomiji). Izvid zaenkrat še ni strukturiran, zato nam v RZ iz laboratorijev pošiljajo papirne kopije. Kodiranje izvidov v skladu z dogovorjenim šifrantom je poseben izziv za diplomirano medicinsko sestro, ki ima za nalogo prevesti napisani izvid v številke s šifranta. Ker pa vrsta posega in histološka diagnoza vplivata na nadaljnjo obravnavo žensk in na nadaljevanje presejanja, je pomembno, da so podatki z izvidov zapisani pravilno. Povprečno letno registriramo 8.500 izvidov histopatoloških preiskav; trenutno imamo v RZ evidentiranih več kot 100.000 izvidov.

Nadaljnji potek dela s histopatološkimi izvidi je podoben kot pri citoloških izvidih: tudi tu poizvedujemo po manjkajočih izvidih, prosimo za dopolnitev pomanjkljivih podatkov, ki jih najdemo bodisi pri vnosu ali po logičnih preverbah.

Izvid triažnega testa HPV

Triažni test HPV naredi ginekolog na kontrolnem pregledu ob točno določenih indikacijah: pri ženskah s patološkimi spremembami materničnega vratu nizke stopnje (APC-N, PIL-NS pri ženskah, starih 35 let in več, AŽC-N po negativni abraziji in histološka diagnoza PIL-NS (CIN 1)) ali po zdravljenju predrakavih sprememb (praviloma PIL-VS (CIN 2 ali CIN 3)).

Izvid testa HPV je standardiziran; iz dveh laboratorijev, ki pri nas opravljata te preiskave, podatke pošiljajo enkrat mesečno v datotekah, ki so pripravljene po navodilih, ki jih predpisujejo Metodološka navodila za informacijski sistem izidov triažnih testov HPV. Če EMŠO na izvidu ni popolna, se izvid ne vpiše k ustrezni ženski, zato jo je treba po določenem ključu poiskati ročno. Za vse nepopolne izvide ali pri napakah, ki jih pokažejo logične preverbe, zaprosimo laboratorije za dopolnitve oz. popravke.

Letno registriramo več kot 10.000 izvidov iz obeh laboratorijev; trenutno imamo v RZ evidentiranih preko 70.000 izvidov

Dejavnosti, ki jih omogočajo podatki RZ

Vabljenje na presejalni pregled

Iz RZ pošiljamo vabila na presejalni pregled samo tistim ženskam, starim 20–64 let s stalnim prebivališčem v RS, ki v RZ nimajo evidentiranega nobenega izvida BMV ali pa je od zadnjega izvida minilo 4 leta ali več in nimajo evidentirane histerektomije ali amputacije materničnega vratu. Letno pošljemo med 40.000 in 90.000 vabil. Čeprav so pri nas ginekologi zadolženi, da povabijo na presejalni pregled svoje opredeljene ženske, če se te pravočasno ne naročijo same, se lahko zgodi, da te vabila iz ambu-

lante vseeno ne dobijo, se nanj ne odzovejo, nekaj žensk pa tudi nima izbranega ginekologa. Zato v RZ spremljamo udeležbo in ženske opomnimo, naj se naročijo na presejalni pregled.

Ženske, ki jim je treba poslati vabilo na presejalni pregled, izberemo s pomočjo »statusa za vabljenje«, ki za vsako žensko opiše, kje v presejalnem krogu trenutno je. Neustrezne so vse, ki ne ustrezajo izbornim merilom; ustrezna postane, ko vstopi v primerno starostno obdobje in ustreza drugim merilom za izbor. Ko je izbrana in je umeščena na seznam za vabilo, se z datumom potrdi, da je bilo vabilo poslano; ko registriramo njen citološki izvid, ki je normalen, se njen status avtomatično spremeni v status čakanja na naslednji presejalni izvid: če je izvid patološki, vstopi v status »posebne obravnave«. V tem primeru pričakujemo kontrolni BMV, izvid triažnega testa HPV ali izvid histološke preiskave. Novo vabilo lahko dobi šele po tem, ko v RZ zabeležimo normalni izvid BMV. Če se zgodi, da se ženska vabilu ne odzove, se umesti na seznam za ponovno vabilo. Če se ženska ne odzove na dve vabili, ki ju pošljemo iz RZ, postane dokončna neodzivnica. Ženska nam lahko pisno sporoči, da ne želi na pregled; v tem primeru se njen status za vabljenje spremeni v »ne želi sodelovati«. Večina statusov je prehodnih in se spreminjajo glede na vrsto izvidov. Status se dokončno spremeni, ko ženska umre ali iz histološkega izvida razberemo, da je imela odstranjeno maternico ali maternični vrat.

