BC CANCER CERVIX SCREENING
Provincial Health Services Authority

BC Cancer Cervix Screening Pathology Standards 2020

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Pathology Standards
Cervix Screening Program

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About BC Cancer

BC Cancer provides a comprehensive cancer control program for the people of B.C. BC Cancer is committed to providing all patients with access to a full range of quality cancer services, regardless of where in B.C. they live.

Vision

A world free from cancer

Mission

To reduce the burden of cancer in British Columbia.

Table of Contents

1. Introduction

1.1 Cervix Screening Program

Cervical cancer was the fourth most common cancer in women worldwide in 2018, with an estimated 570,000 cases and 311,000 deaths Cervix screening has decreased the incidence rates in jurisdictions where it has been successfully implemented. British Columbia implemented the first population based cervix screening program in the world in 1955 and cervical cancer incidence decreased by 70% from 1955 to 1985.[2] The primary goals of the Cervix Screening Program are to detect and remove cervical cancer precursors to prevent the development of cervical cancer and to detect asymptomatic cervical cancer at an early clinical stage to decrease mortality.

Pathologists who report cervix biopsies and excisional samples provide critical diagnostic information to inform management decisions. Standardized specimen handling and reporting will contribute to system wide equality of care and will facilitate information gathering, program evaluation and national and international comparison and benchmarking.

The information and recommendations in this document were developed with input from each Regional Health Authority in British Columbia, the BC Agency for Pathology and Laboratory Medicine, the British Columbia Association of Laboratory Physicians (BCALP) and BC Cancer. As far as possible, the guidelines are based on national and international evidence and best practice.

1.2 Purpose of the Standards

The purpose for developing pathology standards for the Cervix Screening Program is to:

- eliminate variability in diagnosis and nomenclature of cervical cancer precursors
- include key information for patient management
- include relevant information needed for patient surveillance

1.3 General Principles

Quality assurance is an essential component of a population-based screening program, and measurements of quality should be applied to all participating laboratories. Uniform provincial standards provide the opportunity to monitor system performance and patient outcomes in a way that supports comparison and learning across jurisdictions. Consistency in reporting will help to ensure meaningful systems performance and patient outcomes monitoring, and will assist physicians in determining appropriate treatment plans and recall intervals for screening patients.

A centralized consultation service is available for individual pathologists to refer complex and difficult cases prior to final diagnosis.

Quality assurance is a process of education, consultation and collegiality that will optimize patient outcomes.

Laboratory Standards

All participating laboratories must be accredited by the Diagnostic Accreditation Program (DAP) of the College of Physician and Surgeons of BC. All pathology reports originating from screening patients will be submitted to a central registry that can be assessed by individual(s) charged with the responsibility for implementing province-wide pathology performance indicators. Selected pathology slides and reports will be made available for forwarding to individuals charged with the responsibility for implementing Pathology Performance Indicators.

Participating Pathologist Standards

It is anticipated that all pathologists participating in the Cervix Screening Program will already have experience in the diagnosis of cervical histopathology reporting. Annual Pathology Quality Reports will be distributed to allow for self-assessment and comparison to the rest of the program.

2. Cervical Surgical Pathology

2.1 Pre-analytical Process

2.1.1 Requisition and Specimen Labeling

Please ensure that the laboratory requisition and specimen labeling is in accordance with regulations of Government of British Columbia and DAP standards.

2.2 Technical analytical process

2.2.1 Gross Description and Dissection

Awareness of the cervix screening results and colposcopy findings are important. Colposcopists submitting cervical samples are encouraged to supply relevant information. Recent cervix screening results are also available in CareConnect, the B.C. Provincial clinical archive.

2.2.1.1 Cervical Biopsies and Endocervical Curettage Samples

Each laboratory will have standards for sample grossing and processing. If possible, embed samples on edge to facilitate interpretation. Cutting up to three levels is recommended.[3] Further levels may be considered depending on the findings in the initial sections or relevant clinical information.