Vsakemu vabilu na pregled je dodan tudi vprašalnik; s pisnimi odgovori nam povabljene sporočijo, ali se bodo udeležile presejalnega pregleda ali pa razlog, zakaj se ga ne bodo. Odgovori na vprašanja so RZ v pomoč pri odkrivanju manjkajočih izvidov BMV, HPV ali histopatoloških preiskav. Sprejemanje in vnašanje odgovorov poteka ročno, kljub temu v RZ vnesemo vse odgovore.

Spremljanje kontrolnih pregledov po izvidu BMV s patološkimi spremembami in kakovosti dela izvajalcev

Številne raziskave so pokazale, da priložnostno presejanje za RMV, kljub velikemu številu presejalnih BMV, ne daje pravih rezultatov. Prvi razlog za neuspeh priložnostnega presejanja je neenakomerna udeležba žensk, saj nekatere na preglede prihajajo prepogosto, druge, večinoma najbolj ogrožene, pa premalokrat ali sploh ne. Drug razlog pa je v tem, da ženske, pri katerih presejalna preiskava pokaže spremembe, ne pridejo pravočasno na kontrolni pregled oz. na dodatne diagnostične preiskave. Prav tako je lahko vprašljiva kakovost obravnave žensk, saj ni vpeljanih sistemov za spremljanje in nadziranje kakovosti dela izvajalcev; tovrstno presejanje namreč ne vključuje zbiranja podatkov v centralnem presejalnem registru. V organiziranih programih so zato vse ženske iz ciljne skupine povabljene na pregled v primernih, na ravni države dogovorjenih intervalih (praviloma 3 leta), prav tako je treba posebej opomniti na kontrolni oz. diagnostični pregled tiste, ki ga glede na presejalni izvid potrebujejo. V Sloveniji naj bi za to, da ženske obvestijo o patološkem izvidu in jih tudi povabijo na dodatne preglede, poskrbeli v ginekoloških ambulantah. Ker se zaradi pomanjkanja časa v ambulantah večkrat zgodi, da vsi rezultati niso pravočasno evidentirani v njihovem informacijskem sistemu ali pa vodijo evidence ročno, lahko pride do napak in zato ženske niso pravočasno obveščene o tem, da morajo prej na kontrolni pregled. Informacijski sistem organiziranih presejalnih programov naj bi zato kot »varnostni sistem« služil tudi temu, da ženske obvešča o kontrolnih pregledih.

V Sloveniji smo leta 2007, ko smo ugotovili, da je naša baza BMV že dovolj popolna, ginekologom pričeli pošiljati sezname žensk, ki v našem registru eno leto po patološkem BMV ali BMV, kjer se sprememb ne da oceniti, nismo registrirali kontrolnega BMV. Sistem smo v zadnjem času dogradili tako, da pri seznamih upoštevamo tudi triažni test HPV in izvid morebitne histopatološke preiskave. V podatkovno bazo vnašamo tudi odgovore ginekologov in opravljamo redne analize.

Priprava podatkov za ponovni pregled vzorcev BMV izbranih bolnic z RMV

Ponovni pregled BMV bolnic z RMV je sestavni del analize kakovosti dela v citoloških laboratorijih. Nekatere ženske namreč zbolijo za RMV kljub temu, da se redno udeležujejo presejalnih pregledov. Razlogi za to so različni, lahko tudi v tem, da BMV ni bil ocenjen pravilno. Zato tudi pri nas skupina citopatologinj vsako leto ponovno pregleda BMV bolnic z RMV, ki jih najdemo s povezovanjem podatkov o novih primerih RMV iz Registra raka RS in o izvidih BMV iz Registra ZORA. Postopek je natančno opredeljen, namenjen pa je predvsem izobraževanju presejalcev in citologov.