2.2.1.2 Cone and LEEP Samples

Document the number of pieces. Measure intact LEEP or cone sample in three dimensions. Do not probe an intact LEEP or cone sample as this may damage the epithelial surface. Section the LEEP or cone in parallel, sagittal serial sections in a bookending or bread loafing manner. This allows accurate determination of extent of small volume tumours and avoids the problem of variable slice thickness at the apex of radially sectioned wedges. Section separate fragments in a serial manner. Do not place more than two fragments in a single cassette.

Deeper levels should be considered if the initial section did not contain the ectocervical and endocervical margin and the transformation zone as expected.

2.3 Professional Analytical Process

2.3.1 Terminology

2.3.1.1 Benign Changes

If the biopsies show only benign changes, report the final diagnosis as negative for intra-epithelial lesion or malignancy (NILM). Specific benign changes can be added as bulleted or indented lines below the main NILM statement. These diagnostic categories are optional but may be helpful to explain cytological findings (Appendix A).

2.3.1.2 Squamous Precursors

Use the three-tiered cervical intraepithelial neoplasia (CIN) terminology. Use of alternative classifications such as the four tiered dysplasia/squamous carcinoma and the two tiered Lower Anogenital Squamous Terminology (LAST) proposal and current WHO classification systems are discouraged.[4,5] Our recommendation to use the three tiered CIN classification is based on the following reasons:

1) CIN categories can be easily translated into the WHO categories.
2) CIN 2 shows biologic differences, compared to CIN 3.[6,7]
3) Most high-quality studies used CIN 3 as the surrogate risk marker of cervical cancer risk.[8,9]
4) CIN 2 is often managed conservatively in young women.
5) The current risk based stratification model for screening and colposcopy referral of the American Society of Colposcopists and Cervical Pathologists is based on the level of risk for CIN 3 and more severe abnormalities. [10]

Try to definitively categorize the changes as either benign or CIN. If it is not possible to definitively confirm or exclude CIN, diagnose as indefinite for CIN with a comment explaining why a definitive interpretation is not possible (e.g. poorly preserved, too scanty, diagnostic features not sufficiently well characterized, insufficient material for confirmatory ancillary testing).

If CIN is present, diagnose as CIN 1, CIN 2 or CIN 3. It may occasionally be impossible to differentiate between CIN 2 and CIN 3, e.g. when there is significant cytologic atypia and p16 is positive but poor orientation precludes further categorization. In this situation diagnose as CIN high grade, cannot be further stratified.

When a high-grade squamous precursor lesion is identified in an excision specimen (cone or LEEP), comment on the status of all margins: ectocervical, endocervical and deep (radial stromal) margins. If all margins are clear state that endocervical, ectocervical and deep radial margins are uninvolved by CIN. If any margin cannot be assessed for whatever reason, report the margin as indeterminate with a comment explaining the reason. More specific information is needed for some glandular abnormalities, see next section for further information.

2.3.1.3 Glandular Precursors

HPV Related Glandular Abnormalities

Use endocervical adenocarcinoma in situ (AIS) terminology for high grade precursors. Lesions showing cellular multilayering like a squamous precursor lesion but also glandular differentiation in the form of mucin vacuoles in all layers of epithelium are diagnosed as stratified mucin-producing intraepithelial lesion (SMILE). The WHO classification regards SMILE as a variant of AIS for purposes of treatment and follow up.[4]

It is not necessary to comment on low grade glandular changes. Every attempt should be made to classify atypical endocervical glands either as AIS or benign reactive endocervical change. Immunohistochemistry for p16 and Ki-67 can be very useful as AIS should show strong and diffuse p16 staining with a high proliferative rate with Ki-67. Be aware that endometrial glands and areas of tubal metaplasia may express p16, but

usually less extensively than AIS. It may occasionally be impossible to render a definitive diagnosis of AIS, especially on small biopsies. In this situation, diagnose as endocervical glandular atypia, with qualifier of severe endocervical glandular atypia when appropriate. If possible, indicate whether the changes are suspicious for AIS or if a reactive process is favoured.