Zaključek

Informacijski sistem DP ZORA je v času, ko je nastajal, pomenil pomembno pridobitev za to, da je bilo mogoče povečati udeležbo žensk na presejalnih pregledih in da je z analizami podatkov spodbudil prizadevanja za večjo kakovost dela na vseh ravneh, ki prispevajo k zmanjševanju bremena RMV. Velik napredek je bil standardiziran izvid citološke preiskave BMV, ki pa zaradi časovnega zamika pri vnosu podatkov v laboratorijih in še vedno papir-

ne komunikacije med izvajalci ni omogočil vseh prednosti, ki jih tak način obdelave podatkov omogoča. Kljub zastavljenim ciljem nismo uspeli standardizirati izvida histopatološke preiskave, čeprav so podatki s teh izvidov na voljo v informacijskem sistemu; popolnoma odprto je ostalo področje kolposkopije. Podatki o bolnicah in njenih zdravstvenih obravnavah so sicer na voljo v Registru raka RS, vendar bi jih bilo treba dopolniti s kliničnim registrom, da bi bili na razpolago vsi podatki, potrebni za vrednotenje klinične obravnave bolnic.

Po 15 letih delovanja je informacijski sistem DP ZORA tehnološko zastarel, potrebuje pa še dopolnitev s podatki o vseh postopkih z udeleženkami DP ZORA. Napredek na področju informacijske tehnologije in nova dognanja o povezavi med okužbo s HPV in nastankom RMV so izziv za celovito prenovo informacijskega sistema DP ZORA, ki bo vključila tudi manjkajoče procese, pa tudi morebitne spremembe presejalne politike. Novi viziji in predvideni prenovi so namenjeni naslednji prispevki.

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Nove funkcionalnosti prenovljenega informacijskega sistema DP ZORA

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Povzetek

V letu 2016 je Onkološki inštitut Ljubljana, nosilec DP ZORA, v sodelovanju z vodji strokovnih skupin DP ZORA ter drugimi strokovnjaki s področja ginekologije, citopatologije, histopatologije in molekularne diagnostike in v sodelovanju s sodelavci podjetja Marand d.o.o. pripravil koncept prenove informacijskega sistema DP ZORA z novimi funkcionalnostmi. Obstoječi informacijski sistem DP ZORA je bil vzpostavljen pred 15 leti in zaradi zastarelosti ne izpolnjuje več potreb DP ZORA, ciljne populacije in izvajalcev. Projekt prenove bo predvidoma potekal dve leti, proti koncu bodo v testno okolje vključeni tudi izvajalci. Koncept predvideva vzpostavitev brezpapirne, elektronske povezave med ginekologi in laboratoriji, ki sodelujejo v DP ZORA, in zadostuje vsem etičnim, strokovnim in zakonskim določilom glede varovanja osebnih in zdravstvenih podatkov ter zagotavlja varno in kakovostno obravnavo žensk. Prenovljena bo baza podatkov, ki se bo lahko povezalav sistem eZdravja. Predvidena je vzpostavitev novih povezav z zunanjimi bazami podatkov, kot so Elektronski register cepljenih oseb in informacijski sistem Zavoda za zdravstveno zavarovanje. Vsi izvajalci DP ZORA bodo povezani v e-krog, kar bo omogočilo brezpapirno naročanje preiskav in posredovanje e-izvidov. Izbrani ginekolog bo sproti obveščen o izvidih njegovih opredeljenih žensk na sekundarni ali terciarni ravni. Ginekologi in laboratoriji bodo lahko preverili predhodne izvide ženske v obravnavi, če bodo te podatke potrebovali za odločitev o diagnozi ali nadaljnji obravnavi. V dogovoru s ključnimi strokovnjaki bodo standardizirani tako izvidi s področja cervikalne patologije kot kolposkopski izvidi. Prešli bomo na prenovljen sistem vabljenja žensk na presejalne preglede in pisno obveščanje žensk o presejalnih izvidih. Nov informacijski sistem bo ginekologe sproti opozarjal na zamujene kontrolne preglede ali zdravljenja; sedaj jim Register ZORA ta podatek posreduje le enkrat letno. Sodoben, visoko parametriran procesni koncept bo omogočil lažje spreminjanje vnaprej dogovorjenih parametrov brez dodatnega programiranja, kar za nosilca DP ZORA pomeni hitrejše prilagajanje sistema spremembam in manjše stroške nadgrajevanja sistema in vzdrževanja. Nov informacijski sistem DP ZORA bo prinesel pomembne prednosti za ženske, za izvajalce DP ZORA, za nosilca DP ZORA in za državo. Zagotavljal bo bolj varno in kakovostno obravnavo žensk, enako in bolj kakovostno informiranost in obravnavo v skladu s sodobnimi smernicami, večjo sledljivost postopkov obravnav in manj napačnih obravnav. V prispevku so opisana tudi izhodišča, nujna za prenovo informacijskega sistema DP ZORA in predvidena časovnica.

Ključne besede: Register ZORA, informacijski sistem DP ZORA, prenova presejalne politike DP ZORA

Uvod

V Sloveniji imamo organiziran populacijski presejalni program za zgodnje odkrivanje predrakavih sprememb in raka materničnega vratu (DP ZORA) že od leta 2003. Sedež programa je na Onkološkem inštitutu Ljubljana, kjer deluje koordinacijski center programa z informacijskim sistemom (IS). Sedanji IS je bil vzpostavljen pred 15 leti. Je zastarel, zato ne izpolnjuje več potreb programa ZORA, ciljne populacije in vseh izvajalcev. V letu 2016 je Onkološki inštitut Ljubljana (OIL) v sodelovanju z vodji strokovnih skupin DP ZORA ter drugimi strokovnjaki s področja ginekologije, citopatologije, histopatologije in molekularne diagnostike in v sodelovanju s sodelavci podjetja Marand pripravil koncept prenove IS DP ZORA z novimi funkcionalnostmi.

Prenova informacijskega sistema in presejalne politike DP ZORA bosta dolgoročno omogočala hitrejšo neposredno komunikacijo med vsemi deležniki programa, varno, zanesljivo in sledljivo izmenjavo podatkov ter brezpapirno dokumentacijo. Sodobne tehnološke rešitve bodo zagotavljale manjše stroške obravnav in administrativne stroške ter učinkovitejše obvladovanje velike količine zdravstvenih in z zdravstvom povezanih podatkov ter informacij. Upravljavcu bo prenovljen sistem omogočal boljšo preglednost nad stanjem, hitre analize in z dokazi podprte strokovne odločitve. Izvajalcem bo tak sistem omogočal hiter, varen in legitimen dostop do vseh zakonsko opredeljenih podatkov o ženski, do katerih so upravičeni in s tem kakovostnejšo obravnavo v skladu s strokovnimi smernicami. Uporabnicam zdravstvenega sistema bo prenovljen sistem omogočal kakovostnejšo obravnavo v skladu s smernicami. Z novimi tehnološkimi rešitvami bo zagotovljena sledljivost vpogledov in vnosov podatkov v informacijski sistem in s tem boljša zasebnost in zaupnost.

Opis prenovljenega IS DP ZORA in novih funkcionalnosti

Prenova baze podatkov DP ZORA

V okviru projekta prenove informacijskega sistema DP ZORA bo med drugim prenovljena **baza podatkov** DP ZORA. Vsi izvidi brisov maternične vratu (BMV), histopatoloških preiskav, testov HPV in kolposkopskih pregledov bodo v bazi zapisani v obliki openEHR, odprtem standardu za upravljanje, shranjevanje, priklic in izmenjavo elektronskih zdravstvenih zapisov (angl. *electronic health record* – EHR) ki bo se bo lahko povezal v sistem eZdravja. Namen uporabe openEHR v eZdravju je vzpostavitev zbirke kliničnih in demografskih podatkovnih modelov za uporabo v slovenskem zdravstvenem informacijskem sistemu. Osnovni gradniki openEHR so arhetipi, definicije zapisov posameznega podatka, ki se definirajo enkrat in se lahko v celoti ali po posameznih delih uporabijo v različnih predlogah in v različnih sistemih. Podprta je večjezičnost, tako lahko uporabimo arhetipe, definirane v drugih državah, in jih prilagodimo lokalnim posebnostim. Vse to omogoča lažje povezovanje in izmenjavo podatkov s slovenskimi in tujimi sistemi in manjšo odvisnost od posameznega ponudnika IT storitev.