When an HPV related AIS lesion is identified in an excision specimen (cone or LEEP), report the status and give measurements of AIS relative to nearest endocervical, ectocervical and deep radial margin. If any margin cannot be assessed for whatever reason, please report margin as indeterminate with a comment explaining the reason. As there is limited data on appropriate follow up of AIS after cone or LEEP, the distance to margin is one of the parameters used by clinicians to guide decisions regarding re-excision or hysterectomy.

Non-HPV Related Glandular Abnormalities

It is recognized that a subset of cervical adenocarcinomas are not HPV related, with gastric type cervical adenocarcinoma as the best characterized example. Criteria to recognize gastric type adenocarcinoma are published but these lesions are rare and diagnostic features can be subtle.[11] Precursor lesions for non-HPV related adenocarcinoma are not well established, but lobular endocervical glandular hyperplasia has been suggested as a possible precursor abnormality.[11,12] Nuclear atypia may be less severe than usual type AIS but severe nuclear atypia can be seen. The endocervical cells tend to be columnar in shape with eosinophilic to pale pink cytoplasm and occasional goblet cells. P16 is usually negative.[11]

2.3.1.4 Invasive Carcinoma

Biopsy Samples

Diagnose as invasive squamous carcinoma or invasive endocervical adenocarcinoma and use the current WHO classification.[4]

Excisional Samples (LEEP, CONE and Hysterectomy)

Use current WHO classification and fill in the provincially mandated synoptic report to ensure that all mandatory elements are captured.[4] The International Endocervical Classification and Criteria (IECC) pathogenetic classification may be used as an optional add on. [13]

2.3.2 Use of Ancillary Testing

The use of immunohistochemistry for p16, with or without concomitant Ki-67 expression, can be helpful to support a diagnosis of high grade CIN (CIN 2 and CIN 3). Use of p16 is not recommended when the diagnosis is clear on evaluation of the H&E (e.g. CIN 3). Immunohistochemistry should not be performed on cases of definite CIN 1 as p16 may show block like positive expression in otherwise typical CIN 1 lesions, although the staining pattern tends to be of the basal portion of the epithelium only.[5] If features are suggestive for CIN 2, p16 expression may be helpful to confirm a high grade lesion, with the caveat that CIN 1 may have similar staining. Judicious use of p16 can be instrumental in differentiating high grade CIN from mimics such as attenuated reactive epithelium and immature squamous metaplasia. Other potential uses for p16 includes clarifying LEEP margins when cautery artefact mimics CIN 2 or CIN 3. A positive p16

stain shows strong and diffuse cytoplasmic staining, with or without nuclear staining, in a block like pattern. Single cell or focal staining in small groups of cells is not considered positive.For further information and examples, refer to The British Association of Gynaecological Pathologists' p16 interpretation guide. [14]

2.3.3 Report Content and Required Elements

The final report should contain all elements required by DAP and should include all the elements for excisional and biopsy samples (Table 1). Use standardized terminology to support clinical management decisions, diagnosis coding and statistical comparisons (Appendix A). **For invasive squamous or adenocarcinoma, complete the provincial synoptic report**.

Table 1: Required Details for Excisional and Biopsy Samples

	Biopsy/ECC	LEEP/CONE
	Gross Description	
Specimen Type	Yes	Yes
Number of pieces	Yes (biopsy only)	Yes
Dimension	Largest (biopsy only)	Three Dimensions
Completeness of os	-	Yes
Description of visible lesions	-	Yes
Number of pieces submitted	Yes	Yes
	Diagnosis/Interpretation	
Site	Yes	Yes
Procedure	Yes	Yes
CIN when present	Yes	Yes
AIS when present	Yes	Yes
SMILE when present	Yes	Yes
Invasive Carcinoma when present	Yes	Yes
• Provincial Synoptic Report	-	Yes
Completeness of Excision		
• Endocervical margin	-	Yes
• Ectocervical Margin	-	Yes
• Deep radial margin	-	Yes
Distance to nearest margin (AIS only)		
• Endocervical margin	-	Yes
• Ectocervical Margin	-	Yes
• Deep radial margin	-	Yes

2.3.4 Report Turnaround Time

It is expected that specimens are reported within seven days of accessioning. Provide accession and report sign out date on each report.