V skladu z veljavnim, a zastarelim Zakonom o zbirkah podatkov iz leta 2000, ki je v postopku prenove, baza podatkov DP ZORA vsebuje osebne in zdravstvene podatke o ženskah, izvide BMV, kolposkopske izvide, histopatološke izvide maternič-nega vratu in histerektomij, podatke o izvajalcih in ustanovah ter druge podatke, nujne za delovanje DP ZORA ter spremljanje in nadzor učinkovitosti programa in kakovosti dela izvajalcev. Nov IS DP ZORA bo vseboval tudi nekatere dodatne podatke, ki jih zastareli zakon še ne vsebuje, so pa že zajeti v predlogu novega zakona. Ti podatki so vezani predvsem na novo, s HPV povezano tehnologijo; to so podatki o testu HPV in cepljenju proti HPV. Čeprav zakon iz leta 2000 že predvideva centralno registracijo kolposkopskih izvidov, obstoječi Register ZORA kolposkopskih izvidov še ne registrira; začeli se bodo zbirati šele v novem IS DP ZORA. Evidentiranje kolposkopskih izvidov v centralnem presejalnem registru za spremljanje kakovosti obravnave žensk v organiziranem populacijskem presejalnim programu priporočajo tudi *Evropske smernice za zagotavljanje kakovosti v presejanju za raka maternič-nega vratu* iz leta 2008 ter *Priporočilo Evropskega sveta* iz leta 2003.

V novem IS bodo ohranjene obstoječe **povezave z zunanjimi zbirkami podatkov,** kot so Centralni register prebivalstva (CRP) in Register prostorskih enot (RPE). Predvidena je vzpostavitev novih povezav z zunanjimi bazami podatkov, kot so Elektronski register cepljenih oseb (eRCO) in informacijski sistem Zavoda za zdravstveno zavarovanje RS (ZZZS) in tudi nekatere druge povezave. Dopolnjeno bo tudi **podatkovno skladišče**, ki omogoča epidemiološke analize za spremljanje in nadzor učinkovitosti DP ZORA, kakovosti dela izvajalcev in za posebne raziskave.

Nove funkcionalnosti

- **Vabljenje žensk na presejalne preglede in obveščanje o presejalnih izvidih**

V skladu s priporočili Evropskih smernic in Priporočili Evropske zveze bo IS omogočal posodobljen način centralnega vabljenja žensk na presejalne preglede in centralno obveščanje o izvidih presejalnih pregledov. S tem želimo zagotoviti, da bo vsaka ženska med 20 in 64 letom prejela pisno vabilo na presejalni pregled tako, da ga bo lahko opravila v času 3 leta +/- 3 mesece od zadnjega pregleda, in da bo vsaka ženska po pregledu pisno in v ustreznem časovnem okvirju obveščena o izvidu presejalnega pregleda z navodili, kako ravnati naprej.

Nov IS predvideva dve možnosti za pošiljanje vabil. Ginekolog se bo lahko odločil, ali želi svoje opredeljene ženske še naprej vabiti sam ali bo to prepustil koordinacijskemu centru DP ZORA. Če bo ginekolog vabil sam, bo koordinacijski center deloval kot varovalka (podobno kot sedaj) in bo ženski poslal centralno vabilo samo v primeru, če bo iz IS razvi-

dno, da ženska ni imela BMV že štiri leta. Ginekolog, ki bo centralno vabljenje prepustil koordinacijskemu centru, bo redno prejemal elektronske sezname žensk, ki jih bo koordinacijski center vabil, in bo lahko koordinacijskemu centru tudi sporočil, katere ženske so ustrezne za vabljenje in katere ne (na primer tiste, ki so se na pregled že naročile same v ustreznem terminu od zadnjega BMV ali pa imajo kakršnekoli zdravstvene težave ali druge razloge, da vabila ne bodo prejele). Lahko bo tudi določil termine, na katere želi povabiti ženske, ali pa bodo ženske prejele vabilo, v katerem bodo pozvane, da pokličejo ginekološko ambulanto in se same dogovorijo za termin. Predvidena je elektronska povezava preko spletnih servisov za tiste ginekološke ambulante in ustanove, ki se bodo tako odločile. Ženske brez izbranega ginekologa bodo pravočasno prejele vabilo koordinacijskega centra. Ženske, ki se ne bodo odzvale na vabilo in opomnik, bodo čez tri leta ponovno vabljene (ne bo več t. i. dokončnih neodzivnic).

- **Elektronski zahtevek za laboratorijsko preiskavo in izvid**

Nov IS predvideva elektronsko, brezpapirno posredovanje **standardiziranega zahtevka** (napotnice) za pregled BMV, pregled tkivnega vzorca in test HPV v laboratorij in tudi elektronsko, brezpapirno posredovanje **standardiziranega izvida** BMV, histopatološkega pregleda in izvida testa HPV ginekologu, ki je preiskavo naročil. Izbrani ginekolog bo o izvidu elektronsko obveščen, če bo žensko napotil na sekundarno ali terciarno raven. S tem bo imel pregled nad tem, kaj se z njegovimi opredeljenimi ženskami dogaja po napotitvi in bo lahko pravočasno ukrepal, če bo videl, da se ženska priporočenih pregledov ni udeležila.

Vsebina citološkega zahtevka in izvida je že dogovorjena in v uporabi in bo tudi v prihodnje ostala skladna s klasifikacijo po Bethesdi. Vsebina histopatološkega zahtevka in izvida bo sledila *Smernicam za cervikalno patologijo* iz leta 2015. Vsebina zahtevka za triažni test HPV bo skladna z obstoječo napotnico za triažni test HPV, standardiziran pa bo tudi izvid testa HPV. Vse novosti in spremembe standardiziranih zahtevkov in izvidov na področju cervikalne citologije, patologije in molekularne diagnostike bodo usklajene s ključnimi strokovnjaki, tako kot je bila praksa do sedaj.

- **Druge nove funkcionalnosti za laboratorije**

V prenovljenem IS je predvidena tudi podpora izmenjavi preparatov in vzorcev med laboratoriji za revizijo in dvojno pregledovanja preparatov, kjer to določajo standardi DP ZORA in strokovne smernice. Prav tako so predvidene analize »na klik« za vse laboratorije za spremljanje kakovosti dela, s katerimi bodo lahko v laboratorijih sproti nadzirali obseg in kakovost dela svojih zaposlenih v primerjavi s slovenskim povprečjem. Predviden je tudi vpogled v predhodne izvide ženske, katere vzorec obravnavajo v laboratoriju, in kjer za pravilno diagnozo potrebujejo podatke o predhodnih izvidih.

- **Elektronski kolposkopski zahtevek in izvid**

Nov IS predvideva elektronski, standardiziran kolposkopski izvid z enotnim naborom podatkov za celo Slovenijo in s centralno registracijo kolposkopskih izvidov. V prihodnjih letih bodo v skladu s planom dela DP ZORA v sodelovanju s ključnimi strokovnjaki ter mednarodnimi priporočili posodobljeni standardi za kolposkopijo in pripravljeni *Standardi DP ZORA za izvajalce kolposkopije*. Kolposkopijo bo lahko opravljal vsak ginekolog, ki bo izpolnjeval standarde kakovosti.

Ginekologi, ki sami ne izvajajo kolposkopije, bodo lahko žensko napotili na kolposkopski pregled v kolposkopsko ambulanto na sekundarno ali terciarno raven, pri čemer bodo vse potrebne podatke kolposkopski ambulanti posredovali elektronsko v obliki standardiziranega zahtevka za kolposkopijo.

- **Opozorilni sistem za ginekologe**

Ginekologi bodo sproti opozorjeni na zamujene kontrolne preglede pri ženskah, ki bi jih v skladu s sodobnimi smernicami potrebovale, pa tudi na večja odstopanja v obravnavi glede na priporočila smernic (tako zaradi prekomerne kot pomanjkljive diagnostike ali zdravljenja). Sedaj koordinacijski center DP ZORA z Onkološkega inštituta Ljubljana ginekologe na zamujene preglede opozarja le enkrat letno, ker so tovrstne analize zapletene in zamudne.

- **Elektronska komunikacija med ginekologi na različnih ravneh ginekološkega zdravstvenega varstva, ki obravnavajo isto žensko**

Izbrani ginekolog bo lahko spremljal ženske po napotitvi na sekundarno ali terciarno raven. Informacijski sistem ga bo avtomatično obvestil o vseh laboratorijskih in kolposkopskih izvidih njegovih opredeljenih žensk. Ginekolog na sekundarni in terciarni ravni, h kateremu je bila ženska napotena za nadaljnjo diagnostiko ali zdravljenja sprememb materničnega vratu, bo lahko pregledoval njene predhodne izvide.

- **Elektronska komunikacija med izvajalci DP ZORA in Registrom ZORA**

Vsi izvajalci v DP ZORA (ginekologi na vseh ravneh, citopatološki, histopatološki in molekularni laboratoriji) bodo povezani z Registrom ZORA preko različnih tehničnih rešitev, ki bodo prilagojene različnim potrebam izvajalcev. Komunikacija bo potekala v vse smeri in bo zagotavljala hitro, varno in zanesljivo izmenjavo podatkov za obravnavo posamezne uporabnice zdravstvenega sistema.