3. Quality Assurance

3.1 Laboratories

All staff will be suitably qualified and will maintain all relevant current registration and medical liability insurance. Laboratory practice and facilities will comply with all relevant provincial legislation and local bylaws.

3.2 Cervix Screening Program

The Cervix Screening Program is mandated to evaluate program quality and collects and analyzes outcome data covering all aspects of the screening cascade. Pathology related data collection may include, but is not limited to: demographic data, dates of specimen collection and reporting, final diagnosis, and margin status, laboratory and reporting pathologist identifiers.

To support standardization and reproducibility of pathology reporting, the Screening Program, in collaboration with health authority representatives, have developed a set of performance indicators for cervical pathology reporting (Table 2). These performance indicators will be reviewed by the Cervix Screening Program Quality Management Committee. Health authority level data will be shared with designated administrative and professional leads in each health authority.

3.3 Performance Indicators for Cervical Pathology

3.3.1 Number of Samples Reported

- Cervical biopsies and ECC
- LEEP and Cone

3.3.2 Turnaround Time (Accessioning to Sign-Out)

3.3.3 Interpretation Categories

- Unsatisfactory or non-diagnostic
- Benign
- CIN1
- CIN 2
- CIN 3
- CIN High Grade
- Invasive carcinoma
- Equivocal could not be coded

3.3.4 Interpretation Category Rate by Screening Result

- ASC-US/LSIL
  - Benign rate
  - CIN 1 rate
  - CIN 2 rate
  - CIN 3 rate
  - AIS rate

- ASC-H and AGC (NOS)
  - Benign rate
  - CIN 1 rate
  - CIN 2 rate
  - CIN 3 rate
  - AIS rate

- HSIL and AGC (Favour Neoplastic)
  - Benign rate
  - CIN 1 rate
  - CIN 2 rate
  - CIN 3 rate
  - AIS rate

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Appendix A – List of Diagnostic Categories [15]

Benign

Recommended diagnosis:

- Negative for Intraepithelial Lesion or Malignancy

Optional categories:

- Squamous metaplasia
- Immature Squamous Metaplasia
- Squamous Atrophy
- Transitional Cell Metaplasia
- Chronic Cervicitis
- Papillary Endocervicitis
- Follicular Cervicitis
- Decidual Change
- Tubal Metaplasia
- Tuboendometrial Metaplasia
- Endometrioid Metaplasia
- Endometriosis
- Endocervicosis
- Endosalpingiosis
- Intestinal and/or Gastric (Pyloric) Metaplasia
- Rare Ectopias (Prostate, sebaceous and sweat glands)
- Tunnel Clusters
- Microglandular Hyperplasia
- Nabothian Cysts

Indeterminate

Squamous

- Squamous Atypia (Indeterminate for CIN)

Glandular

- Glandular atypia (Indeterminate for AIS)

Precursors

Squamous

- Cervical Intraepithelial Neoplasia grade 1 (CIN 1)
  - Variant: Exophytic Cervical Intraepithelial Neoplasia grade 1 (CIN 1)
- Cervical Intraepithelial Neoplasia grade 2 (CIN 2)
- Cervical Intraepithelial Neoplasia grade 3 (CIN 3)
- Cervical Intraepithelial Neoplasia (High Grade NOS)

Glandular

- Endocervical Adenocarcinoma-in-situ
  - Variant: Stratified Mucin-Producing Intraepithelial Lesion (SMILE)

Carcinoma

Biopsies

- Use WHO Classification

Excisions

- Use Provincial Synoptic Template

Log Revision History

Date	Action	Pages affected	Details
July 2020	New document	All	