Prednosti novega IS DP ZORA

Nov IS DP ZORA bo prinesel **pomembne prednosti za ženske, izvajalce DP ZORA, nosilca DP ZORA in državo**. Zagotavljal bo varnejšo in kakovostno obravnavo **žensk**, enako in bolj kakovostno informiranost in obravnavo v skladu s sodobnimi smernicami, večjo sledljivost postopkov obravnav ter manj napačnih obravnav.

Zagotovil bo, da bodo vse ženske pravočasno prejele vabilo na presejalni pregled in da bodo vse ženske tudi obveščene o izvidu ter da bodo ob tem prejele tudi navodila za morebitno nadaljnje ukrepanje. To bo po eni strani zmanjšalo administrativne obremenitve v ginekoloških ambulantah in hkrati povečalo udeležbo žensk v presejalnem programu, njihovo obveščenost o izvidih presejalnega pregleda in potrebi po nadaljnji obravnavi. S tem se bo povečala udeležba na kontrolnih pregledih, po drugi strani pa se bo zmanjšalo strokovno neutemeljeno prekomerno presejanje ter obravnava tistih žensk, ki tega ne potrebujejo. To bo še posebej pomembno po prenovi presejalne politike in uvedbi presejanja s testom HPV.

Strokovnjaki, ki bodo obravnavali žensko ali njen vzorec, bodo imeli takojšen dostop do njenih predhodnih izvidov, zaradi česar bo manj napak v obravnavi, ki so posledica napačno prepisanih ali nečitljivih podatkov o predhodnih izvidih ali pomanjkljivem sezamu predhodnih izvidov. Njihova odločitev o nadaljnji obravnavi ali diagnozi bo temeljila na preverjenih in ažurnih podatkih, vsi neujemajoči izvidi se bodo lahko razreševali sproti pri strokovnjakih, ki so za to najbolj usposobljeni.

E-povezava med ginekologi na primarni, sekundarni in terciarni ravni bo pomembno izboljšala komunikacijo med različnimi ravnmi ginekologije. Zmanjšalo se bo število ponovljenih/podvojenih preiskav (BMV, kolposkopij, testov HPV, biopsij…), prav tako pa bo izbrani ginekolog lahko ves čas spremljal, kaj se z žensko dogaja in jo bo lahko kontaktiral, če bo videl, da na pregled ni šla ali da se ni oglasila pri njem po zaključeni obravnavi na sekundarni/terciarni ravni.

Zaradi sistema za opozarjanje ginekologa na zamujene kontrolne preglede in zdravljenje ter na večja odstopanja v obravnavi žensk glede na smernice, se bo sčasoma povečala skladnost obravnav s smernicami – manj bo nepotrebnih, prekomernih ali napačnih obravnav in več bo obravnav, ki so v skladu s sodobnimi strokovnimi spoznanji.

Izvajalcem bo nov IS DP ZORA omogočil boljše upravljanje z ženskami, racionalizacijo dela in izboljšanje organizacije dela. **Nosilcu** DP ZORA bo nov IS omogočil boljši nadzor in hitrejše ukrepanje ob odstopanjih. **Za državo vse to pomeni manj stroškov in več zdravstvene koristi zaradi bolj urejenega in transparentnega sistema.**

Z novim sistemom, v katerem bodo centralno shranjeni ažurni podatki, do katerih lahko dostopajo vsi ključni deležniki, se odpirajo tudi priložnosti za prihodnost, kjer zdravstvena obravnava postaja vse bolj prilagojena posamezniku. Švedski raziskovalci so razvili računalniški algoritem za identifikacijo bolj in manj ogroženih skupin žensk, ki omogoča prilagajanje presejalnega intervala glede na stopnjo ogroženosti (1). Pri manj ogroženih ženskah je presejalni interval lahko daljši brez večjega tveganja za nastanek bolezni. Pri bolj ogroženih je presejalni interval lahko krajši, zaradi česar lahko spremembe materničnega vratu odkrivamo prej. Na podoben način bi lahko prilagajali tudi druge dejavnike in tako optimizirali tako presejanje žensk kot triažo žensk s patološkimi izvidi presejalnega testa.

Izhodišča za načrtovanje tehnične rešitve novega IS DP ZORA

Koncept prenove IS DP ZORA temelji na naslednjih predpostavkah, ki morajo biti izpolnjene zato, da bo nov sistem izpolnjeval potrebe žensk, izvajalcev in upravljavcev DP ZORA:

- Med ginekologi in laboratoriji, ki sodelujejo v DP ZORA, se vzpostavi brezpapirna, elektronska povezava, ki zadostuje vsem etičnim, strokovnim in zakonskim določilom glede varovanja osebnih in zdravstvenih podatkov ter zagotavlja varno in kakovostno obravnavo žensk.
- Izvajalcem DP ZORA povezava v nov IS DP ZORA ne sme povečati stroškov in administrativnih obremenitev, zmanjšati pa mora možnosti napak. Pri tem ne smeta biti ovirana razvoj in delo v laboratorijih in ginekoloških ambulantah z lastnimi laboratorijskimi in ginekološkimi informacijskimi sistemi (LIS in GIS).
- Podatki v IS se vnašajo tam, kjer nastanejo. Vnašajo se sproti (brez časovnega zamika) in

samo enkrat. Napake se preprečuje z logičnimi kontrolami. Popolnost vnosa podatkov se zagotavlja z obveznimi polji. Vsi dokumenti se ustrezno avtorizirajo in časovno označijo z zadnjo verzijo. Podatki so takoj po avtorizaciji dostopni v IS DP ZORA, zato ne prihaja do zamud pri izmenjavi zahtevkov in izvidov med ginekologi in laboratoriji ter kolposkopskih izvidov med ginekologi. Če v procesu nastane pisni dokument (na primer izvid, ki se po pošti pošlje ženski), mora biti natisnjen iz IS po vnosu podatkov in avtorizaciji. Vsi naknadni popravki po avtorizaciji se lahko izvajajo, vendar mora biti vsak popravek avtoriziran in ustrezno dokumentiran.

- V povezavo so vključeni vsi ginekologi, ki izvajajo presejalne ali kontrolne preglede, nadaljnjo diagnostiko s kolposkopijo, zdravljenje in spremljanje po zdravljenju.
- V povezavo so vključeni vsi laboratoriji za citologijo (pregledi BMV in morda drugi morfološki testi, kot na primer imunocitokemični testi v prihodnosti), laboratoriji za patologijo (ki pregledujejo tkivne vzorce materničnega vratu in histerektomije), laboratoriji za molekularno diagnostiko (ki izvajajo teste HPV in v prihodnje morda druge molekularne teste).
- Visoko parametriran procesni koncept bo omogočal lažje spreminjanje vnaprej dogovorjenih parametrov (odločitvene tabele in šifranti) brez dodatnega programiranja, kar za nosilca DP ZORA pomeni hitrejše prilagajanje sistema spremembam in manjše stroške nadgrajevanja sistema in vzdrževanja.
- Minimalni pogoj za povezovanje izvajalcev v nov IS DP ZORA je osebni računalnik in dostop do interneta.

Časovnica prenove IS DP ZORA

V skladu s konceptom prenove IS DP ZORA in projektno dokumentacijo načrtujemo, da bo prenova trajala dve leti. V **letih 2017 in 2018** bomo v sodelovanju s ključnimi strokovnjaki s področja ginekologije, citologije, patologije, molekularne diagnostike ter informatike prenovili IS DP ZORA. V sodelovanju z Ministrstvom za zdravje (MZ) in ZZZS bomo dopolnili zakonodajo; večina zakonskih aktov je že v pripravi (npr. Presejalni pravilnik, Zakon o zbirkah podatkov, Standardi DP ZORA za izvajalce ipd.), nekatere (predvsem v povezavi z openEHR in eZdravjem), pa bomo morali še pripraviti. Prav tako bomo v sodelovanju z ZZZS ponovno vzpostavili povezavo med IS DP ZORA in IS ZZZS, prek katere bomo pridobili podatek o izbranem ginekologu, če bo možno pa tudi nekatere druge podatke, ki jih potrebujemo za ustrezno vabljenje žensk na presejalne preglede in spremljanje obravnave in bodo zmanjšali nepotrebno vabljenje in obravnavo žensk, ki tega ne potrebujejo.

Prenova IS DP ZORA je predpogoj za nujno potrebno prenovo presejalne politike DP ZORA, ki jo svetujejo leta 2015 posodobljene Evropske smernice za zagotavljanje kakovosti v presejanju za raka materničnega vratu.

Literatura

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